The Prognostic Value of High-risk Human Papillomavirus Infection Status in Surgically Treated Stage IB1-IIA2 Cervical Squamous Cell Carcinoma

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Research

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Abstract

Background: High-risk HPV(hr-HPV) infection is important for the development of invasive cervical cancer. As a developing country with the largest population in the world, China has a great burden of cervical cancer. The cervical cancer screening strategies consisted of cytology and virology, which has been studied by HPV-typing test and HPV-DNA quantitative test since decades ago. The cervical cancer incidence rate has been declined due to the early treatment of precancerous lesions, but postoperative HPV infection is still an issue for cervical cancer patients. This study aims to investigate the association between HPV infection status and recurrence of early-stage cervical cancer through a novel PCR-based HPV test, which could do both HPV typing-test and DNA quantitative-test.

Methods: Patients diagnosed with cervical cancer staged IB1- IIA2, who were treated by radical hysterectomy and lymphadenectomy at Cancer Hospital Chinese Academy of Medical Sciences(CAMS) between January 2014 and December 2016 were accrued. The clinicopathological factors, pre- and post-operative HPV infection status, and the prognosis were investigated. Cox regression was used to identify factors associated with LRFS, MFS and OS.

Results: A total of 312 patients were enrolled in this study, who were treated by radical resection and accepted pre- and post-operative HPV tests, with a median follow-up time of 60 months(range 14~79 months). The 5-year LRFS rate, MFS rate, and OS rate were 97.8%, 98.4%, and 98.7%. The pre-operative HPV infection rate was 85.3%(266/312), 74 patients had a high level of HPV-DNA(>$5x10^6$ copy number/10^4 cells). Twenty-nine patients had a postoperative persistent high level of HPV-DNA(9.3%). Postoperative persistent high level of HPV-DNA within 12 months(p=0.013), postoperative persistence of HPV-16/18 within 24 months(p=0.004), and deep stromal invasion(>2/3)(p=0.007) were associated with a poor LRFS.

Conclusion: Pre-operative HPV-16/18 infection and high level of HPV-DNA were not associated with local recurrence of cervical cancer. Most initial HPV-positive patients had HPV cleared within 24 months postoperatively. Postoperative HPV-16/18 persistence within 24 months, postoperative persistence of high HPV-DNA level within 24 months, and deep stromal invasion(>2/3) were independent risk factors for local recurrence of cervical cancer.

1. Background

Cervical cancer is the fourth most common cancer for women. In 2018, 570,000 new cases and 311,000 deaths were estimated worldwide, including 106,000 cases and 48,000 deaths in China. China contributed 18.6% of the new cases and 15.4% of the deaths of the global cervical burden[1]. The cervical cancer screening strategies were based on the HPV test and the Papanicolaou (Pap) test[2]. Most patients with stage IA1-IIA2 cervical cancer were treated by surgery. Patients with pathological risk factors will receive adjuvant radio(chemo)therapy.

Persistent high-risk human papillomavirus(HR-HPV) infection of the low genital tract is an independent risk factor for the development of cervical intraepithelial neoplasms(CIN) and invasive cervical cancer[3, 4]. Currently, most of the HPV tests were based on hybrid capture 2 (HC2) or real-time polymerase chain reaction(RT-PCR) [5]. Among the marketed HPV tests, the Cobas® HPV Test was based on the RT-PCR technique[6]. However, HPV viral load also had an impact on the prognosis of cervical cancer patients[7–11]. Though many previous studies try to clarify the influence of HVP viral load, conclusions about the prognostic value of HPV viral load remained controversial for years[7, 12, 13].

The HPV qRT-PCR Kit(Liferiver, Shanghai, China), which covered 15 types of hr-HPV(16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 and 82), could do both typing and quantifying tests to confirm the HPV-DNA level of each type. In order to discover the relationship between HPV infection status and the prognosis of cervical cancer treated by radical surgery through this HPV test, we conduct a retrospective study by reviewing the data of stage IB1-IIA2 cervical cancer patients treated by radical hysterectomy.

