Significance of the Viral Load of High-risk Hpv in the Diagnosis and Prediction of Cervical Lesions: A Retrospective Study

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Abstract

Background: The significance of HPV viral load in the detection of cervical lesions is still controversial. This study analyzed the correlation between the high-risk (HR)-HPV viral load and different cervical lesion degrees.

Methods: This was a retrospective study of the patients who first visited the hospital between January 2015 and June 2018. Patients with positive HR-HPV were screening for cervical cancer. The HR-HPV DNA load was measured by the second generation hybrid capture (HC2) technology. The patients grouped as normal, CIN I, CIN II, CIN III, and cervical cancer. Multivariable logistic regression was performed to explore the association between HR-HPV DNA load and cervical lesions.

Results: Finally, 265 patients were grouped as normal (n=125), CIN I (n=51), CIN II (n=23), CIN III (n=46), and cervical cancer (n=20). Among them, 139 (52.5%) had a low viral load, 90 (34.0) had a moderate viral load, and 36 (13.4%) had a high viral load. Taking the normal control group as a reference, a high viral load was an independent factor for CIN I (CIN I: OR=3.959, 95%CI: 1.300-12.059, P=0.015) CIN II (OR=6.211, 95%CI: 1.641-23.513, P=0.007), CIN III (OR=7.002, 95%CI: 2.308-21.244, P=0.001), and cervical cancer (OR=9.439, 95%CI: 2.394-37.22, P=0.001).

Conclusion: Cervical lesions are closely related to HR-HPV infection. Higher HR-HPV viral load in cervical lesions was associated with a higher risk of high-grade cervical lesions.

Background

According to the latest data from the World Health Organization/International Agency for Research on Cancer, cervical cancer (CC) is the fourth major malignant tumor in women worldwide [1]. In 2018, there were an estimated 570,000 new cases of CC in the world and 311,000 deaths, with 85% of the new cases being in developing countries [2]. In China, the incidence of CC has been increasing in recent years, but the mortality has been decreasing [3–5], probably because of the implementation of screening and early treatment of cervical lesions [6].

Epidemiological and molecular biological data show that human papillomavirus (HPV) infection can lead to cervical precancerous lesions and CC [7]. HPV is a member of the Papovaviruses family with a core of small double-stranded circular DNA, consisting of 7800–7900 base pairs, which is the smallest DNA virus [8]. Active papillomavirus infection occurs when infected basal cells replicate and fill an area. HPV synthesizes six early proteins (E1-E7) and two late capsid proteins (L1 and L2) during its replication. E6 and E7 have immortalizing and transforming properties that are retained and expressed during all stages of carcinogenic progression and believed to be responsible for the oncogenicity of HPV. E6 inactivates the tumor suppression protein p53, and E7 inactivates the retinoblastoma protein (pRb), which halts the prevention of DNA damage [9]. Persistent HPV infection results in squamous intraepithelial lesions that are graded as cervical intraepithelial neoplasia (CIN) 1, CIN 2, and CIN 3 according to how much epithelium is impacted [9]. Different types of HPV have different potentials of causing CC. High risk (HR)-HPV is the main cause of CC. HR-HPV subtypes such as HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, and 59 are closely associated (in decreasing oncogenic potential) with the occurrence of CC, and these associations are seen throughout the world [10], but there are some regional differences in the prevalence of the different HPV subtypes [11, 12]. The HR-HPV viral load indicates the activity of HPV-DNA in the body [13, 14]. Studies showed that the type of HPV infection is closely related to the severity of cervical lesions and treatment prognosis [10–12], but there are inconsistent results from the studies on the correlation between the HPV viral load and the severity of cervical lesions [13–19]. At present, the correlation between the HPV viral load and cervical lesions has not been determined, and the significance of the HPV viral load in the detection and treatment of cervical lesions is still controversial [17, 19].

Therefore, the objective of this study was to investigate the changes in HR-HPV viral load in patients with different degrees of cervical lesions, in order to clarify the correlation between the viral load of HPV and cervical lesions and to explore the clinical value of HR-HPV viral load for the predictive diagnosis of CC.

Methods

Study design and patients

This was a retrospective study of the patients who first visited the Gynecology Clinic of the Second Affiliated Hospital of Kunming Medical University between January 2015 and June 2018. This study was approved by the ethics committee of the Second Affiliated Hospital of Kunming Medical University. As a retrospective study, informed consent was exempted.

