



Impact of Human Papillomavirus on Survival, Inflammation, and Immune Function in Patients with Cervical Cancer Undergoing Surgery

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Abstract



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Keywords

- ▶ HPV-16
- ▶ HPV-18
- ▶ cervical cancer
- ▶ survival
- ▶ inflammation
- ▶ immunity

No studies have examined the impact of human papillomavirus (HPV)-16 and HPV-18 on survival, inflammation biomarkers, and immune function in early-stage cervical cancer patients undergoing surgery. Patients diagnosed with early-stage cervical cancer were screened for high-risk HPV prior to surgery. The influence of HPV infection on survival, inflammatory markers, and immune function was investigated. Findings revealed that patients in the HPV-18 positive subgroup exhibited poorer disease-free survival (DFS) and elevated levels of interleukin-6 and C-reactive protein, along with decreased CD4+ T cells compared to patients who tested negative for HPV-18. Notably, early-stage cervical cancer patients with HPV-18 infection experienced worse DFS, heightened inflammatory markers, and compromised immune function.

Introduction

Cervical cancer is the second leading cause of cancer-related death for women worldwide,¹ diagnosed with the average age of 50.² Today, it is well studied that human papillomavirus (HPV) has a vital role in the cervical cancer carcinogenesis.³ HPV infection accounts for 95% of cervical cancer in females in the world,³ especially for women with weak immune system. High-risk HPVs include types 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 70.⁴ Among various HPV types, two common high-risk genotypes, HPV-

16 and HPV-18, cause 70% of cervical cancers and precancerous lesions according to the World Health Organization.⁴ Although the role of HPV infection as a trigger of carcinogenesis is well established, its function during the cervical cancer development and prognosis is still controversy. A nationwide population-based cohort study recruiting 4,254 confirmed cervical cancer cases from Sweden proved that patients with high risks HPV infections had a better prognosis compared with patients without high-risk HPV infections.⁵ However, the limitation of this study is that no survival databased on the various genotypes was researched.

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An Indian study of 150 cervical cancer patients treated with radiotherapy and/or chemotherapy proved that HPV-16 and HPV-18 infection was associated with early relapse.⁶ Patients with persistent HPV-16 and HPV-18 infection had a higher overall relapse compared with patients with HPV clearance by 9 months (49 vs. 28%, $p = 0.024$). Studies did not reach consistency regarding the effect of HPV infection on survival in cervical cancer patients. A study of 171 patients with cervical adenocarcinomas suggested that patients with HPV 45 other than HPV-16 or HPV-18 had a worse 5-year survival rate (HPV-45 = 57%, HPV-16 = 87%, HPV-18 = 81%).⁷ Thus, more clinical studies are needed to confirm the prognostic value of HPV-16 and HPV-18 in cervical cancer patients.

It is known that during the cervical cancer progression, many abnormal events such as inflammation and immune function destruction happened. HPV infection is associated with immune deficiency.⁸ Most of the HPV infections could be cleared by immune system when patients have normal immune function. However, for those with immune deficiency, they are more likely to develop into persistent infection of HPV and thus lead to invasive cervical cancer.⁸ Inflammation is the central pathogenesis of host immune defense against many pathogens.⁹ Previous studies have suggested the association of HPV infection and chronic inflammation.¹⁰ Inflammation plays a vital role in immunosurveillance.¹¹ HPV infection may lead to patients' increased inflammation levels and thus escape of immunosurveillance. However, no study investigated details of impact of HPV on survival, its effect on inflammation biomarkers including C-reactive protein (CRP), interleukin-6 (IL-6), and immune

functions including CD3⁺ T cells, CD4⁺ T cells, and CD8⁺ T cells in cervical cancer patients undergoing surgery.

In this study, we investigated the impact of HPV-16 and HPV-18 on survival, inflammation biomarkers like CRP and interleukin-6 (IL-6) and immune function including CD3⁺ T cells, CD4⁺ T cells, and CD8⁺ T cells in early-stage cervical cancer patients undergoing surgery.

Patients and Method

Patients

We screened 229 patients during the study period, in which 139 patients with early-stage cervical cancer aged between 49 and 73 years old were retrospectively recruited in this study, who were diagnosed between January 1, 2018, and September 15, 2019. Cervical cancer patients with pathology diagnosis were included. The study was approved by the Ethics Committee of our hospital (No. 2018920121). All patients signed the written informed consent. We recorded patients' baseline clinical data, including age and histologic type, the International Federation of Gynecology and Obstetrics (FIGO) stage 2018, tumor size, and lymph node metastasis (→Table 1). FIGO stage I and II are defined as early-stage cervical cancer.