2. Methods

2.1 Patients characteristics

Patients diagnosed with stage IB1-IIA2(FIGO stage, 2014) cervical cancer and treated at the Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) from January 2014 to December 2016, were eligible for this study. The eligibility criteria included the following: (1)patients treated by radical hysterectomy with pelvic ± para-aortic lymphadenectomy; (2)accepted pre- and post-operative HPV tests by HPV qRT-PCR Kit(Liferiver, Shanghai, China); (3)squamous cell carcinoma. The exclusion criteria: (1) Initial treated by neo-adjuvant radio(chemo)therapy; (2) only accepted other HPV tests.

2.2 Treatment

All Patients were treated by radical hysterectomy(RH) and pelvic ± para-aortic lymphadenectomy, including laparotomy and laparoscopy. Ipsilateral ovary or bilateral ovaries was preserved for patients younger than 45 years old. Patients with LVSI, positive surgical margin, stromal invasion (> 2/3), or lymph node metastasis received adjuvant radiotherapy or concurrent radio(chemo)therapy(CCRT). The total dosage of radiotherapy was 45 ~ 50Gy. Cisplatin(40 mg/m2) was administered per week during CCRT. The volume of external beam radiotherapy(EBRT) covered the region of previous gross disease, the parametrial space, uterosacral ligaments, the proximal 3 cm of the vagina, and all pelvic nodal volumes at risk.

2.3 Follow-up

The follow-up time was the duration from the date of surgical operation to the end of June 30th, 2020, or the date of death. Local recurrence-free survival(LRFS) was defined as the time duration between the date of surgical operation and the detection of recurrent disease within the pelvis. Metastasis free survival(MFS) was defined as the time duration between the date of surgical operation and the detection

of distant metastasis. Overall survival(OS) was defined as the time duration between the surgical operation and death.

2.4 HPV status

2.4.1 HPV DNA testing

All patients accepted the HPV-DNA test within one month pre-operatively and at multiple time points during the follow-up period postoperatively. ThinPrep cytology specimens were tested by HPV qRT-PCR Kit (Liferiver, Shanghai, China), which detects viral DNA by nucleic acid hybridization with a pooled probe set for 15 high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 and 82). The nucleic acid was extracted by an automatic nucleic acid extracting machine(Autrax Bio-system®, Liferiver, Shanghai, China). All PCR reactions were performed by qRT-PCR machine(SLAN-96P Real-time PCR system, Shanghai Hongshi Corp, China) with a detection range of 5×10^2 copies to 5×10^7 copies/10^4 cells. All data collected was based on the official report by the laboratory test center of Cancer Hospital, Chinese Academy of Medical Sciences (CAMS).

2.4.2 HPV infection status

Patients infected by two or more genotypes of HPV were defined as coinfection. HPV-DNA level > 5×10^6 copies/104 cells were defined as high-level (For patients infected by multiple genotypes, any type of HPV-DNA level > 5×10^6 copies/10^4 cells). Pre-operatively, all patients were classified into negative, low-level, and high-level groups. According to the post-operative clearance time, patients were classified into five groups: pre- and post-operative negative group, cleared within 12-month, during 12-24m, after 24 m, and uncleared groups. Based on the time of high HPV-DNA persistence, patients were classified into post-operative persistence within 12 months, 12–24 months, and longer than 24 months groups.

2.5 Statistics

Local recurrence-free survival, metastasis-free survival, overall survival, and follow-up time were continuous variables. Age, tumor size, FIGO stage, histological grade, lymphovascular space invasion(LVSI), lymph nodes metastasis, HPV infection status, HPV-DNA level were categorical variables. The data were analyzed by Statistical Package for the Social Sciences Software for macOS (SPSS Inc., Version 26, Chicago, IL, US). Kaplan-Meier survival curves of different HPV infection status groups were compared by using the log-rank test. Univariate and multivariate analysis of LRFS, MFS, and OS were carried out by using the Cox proportional hazards model. For all statistical tests, p values are 2-sided, and $p < 0.05$ was considered significant.