The inclusion criteria were: 1) patients with positive HPV-DNA who underwent cervical cancer screening according to the latest version of the American College of Obstetricians and Gynecologists (ACOG) guidelines for cervical cancer screening and prevention practice [20]; and 2) patients with complete colposcopy and pathological biopsy to determine the degree of lesions. There were no exclusion criteria.

Data Collection And Grouping

The age of the patients, the HPV-DNA viral load, and the pathological degree of cervical lesions at the time of screening were obtained from the clinical records. The patients were divided into five groups: normal group, CIN I group, CIN II group, CIN III group, and invasive CC group.

Detection Of Hpv-dna Load

The second generation of hybridized capture II (HC2) gene hybridized signal amplification system from the Digene Company (Gaithersburg, MD, USA) was used to detect the content of HPV-DNA in the samples. This assay can detect 13 types of high-risk HPV subtypes at one time. All assays were strictly performed according to the manufacturer's instructions. The cells were dissolved to break down the double-strand DNA and release single-strand HPV DNA. The single-strand DNA was complementary bound with RNA to form an RNA-DNA hybrid. The DNA-RNA hybrid complex was captured by the primary antibody, and then they were fixed. The alkaline phosphatase-bound secondary antibody was added to reveal the hybrids using chemiluminescence colorimetry. The relative light units (RLUs) and positive control values (CO) of the samples were detected. The RLUs were measured by the DML 2000 analyzer, and the results were presented as the relative fluorescence unit value. The ratio of the RLU to the CO value of the positive standard was used to indicate the viral load. RLU/CO < 1.0 was considered a negative result. RLU/PC ≥ 1.0 was considered as positive results, which means that the amount of HPV-DNA per ml of sample was > 1.0 pg, that is. The higher the DNA content in the samples, the higher the RLU, and the greater the RLU/CO ratio, the higher the viral load. According to Lorincz et al. [21], the viral load of HR-HPV DNA was classified into three levels: low viral load (1.00-99.99 RLU/CO), moderate viral load (100.00-999.00 RLU/CO), and high viral load (≥ 1000.00 RLU/CO).

Pathological Results

A colposcopy biopsy was performed after the diagnosis by a specialist gynecologist with 12 years of experience in the diagnosis and treatment of cervical and vaginal diseases. The cervix, vagina, and vulva were examined at the same time. Each quadrant of the cervix was assessed. The basic principles of direct biopsy or quadrant biopsy were followed. Multi-point biopsies were taken in the vinegar white area and iodine stained suspected lesion area and were sent directly for

pathological examination. If no abnormality was found under the microscopic examination in each quadrant, samples would be taken at the squamous columnar junction, or the transformation area at 3, 6, 9, and 12 o'clock of the cervix, and a sample would be taken by cervical curettage (ECC). The specimens taken by colposcopy were submitted to the pathology department of the same hospital for histopathological examination and immunohistochemistry if necessary. The final cervical pathological diagnosis was determined after quality control by two pathologists with 10 years of experience. The results were presented according to: normal (no squamous epithelial lesions), cervical intraepithelial neoplasia grade 1 (CIN I), cervical intraepithelial neoplasia grade 2 (CIN II), cervical intraepithelial neoplasia grade 3 (CIN III), and CC.

Statistical analysis

SPSS 24.0 (IBM, Armonk, NY, USA) was used for data processing and statistical analysis. Categorical data were presented as frequencies and percentages and analyzed using the chi-square test or Fisher's exact test, as appropriate. The continuous data were tested for normal distribution using the Kolmogorov-Smirnov test and analyzed using the Student t-test or ANOVA with the LSD post hoc test. Unconditional logistic regression analysis was performed for univariable and multivariable analyses to calculate the odds ratio (OR) and 95% confidence interval (CI) for the presence of cervical lesions in different viral load levels, using the normal group as the reference. P-values < 0.05 were considered statistically significant.

Results

Characteristics of the patients

A total of 11,422 patients were screened for cervical cancer using HC2, and 1542 (13.5%) were positive for HPV. There were 385 patients who underwent colposcopy and 265 who underwent cervical biopsy. Therefore, 265 patients, aged 20–73, were included in this study: 125 in the normal group, 51 in the CIN I group, 23 in the CIN II group, 46 in the CIN III group, and 20 in the CC group. The patients in the CC group were significantly older than the patients in the normal, CIN I, and CIN II groups (all P < 0.05) (Table 1).