HPV Test

A sample of cervical cells is taken from the cervical area with the help of swab when patients did a pelvic exam to screen for the high risks HPV before surgery. The cervical cells sample is then placed into a bottle containing a special liquid preservative. The same sample of cells can be used for the

Table 1 Patients' baseline characteristics

Characteristics	HPV-18+	HPV-18-
Number of patients	15	124
Age mean, year (range)	60 (49–73)	59 (49–73)
Histologic type, <i>n</i> (%)		
Squamous	13 (87%)	86 (69%)
Adenocarcinoma	2 (13%)	24 (19%)
Adenosquamous	0	11 (9%)
Other	0	3 (2%)
FIGO stage		
I	10 (67%)	81 (65%)
II	5 (33%)	43 (35%)
Tumor size (cm)		
<2	10 (67%)	76 (61%)
2–4	3 (20%)	26 (21%)
>4	2 (13%)	22 (18%)
Lymph node metastasis		
Yes	4 (27%)	23 (19%)
No	11 (73%)	101 (81%)

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; HPV-18, human papillomavirus-18.

HPV test. HPV genotypes was performed by the HPV GenoArray test kit (Guangdong HybriBio Biotech Co Ltd.), which could detect 21 HPV genotypes, including HPV-16 and HPV-18. We tested HPV genotypes according to the manufacturer's protocol.¹²

Treatment and Survival Analysis

All patients received surgery for cervical cancer. Patients' surgery methods were simple hysterectomy and radical hysterectomy including retroperitoneal lymphadenectomy. Surveillance after treatment included visits every 3 months for the first 2 years, every 6 months between years 3 and 5, and annual visit after 5 years. Patients' disease-free survival (DFS) was recorded. It is defined as the length of time after surgery that the patient survives without any signs or symptoms of that cancer. The sites of relapse are vaginal vault, bladder, and rectum. Treatment of recurrent cervical cancer includes chemotherapy, radiation therapy, targeted therapy, immunotherapy, and surgery.

Inflammation and Immune Function Analysis

All the blood samples were collected into the standard tubes in the same room at room temperature before surgery. Inflammatory markers including CRP, IL-6 and immune function parameters including CD3⁺ T cells, CD4⁺ T cells, and CD8⁺ T cells were measured following standard laboratory procedures at the Department of Clinical Chemistry, affiliated hospital of Hebei university of engineering.

Statistical Analysis

Patient inflammatory markers including CRP, IL-6 and immune function parameters including CD3⁺ T cells, CD4⁺ T cells and CD8⁺ T cells analyses were compared using Mann-Whitney U test for categorical variables and Fisher's exact test and continuous variables. Statistical significance was defined as *p*-value less than or equal to 0.05. DFS was displayed with Kaplan–Meier curves and compared through log-rank tests between HPV-16-positive and -negative subgroups and also HPV-18-positive and -negative subgroups. Median survival times and corresponding 95% confidence intervals (CIs) were computed. Univariate Cox proportional hazards models were used to calculate the hazard ratios (HRs) and corresponding 95% CIs. All statistical analysis was performed using SPSS, version 16.0 (IBM Corporation, Armonk, New York, United States).

Results

Baseline Characteristics

Fifteen out of 139 (10.8%) patients were tested HPV-18 positive. Sixty out of 139 (43.2%) patients were tested HPV-16 positive. Patients age, histologic type, FIGO stage, baseline tumor size, and lymph nodes metastatic in HPV-18-positive and -negative subgroups were summarized in [Table 1](#). The mean age in HPV-18-positive group was 60 versus 59 years in the HPV-18-negative group. The differences of histologic type, FIGO stage, baseline tumor size, and

lymph nodes metastatic between HPV-18-positive and -negative subgroups were not significant. Eight patients had human immunodeficiency infection.

Impact of HPV-18 on DFS

Patients in the HPV-18-positive subgroup had worse DFS compared with patients in the HPV-18-negative subgroup ([Fig. 1](#)) HPV-18 positive vs. HPV-18 negative: 40.1 vs. 50.6 months, HR: 3.768, 95% CI: 1.669–8.504, Log rank *p* = 0.001).

Impact of HPV-16 on DFS

The DFS difference of HPV-16-positive and HPV-16-negative subgroup was not significant ([Fig. 2](#), HPV-16 positive vs. HPV-16 negative: 47.9 vs. 49.0 months, HR: 1.278, 95% CI: 0.675–2.419, Log rank *p* = 0.452).