3. Results

3.1 Characteristics of patients

A total of 1030 cases data were reviewed, while 312 cases were met the inclusion criteria during the period from Jan 2014 to Dec 2016. All 312 patients were treated by radical hysterectomy with lymphadenectomy, while 123 patients(39.4%) with pathological risk factors received post-operative adjuvant radio(chemo)therapy. The median age of the 312 patients was 47(range, 25 ~ 73) years. No patients had parametrial invasion or positive resection margins, which were confirmed by pathologists. The median follow-up time was 60(range 14 ~ 79) months. The characteristics of the patients were shown in Table 1.

Table 1
Characteristics of patients (n = 312)

Characteristic	No. (%)
Age (yr)	
Median (range)/year-old	47(25 ~ 73)
< 50	198(63.5)
≥ 50	114(36.5)
FIGO stage(2014)	
IB1	226(72.4)
IB2	45(14.4)
IIA1	27(8.7)
IIA2	14(4.5)
Histological Grade	
Low	32(10.3)
Moderate	142(45.5)
High	138(44.2)
Tumor size	
< 4 cm	254(81.4)
≥ 4 cm	48(15.4)
Stromal invasion	
< 2/3	284(91)
≥ 2/3	28(9)
LVSI	
No	190(60.9)
Yes	122(39.1)
Lymph node metastasis	
No	279(89.4)
Yes	33(10.6)
Parametrial invasion	0
Positive resection margin	0

Characteristic	No. (%)
Treatment	
RH	189(60.6)
RH + Adjuvant radio(chemo)therapy	123(39.4)
Surgery type	
LRH	197(63.1)
ARH	115(36.9)
Local recurrence	7(2.2)
Distance recurrence	5(1.6)
Death	4(1.3)
Median Follow-up (range)	60(14 ~ 79)
Values are presented as number (%).	
LVSI, lymphovascular space invasion. FIGO, International Federation of Gynecology and Obstetrics. LRH, laparoscopic radical hysterectomy. ARH, abdominal radical hysterectomy.	

3.2 HPV status

3.2.1 Pre-operative HPV analysis

Among the 312 patients, 266 patients were HPV-positive pre-operatively(84.4%, 266/312), including 227 patients infected by HPV-16/18(85.3%, 227/266) and 39 patients infected by other 13 types of hr-HPV(14.7, 39/266). 192 patients were in the low HPV-DNA level group, and 74 patients were in the high HPV-DNA level group(Table 2).

Table 2
HPV infection status (n = 312)

Characteristic	No. (%)
Pre-operative HPV infection status	
Negative	46(14.7)
Single genotype	214(68.6)
Multiple genotypes	52(16.7)
HPV-16/18 positive	227(72.8)
Other hr-HPV	39(14.7)
Pre-operative HPV-DNA level	
Low level[1]	192(61.5)
High level[2]	74(23.7)
Post-operative HPV infection status	
Negative	224(73.1)
Single genotype	61(19.6)
Multiple genotypes	27(8.7)
HPV-16/18 positive	16(6)
Other hr-HPV	72(27.1)
Post-operative HPV clearance status	**N = 266***
Clearance (< 12 m)	209(78.6)
Clearance (12-24m)	21(7.9)
Clearance (> 24 m)	4(1.5)
Uncleared	32(12)
Post-operative HPV-DNA level	
Persistent negative	224(71.8)
Low level[1]	59(18.9)
Persistent High level[2] (< 12 m)	11(3.5)
Persistent High level[2] (12-24m)	8(2.6)
Persistent High level[2] (> 24 m)	10(3.2)

Characteristic	No. (%)
Post-operative HPV-DNA level reduction	227(85.3)
Values are presented as number (%).	
1.Low level, HPV-DNA < 5×10^6 copies/10^4 cells	
2.High level, HPV-DNA > 5×10^6 copies/10^4 cells	