Table 1
Characteristics of the patients

Characteristic, n (%)	Normal group (n = 125)	CIN I group (n = 51)	CIN II group (n = 23)	CIN III group (n = 46)	Cervical cancer (n = 20)	P
Age (years old), Median (IQR)	38 (30,47)*	40 (29.5,46)*	34 (29,40.5)*	44 (34,50)	50 (42.5,54.5)	< 0.001
*P < 0.05 vs. the cervical cancer group.						
CIN: cervical intraepithelial neoplasia; IQR: interquartile range.						

Hpv-dna Loads And Correlation With Pathological Types

Among the 265 patients, 139 (52.5%) had a low viral load, 90 (34.0) had a moderate viral load, and 36 (13.4%) had a high viral load. There were significant differences in viral load among the five pathological groups (P < 0.001). The viral load of patients in the CIN III and CC groups was higher than that of patients in the normal group, but there were no significant differences among the other groups (Table 2).

Table 2
Viral load of HPV-DNA in groups with different pathological results

HPV-DNA load	Normal group (n = 125)	CIN I group (n = 51)	CIN II group (n = 23)	CIN III group (n = 46)	Cervical cancer (n = 20)	P
HPV-DNA viral load RLU/CO, Median (IQR)	48.52 (4.16,180.87)	156.34 (10.54,578.08)	159.13 (36.19,701.465)	266.87 (16.56,958.13)*	307.005 (72.76,1386.075)*	< 0.001
Low load group, n (%)	82 (65.6%)	24 (47.1%)	10 (43.5%)	16 (34.8%)*	7 (35%)*	< 0.001
Medium load group, n (%)	36 (28.8%)	19 (37.2%)	8 (34.8%)	20 (43.5%)	7 (35%)	/
High load group, n (%)	7 (5.6%)	8 (15.7%)	5 (21.7%)	10 (21.7%)	6 (30%)	/
*P < 0.05 vs. the normal group.						
CIN: cervical intraepithelial neoplasia; IQR: interquartile range.						

Taking the normal control group as a reference, the correlations between all grades of cervical lesions and viral load were analyzed and compared using multivariable analysis. The results showed that the viral load was an independent risk factor for the occurrence of CIN I and CIN II (CIN I: high load, OR = 3.959, 95%CI: 1.300-12.059, P = 0.015; CIN II: high load, OR = 6.211, 95%CI: 1.641–23.513, P = 0.007), but age was not an independently associated factor (P > 0.05). For CIN III, age was still not an independent factor, but a moderate load of HPV (OR = 2.775, 95%CI: 1.283–5.999, P = 0.009) and a high load of HPV (OR = 7.002, 95%CI: 2.308–21.244, P = 0.001) were independent risk factors. For cervical cancer, age (OR = 1.080, 95%CI: 1.032–1.13, P = 0.001) and high load (OR = 9.439, 95%CI: 2.394–37.22, P = 0.001) were both independent risk factors (Table 3).

Table 3
Correlation between pathological types and HPV-DNA load

	CIN I				CIN II			
	Univariable		Multivariable		Univariable		Multivariable	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age	0.995 (0.964,1.027)	0.75	0.993 (0.962,1.025)	0.655	0.975 (0.932,1.02)	0.275	0.971 (0.927,1.017)	0.22
Low load	Ref		Ref		Ref		Ref	
Moderate load	1.803 (0.879,3.698)	0.108	1.809 (0.882,3.712)	0.106	1.822 (0.664,4.998)	0.244	1.837 (0.667,5.054)	0.239
High load	3.905 (1.285,11.869)	0.016	3.959 (1.300,12.059)	0.015	5.857 (1.561,21.973)	0.009	6.211 (1.641,23.513)	0.007
CIN: cervical intraepithelial neoplasia; OR: odds ratio; CI: confidence interval.								

Table 3
[Continued]

	CIN III				Cervical cancer			
	Univariable		Multivariable		Univariable		Multivariable	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age	1.033 (1.002,1.066)	0.039	1.031 (0.998,1.064)	0.066	1.077 (1.033,1.123)	< 0.001	1.080 (1.032,1.13)	0.001
Low load	Ref		Ref		Ref		Ref	
Moderate load	2.847 (1.324,6.121)	0.007	2.775 (1.283,5.999)	0.009	2.278 (0.744,6.971)	0.149	2.040 (0.643,6.472)	0.226
High load	7.321 (2.426,22.093)	< 0.001	7.002 (2.308,21.244)	0.001	10.041 (2.64,38.19)	0.001	9.439 (2.394,37.22)	0.001

CIN: cervical intraepithelial neoplasia; OR: odds ratio; CI: confidence interval.