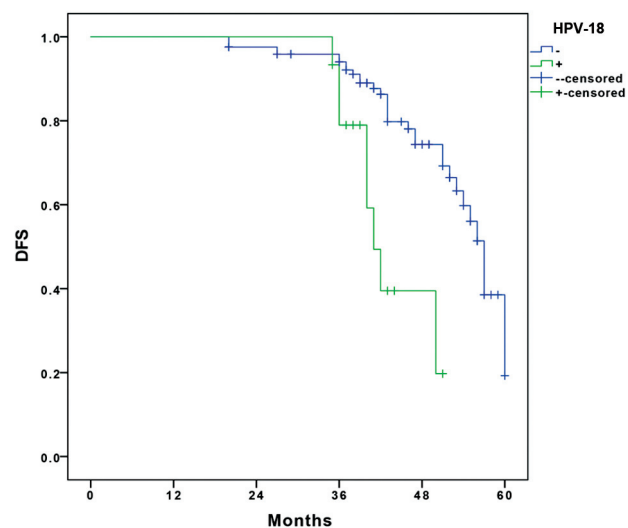


Fig. 1 Kaplan–Meier curve of prognostic relevance of human papillomavirus-18 (HPV-18) infection on disease-free survival (DFS).

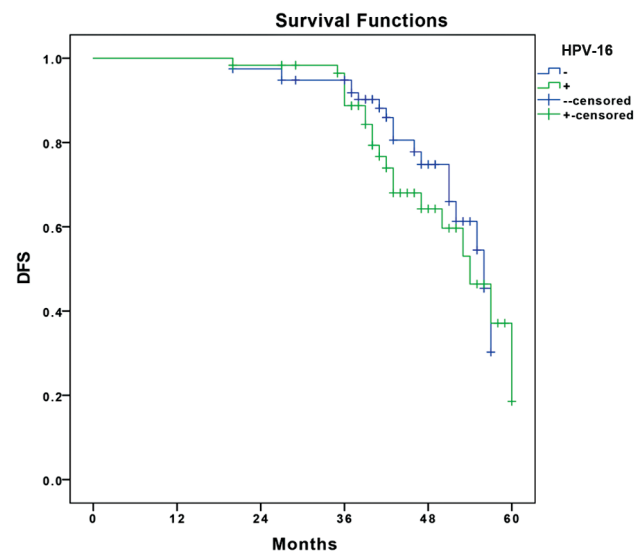


Fig. 2 Kaplan–Meier curve of prognostic relevance of human papillomavirus-16 (HPV-16) infection on disease-free survival (DFS).

Impact of HPV-18 on Inflammatory Markers

Patients in the HPV 18 positive subgroup had higher level of IL-6 compared with patients in the HPV-18-negative subgroup (HPV-18 positive: 23.6 ± 1.684 pg/mL, $n = 15$ vs. HPV-18 negative: 10.89 ± 0.474 pg/mL, $n = 124$, $p < 0.001$, **Fig. 3A**). Patients in the HPV-18-positive subgroup had higher level of CRP compared with patients in the HPV-18-negative subgroup (HPV-18 positive: 9.667 ± 0.3473 mg/L, $n = 15$ vs. HPV-18 negative: 7.073 ± 0.3863 mg/L, $n = 124$, $p = 0.0221$, **Fig. 3B**).

Impact of HPV-18 on Immune Function

Patients in the HPV-18-positive subgroup had lower level of CD4⁺ T cells compared with patients in the HPV-18-negative subgroup (HPV-18 positive: $17.13 \pm 2.102\%$, $n = 15$, HPV-18 negative: $27.94 \pm 0.6797\%$, $n = 124$, $p < 0.001$, **Fig. 4B**). The impact of HPV-18 on CD3⁺ T cells did not reach statistical difference between two subgroups (HPV-18 positive: $71.02 \pm 0.3847\%$, $n = 15$ vs. HPV-18 negative: $70.97 \pm 0.2162\%$, $n = 124$, $p = 0.9428$, **Fig. 4A**). The impact of HPV-18 on CD8⁺ T cells did not reach statistical difference between two subgroups (HPV-18 positive: $31.62 \pm 1.051\%$, $n = 15$ vs. HPV-18 negative: $30.67 \pm 0.8827\%$, $n = 124$, $p = 0.7114$, **Fig. 4C**).

Discussion

Our study found that early-stage cervical cancer patients undergoing surgery with HPV-18-positive had worse DFS

compared with HPV-18-negative patients. Patients with HPV-18-positive had higher inflammatory levels, for example, higher IL-6 and CRP and also lower immune functions, for example, lower CD4⁺ T cells compared with HPV-18-negative patients. The HPV-16 status had no impact on DFS for cervical cancer patients.