3.2.2 Post-operative HPV analysis

All patients had undergone an HPV test every 3 to 12 months postoperatively. Among the 226 pre-operative HPV-positive patients, 209 patients were HPV-negative within 12 months, 21 patients were HPV-negative during 12–24 months, and four patients were HPV-negative after 24 months, and 32 patients had persistent HPV infection at the end of 24-month. 86.5% of patients had HPV cleared at the end of 24-month postoperatively. Two hundred twenty-four patients were HPV negative(73.1%), 22 patients were infected by HPV-16/18(7%), 62 patients were infected by other types of hr-HPV(19.9%)(Table 2).

According to the post-operative level of HPV-DNA, 59 patients had a low level of HPV-DNA, eleven patients had a persistence high-level within 12 months, eight patients up to 12–24 months, and ten patients had longer than 24 months. Compared with the pre-operative level of HPV-DNA, 227 patients had a reduction of the HPV-DNA level postoperatively (Table 2).

3.3 prognosis

The median follow-up time of the 312 patients was 60 months(range 14 ~ 79 months). Seven patients had local recurrence, and five patients had distant metastasis. The median local recurrence time was 12 months(range 6 ~ 18 months). Three patients died of uncontrolled local recurrence, while one patient died of liver metastasis. The 5-year LRFS rate was 97.8%(305/312), the 5-year MFS rate was 98.4%(307/312) and the 5-year OS rate was 98.7%(308/312). The Kaplan-Meier curves showed that postoperative persistent high level of HPV-DNA within 12 months ($p < 0.001$) and postoperative persistence of HPV-16/18 within 24 months($P < 0.001$) were associated with poor LRFS(Fig. 1.)

The univariate and multivariate analysis were demonstrated in Table 3. On univariate analysis, lymph nodes metastasis($p = 0.015$), postoperative persistent infection of HPV-16/18 < 24 m ($p < 0.001$), and postoperative persistent high level of HPV-DNA < 12 m ($p < 0.001$) or > 24 m ($p = 0.002$) had impact on LRFS. Pre-operative HPV-DNA level and HPV-16/18 infection had no impact on LRFS, MFS, and OS. On multivariate analysis, stromal invasion($p = 0.009$), postoperative persistent high level of HPV-DNA < 12 m ($p = 0.011$) and postoperative persistent infection of HPV-16/18 < 24 m ($p = 0.004$) had impact on LRFS. No independent risk factors of MFS or OS were found.

Table 3
Univariate and multivariate analysis of survival

		Univariate analysis(p-value)			Multivariate analysis(p-value)		
	N	**LRFS**	**MFS**	**OS**	**LRFS**	**MFS**	**OS**
Tumor size							
≥ 4 cm vs < 4 cm	254 vs 48	0.426	0.952	0.549	0.809		0.901
LVSI							
Yes vs No	122 vs 190	0.337	0.093	0.655	0.713		0.919
Stromal invasion							
≥ 2/3 vs < 2/3	28 vs 284	0.091	0.658	0.682	0.007*		0.938
Lymph nodes metastasis							
Yes vs No	33 vs 279	0.015*	0.491	0.368	0.599		0.924
FIGO stage(2009)							
IB2-IIA2 vs IB1	86 vs 226	0.374	0.643	0.436			
Surgery type							
LRH vs ARH	197 vs 115	0.275	0.872	0.59			
Pre-operative infection status							
HPV-16/18 vs Negative	227 vs 46	0.986	0.868	0.586			
Other hr-HPV vs Negative	39 vs 46	0.909	0.988	1			
Pre-operative HPV-DNA level							
Low level vs Negative	192 vs 46	0.546	0.823	0.962			
High level vs Negative	74 vs 46	0.401	0.316	0.954			
Post-operative clearance time (Initial HPV positve)	**N = 266**						