Discussion

The correlation between HPV viral load and cervical lesions is poorly known, and the significance of HPV viral load in the detection and treatment of cervical lesions is still controversial [17, 19]. Therefore, this study aimed to analyze the correlation between the HR-HPV viral load and different cervical lesion degrees, and the value of HR-HPV viral load in the early diagnosis and prediction of cervical lesions. The results suggest that cervical lesions are closely related to HR-HPV infection. Higher HR-HPV viral load in cervical lesions was associated with a higher risk of high-grade cervical lesions. Nevertheless, the HR-HPV DNA load could be used for triage [15].

In this population, the rate of HPV positivity among the screened women was 13.5%, which is a little lower than the national rate in China [22]. The patients with CIN III and CC were older than those with normal results, CIN I, and CIN II, which is consistent with the literature, i.e., that age is a risk factor for advanced cervical lesions [1, 4, 9, 20].

Since the integration of the HPV DNA into the host cells is necessary for malignant transformation by the E6 and E7 proteins, the HBV DNA load has been suggested to be used as a marker of the risk of dysplasia and CC [17, 23]. In addition, the quantification of the DNA load could have a direct relationship with the risk of cervical lesions [24–26]. Many HPV infections will not lead to cervical lesions since a persistent infection is necessary for malignant transformation, and many infections are self-resolving [27]. Therefore, high viral loads should suggest persistent infections, and high viral loads indicate a lower possibility of self-resolution [28]. Hildesheim et al. [29] showed that a viral load threshold of 10 pg/mL indicated persisting HPV infection. Nevertheless, this association is still controversial [21, 30]. Lorincz et al. [21] reported that there was no association between the viral load of 13 HR-HPVs and the risk of CIN III and CC, while Wu et al. [24] showed that the HPV-18 viral load was low in precancerous lesions but high in CC. On the other hand, the present study supports the hypothesis that high HR-HPV viral loads are associated with more advanced cervical lesions. This view is supported by Long et al. [19], who showed that the viral load of HPV-16, HPV-58, and HPV-33 was associated with high-grade cervical lesions, as well as by other studies in various populations [13–19, 31–33]. Berggrund et al. [14] showed that the HR-HPV viral load could indicate the course of the infection, as well as the presence of CIN II, CIN III, and CC. A previous study also showed a correlation between the HC2 viral load and CIN grade [34]. Nevertheless, a study suggested that a single measure of HOV viral load could not reliably indicate the presence of CIN [35]. Therefore, future studies could consider performing serial measurements.

This study has limitations. It was performed at a single center, and the sample size was relatively small, mainly because not all patients underwent HC2 analysis. The data that could be analyzed were limited to those available in the medical charts. The exact HPV subtype was not available for many patients, who were simply indicated as positive in their chart. Additional studies are still necessary to refine our understanding of the relationship between HPV DNA load and cervical lesions. Since only HR-HPV-positive patients were included, the frequency of HR-HPV positivity in each pathological group could be analyzed.

Conclusions

In conclusion, the results suggest that cervical lesions are closely related to HR-HPV infection. Higher HR-HPV viral load in cervical lesions was associated with a higher risk of high-grade cervical lesions. Therefore, HR-HPV viral load could be used as a marker of the risk of finding high-grade cervical lesions at biopsy.

List Of Abbreviations

high-risk (HR); cervical cancer (CC); human papillomavirus (HPV) ; cervical intraepithelial neoplasia (CIN); hybridized capture II (HC2); relative light units (RLUs); control values (CO); cervical intraepithelial neoplasia grade 1 (CIN I); cervical intraepithelial neoplasia grade 2 (CIN II); cervical intraepithelial neoplasia grade 3 (CIN III); odds ratio (OR); confidence interval (CI)

Declarations

Ethics approval and consent to participate: This study was approved by the ethics committee of the Second Affiliated Hospital of Kunming Medical University. As a retrospective study, informed consent was exempted.

Consent for publication: Written informed consent to publish this information was obtained from study participants.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions:

YL: Completed the design, case collection, data statistics, and article writing.

CX: case collection, data statistics, article writing.

JP: case collection, article writing.

CS: case collection, data statistics.

HZ: case collection, data statistics, fund support, completed the design.

All authors have read and approved the manuscript

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