Previous studies indicated that both HPV-16 and HPV-18 were prognostic parameter for cervical cancer patients. A Chinese study recruiting 306 stage I-IV cervical cancer patients indicated that HPV-16 was the most common genotype, with prevalence of 60.8%. In this study, patients with HPV-16 infection had better overall survival (OS) (HR: 0.36, 95% CI = 0.18–0.74, $p = 0.005$).¹³ A Korean study of 116 stage I-IV cervical cancer patients indicated also that patients with HPV-16 positive had better OS compared with HPV-16-negative patients (HR: 0.558, 95% CI = 0.326–0.955, $p = 0.033$).¹⁴ However, studies did not reach consistency. There are also studies indicating that HPV-16 status did not have a prognostic relevance,^{15,16} which reached the same conclusion as our study. We focused on early-stage cervical cancer patients and also found that HPV-16 status was not significant for DFS.

Previous studies indicated that HPV-18 positive was associated with worse OS.^{17,18} A study including 291 stage I-IV cervical cancer patients from United States suggested that 58 out of 291 patients (20%) were HPV-18 positive with worse OS (HR: 2.59, 95% CI = 1.08–6.22).¹⁷ A large Chinese cohort study including 24,041 cervical cancer patients also proved that HPV-18-positive patients had worse OS compared with HPV-18-negative patients (HR: 1.704, 95% CI = 1.095–2.654).¹⁸ A Brazilian study

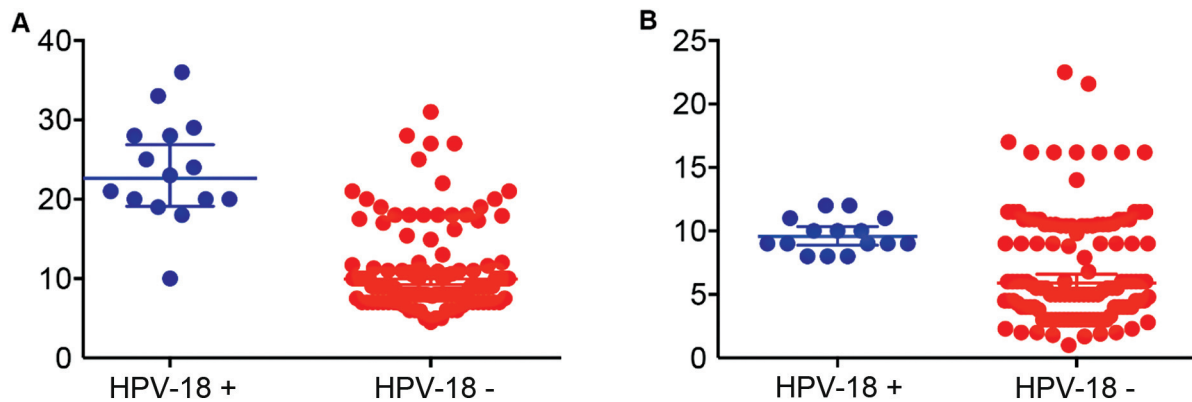


Fig. 3 (A) Impact of human papillomavirus-18 (HPV-18) on interleukin-6, (B) Impact of human papillomavirus-18 on C-reactive protein.

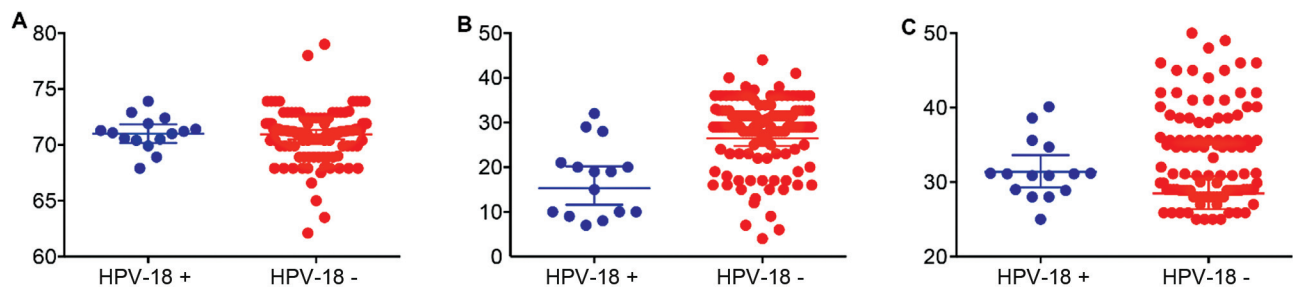


Fig. 4 (A) Impact of human papillomavirus-18 (HPV-18) on CD3⁺ T cells. (B) Impact of HPV-18 on CD4⁺ T cells. (C) Impact of HPV-18 on CD8⁺ T cells.