		Univariate analysis(p-value)			Multivariate analysis(p-value)	
Cleared (within 12 m) vs Pre- and Post-opearative Negative	209 vs 38	0.225	0.962	0.957		
Cleared (12-24m) vs Pre- and Post-opearative Negative	21 vs 38	0.988	0.959	1		
Cleared (after 24 m) vs Pre- and Post-opearative Negative	4 vs 38	0.994	0.959	1		
Uncleared vs Pre- and Post-opearative Negative	32 vs 38	0.091	1	0.941		
Post-operative HPV-DNA level						
Low level vs Persistent negative	59 vs 224	0.977	0.869	0.988	0.966	0.883
High level (< 12 m) vs Persistent negative	11 vs 224	< 0.001*	0.995	< 0.001*	0.04*	0.962
High level (12-24m) vs Persistent negative	8 vs 224	0.04*	0.059	0.996	0.491	0.979
High level (> 24 m) vs Persistent negative	10 vs 224	0.991	0.994	0.995	0.992	0.981
Post-operative HPV-16/18 infection status						
HPV-16/18 persistence < 24 m vs Negative and other hr-HPV	11 vs 290	< 0.001*	0.781	< 0.001*	0.017*	0.9
HPV-16/18 persistence > 24 m vs Negative and other hr-HPV	11 vs 290	0.991	0.797	0.012*	0.066	0.894
LVSI, lymphovascular space invasion. FIGO, International Federation of Gynecology and Obstetrics. LRH, laparoscopic radical hysterectomy. ARH, abdominal radical hysterectomy.						
LRFS, local recurrence-free survival; MFS, metastasis-free survival; OS, overall survival						

4. Discussion

Currently, about 40 types of HPV had been detected in the lower genital tract of women. The infection of hr-HPV was crucial for carcinogenesis in cervical cancer[4, 10, 14, 15]. Though the association between HPV infection status and the prognosis of early-stage cervical had been studied through HPV tests, the conclusions remained controversial for decades[7, 9, 13, 16, 17]. HC2-based or PCR-based HPV tests were adopted by most studies, but HC2 could only do a typing test, while PCR could do both typing and quantifying tests[18]. In the present study, the HPV test was based on qRT-PCR, which confirmed that 85.3% of patients were HPV-positive(266/312). Among the pre-operative HPV-positive patients, 85.3% of them were HPV-16/18 positive, which was concordance with other studies(70%-90%)[13, 15, 19–21].

The prognosis of early-stage cervical cancer was majorly dominated by the pathological risk factors, including lymph nodes metastasis, positive resection margin, tumor size, parametrial invasion, deep stromal invasion, and LVSI[22]. Early-stage patients had a better prognosis than advanced-stage patients(IIB-IV[23–25]. However, some patients without pathological risk factors could have recurrent disease occasionally. Thus, some studies focused on the HPV infection status and viral load, but the conclusions of the association between pre-treatment HPV infection status and the prognosis of cervical cancer were controversial. In the present study, the pre-operative HPV-DNA level and HPV-16/18 infection did not show impact on the LRFS, MFS, and OS(Table 3). Similar findings have been reported by Chen et al.[26]. Yong et al. (2008) also found that pre-treatment HPV viral load did not have impact on clinicopathological factors and prognosis[16]. However, Wanram et al. (2009) found that patients with pre-treatment HPV-16 infection and a high viral load would increase the risk of progression of invasive cervical cancer after treatment[17]. Nevertheless, several studies reported contradictive conclusions. Deng et al. (2015) found that pre-treatment low HPV viral load was an independent risk factor for recurrent cervical cancer (HR 2.39, 95%CI 1.11–5.16, p = 0.027)[7]. Joo-Young Kim et al. (2009) adopted a PCR-based typing test and an HC2-based quantifying test of HPV-18. They found that patients with low initial HPV-18 viral load had a poor DFS(HR 2.51, 95%CI 1.39 ~ 4.55, p = 0.002) [9]. These controversial conclusions might be caused by the difference in test methods, treatments, or pathological risk factors.