of 86 stage I cervical cancer patients proved that HPV-18 status was not significant prognostic factor for DFS (HR: 0.797, 95% CI = 0.175–3.640).¹⁵ A population-based clinical of 2,118 stage IA-IIA cervical cancer patients from China proved that HPV-18 was not prognostic for DFS (HR: 1.8, 95% CI = 1.8–2.7).¹⁹ However, our study proved that patients with HPV-18 infection had worse DFS compared with patients without HPV-18 infection. Thus, we investigated mechanisms that associated with the worse DFS of HPV-18 positive patients, evaluating their inflammatory biomarkers including IL-6, CRP, and immune functions including CD3⁺ T cells, CD4⁺ T cells, and CD8⁺ T cells.

Inflammation could contribute to the pathogenesis of many cancer types.^{20,21} Proinflammatory parameters including IL-6 levels play a vital role in inflammatory microenvironments and were associated with severity of cervical cancer. Patients with cervical intraepithelial neoplasia had higher levels of IL-6 compared with control group.²² It was found that expression of IL-6 in cervical cancer tissues was higher than in adjacent non-tumor tissues.²³ Patients with higher level of IL-6 in cervical cancer tissues was significantly associated with larger tumor size, higher FIGO histology, and worse tumor differentiation, indicating that IL-6 was associated with invasion and progression of cervical cancer. IL-6 has the function of inducing the CRP release from liver as part of inflammatory response.²⁴ CRP was an indicator of systematic inflammation. High levels of CRP were also a prognostic factor in patients with locally advanced cervical cancer.²⁵ Cervical cancer patients with higher pre-radiotherapy CRP had worse OS than those with low CRP levels in both univariate and multivariate cox regression models,²⁵ indicating its function as an independent prognostic factor for OS. In a clinical study of 46 cervical cancer patients, CRP level was positively associated with recurrent disease, FIGO stage, patients' age, and lymphovascular invasion. Patients with CRP higher than 5 mg/L had worse 5-year OS rate compared with patients with CRP lower than 5 mg/L (46.9 vs. 100%).²⁶ Our study suggested that early-stage cervical cancer patients with HPV-18 infection had higher levels of IL-6 and CRP, indicating that HPV-18 might promote the carcinogenesis through regulating the inflammatory microenvironment. Patients with increased levels of inflammatory markers pre-surgery tend to have higher levels of inflammatory markers post-surgery. For all patients, they tend to have decreased 19 to 33% fall of IL-6 and CRP levels 1 week after surgery. Patients' increased IL-6 level is correlated with worse DFS, but it is not correlated with OS. Patient's inflammatory levels reflect their reaction to the pathogens and toxicity and dead cells of our immune system. Patients who lacked CD8⁺ T cells had the tendency of worse progression free survival ($p = 0.053$).²⁷ Patients with higher levels of CD4⁺ T cells had better OS (HR = 0.71, 95% CI: 0.57–0.89, $p = 0.003$).²⁸ These indicate that the immunomodulation in cervical cancer has the predictive effect. CD4⁺ T cells are important to help patients maintain antiviral immunity. Cervical cancer patients have higher CD4⁺ T cells levels in their tumor tissues, suggesting its function of anti-cancer immune function.²⁹ Our study indicated that patients with HPV-18 infection had lower level of CD4⁺ T cells, which could be the potential mechanism of its shorter disease progression survival (DFS).

Our study suggested that HPV-18 infections were associated with decreased immune function and higher inflammatory levels. However, we must admit that our study has also limitations. We did not recruit a large number of patients, which means our results still need to be validated in a large clinical trial. Patients HPV-infection can be eliminated during the disease process after treatment. We took only the baseline HPV status rather than the longitudinal analysis of HPV during follow-up. More prospective studies are needed to investigate the HPV infection from baseline until disease progression to further research the clinical prognosis of persistent HPV infection.

Conclusion

Our study suggested that early-stage cervical cancer patients with HPV-18 infection had worse DFS, higher inflammatory levels, and decreased immune function.

Availability of Data and Material

Data are available from the corresponding author on reasonable request.

Ethics

The study was approved by the Ethics Committee of our hospital (No. 2018920121). All patients signed the written informed consent.

Funding Information

None.

Conflict of Interest

None declared.

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