The conclusions of previous studies about the impact of post-treatment clearance of HPV and persistence on the prognosis of cervical cancer were controversial[12, 27]. In the present study, though 86.3% of initial HPV-positive patients had HPV cleared within 24 months, the LRFS, MFS and OS of different post-operative clearance time groups did not shiw statiscal significance(Table 3), but patients with post-operative persistence of HPV-16/18 within 24 months showed a poor survival(p = 0.017). Yong Jung Song et al. found that 81.4% of patients had HPV clearance within 24 months after CCRT, and the patients with HPV persistence within 24 m had a poor local recurrence-free survival(p = 0.008) [27], but they only enrolled patients treated by CCRT and adopted HC2-based typing test and PCR-based quantifying test. Mahantshetty et al. (2018) found that at the end of 24 months after CCRT, patients with HPV-16/18 persistence had a higher recurrence rate than HPV-16/18-negative patients(p = 0.008) [12]. Many previous studies reported that the post-treatment persistence of HPV-16/18 was associated with prognosis in cervical cancer patients treated by CCRT, few studies had reported the postoperative clearance time of hr-HPV in cervical cancer. Thus, the prognostic value of post-operative hr-HPV clearance time and persistence needs to be studied thoroughly in the future.

Few studies had focused on the post-operative HPV infection status of cervical cancer patients, while controversies about the association between the post-treatment HPV viral load and the prognosis of cervical cancer had emerged. In our study, post-operative persistence of high HPV-DNA level within 12 m was an independent risk factor for local recurrence(p = 0.011). Kahla et al. (2016) also found that high initial HPV-16/18 viral load was associated with a poor DFS(p = 0.04), but not with a poor OS(p = 0.2) [13]. However, Mahantshetty et al(2018) found that both of HPV-16 viral load and HPV-18 viral load do not have impact on DFS(p = 0.65, p = 0.14) or OS(p = 0.93, p = 0.32) [12]. It would be necessary to monitor

the post-treatment HPV status, including HPV viral load, to evaluate the association between HPV viral load and the prognosis of early-stage cervical cancer.

Compared to other studies, we confirmed 15 types of hr-HPV and the viral load of each type by using the HPV qRT-PCR Kit(Liferiver, Shanghai, China). This PCR-based HPV test has high sensitivity and specificity[[28, 29]. Although our study is a retrospective study with selection bias, it had a large sample size, initial HPV infection status, and consistent post-operative HPV infection status during the follow-up time. Besides, the data of the other 13 types of hr-HPV viral load could be used for future studies.

5. Conclusion

In summary, we have shown that the qRT-PCR is able to do both typing and quantifying tests of 15 types of hr-HPV. The result showed that pre-operative HPV infection status was not associated with the prognosis of early-stage cervical cancer. However, post-operative persistence of high HPV DNA level and HPV-16/18 could be a predictive factor of clinical outcome for surgically treated early-stage cervical cancer. Patients with post-operative persistence high HPV DNA level and hr-HPV might be screened strictly to detect the local recurrence earlier, which could be appropriately treated.

Abbreviations

HPV, human papillomavirus. HC2, hybrid capture 2. RT-PCR, real-time polymerase chain reaction. LVSI, lymphovascular space invasion. FIGO, International Federation of Gynecology and Obstetrics. RH, radical hysterectomy. LRH, laparoscopic radical hysterectomy. ARH, abdominal radical hysterectomy. CCRT, concurrent radio(chemo)therapy. LRFS, local recurrence-free survival. MFS, metastasis-free survival. OS, overall survival.

Declarations

Ethics approval and consent to participate

This secondary analysis of de-identified data was determined not to be human subjects research by National Cancer Center/Cancer Hospital's research determination committee and thus was exempt from ethics committee review.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed 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

Zeng Jia led content development, wrote the main manuscript text, statistical analysis, prepared figures 1 and Table 1-3. Wu LingYing provided conceptual input and edited article drafts. All authors edited and approved the manuscript.

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Figures

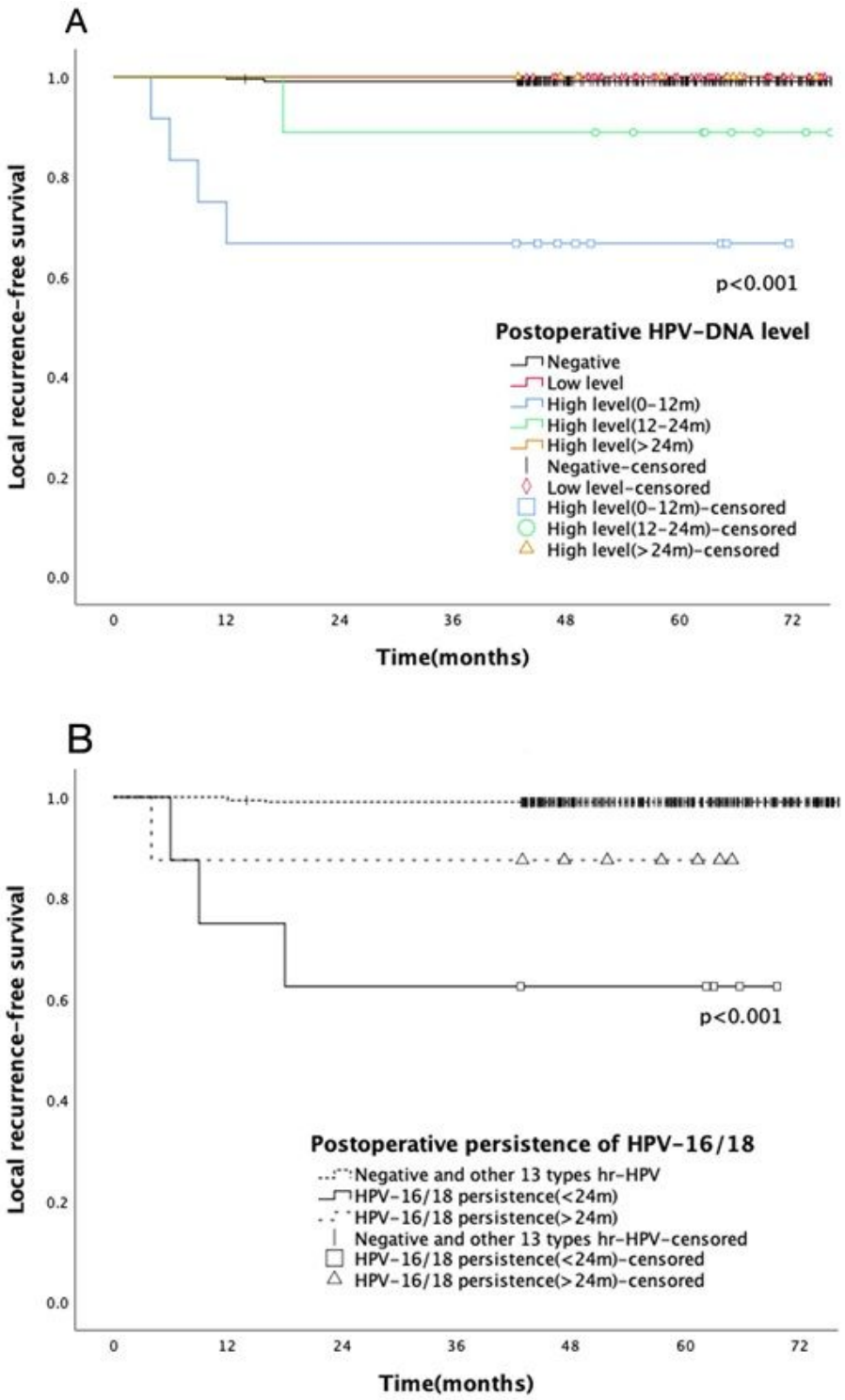
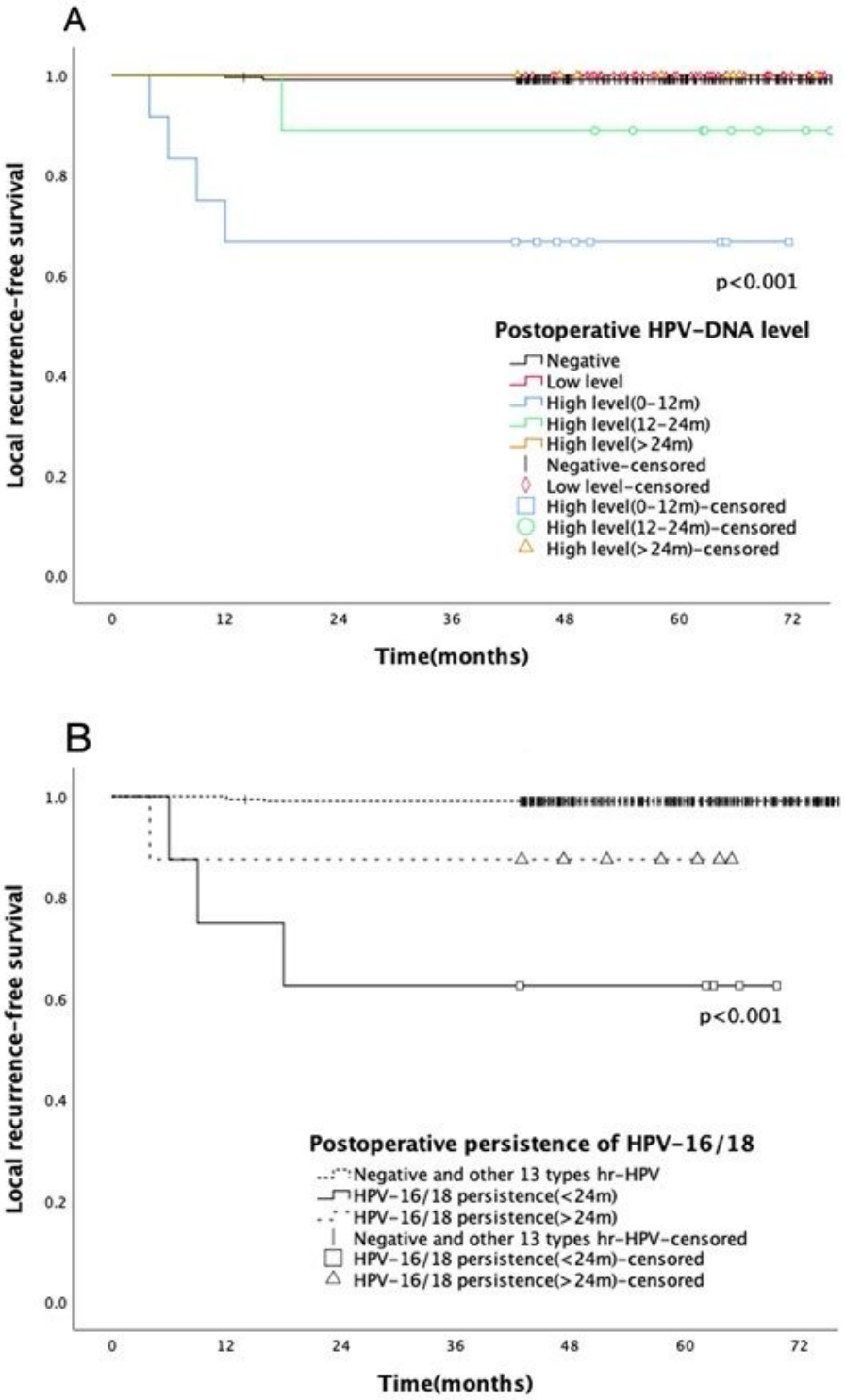


Figure 1

(A) Local recurrence-free survival according to the postoperative HPV-DNA level (B) Local recurrence-free survival according to postoperative persistence of HPV-16/18.



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