Section: Pathology

Original Research Article

DETECTION OF HPV 16 DNA AS A PROGNOSTICATOR IN PATIENTS WITH CERVICAL INTRAEPITHELIAL NEOPLASIA

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ABSTRACT

Background: Cervical cancer is a major global health problem and HPV types 16 and 18 are the main causes of Cervical Intraepithelial Neoplasia (CIN), a precursor of invasive cervical cancer. This study aimed to determine if it was possible to use plasma samples for the detection of HPV 16 DNA as a non-invasive biomarker for assessing disease severity and progression in women with histologically confirmed CIN. **Materials and Methods:** This was a cross-sectional observational study from 2020 to 2022 enrolling 50 women with CIN I, II, and III. HPV nucleic acid was extracted from plasma samples and HPV 16 was detected by real-time PCR. Data on demographic factors, menstrual status, socioeconomic class, and age at first sexual activity were collected to examine their association with HPV 16 positivity. **Result:** The detection rates of HPV 16 DNA were increased with CIN grade. 37.5%, 42.3% and 81.2% of CIN I, II, and III cases were HPV 16 positive, respectively. Rural women exhibited higher HPV 16 positivity (34.4%) compared to urban women (9.5%). Postmenopausal women showed higher rates of HPV 16 DNA positivity (56%). **Conclusion:** Plasma-based HPV 16 DNA detection is a reliable, non-invasive biomarker for monitoring CIN progression and assessing cervical cancer risk. This method could complement traditional screening of cervical carcinoma by cervical cytology. This is evident from our study that effective vaccination can be considered in the reproductive age group women which can reduce the incidence of premalignant and malignant lesions of cervix.

INTRODUCTION

Cervical cancer is the fourth most common cancer in women worldwide with around 660 000 new cases and around 350 000 deaths in 2022. Low and middle-income countries will bear a disproportionately high burden of the disease, with reporting of 85-90% of cases.[1] The second most common type of cancer in Indian women is Cervical cancer which contributes 15.2% of the deaths worldwide and each year taking an estimated 120,000 new cases annually.[2] The pathway of cervical cancer pathogenesis is well known to involve a premalignant sequence of high-risk human papillomavirus (hrHPV) infection, Cervical Intraepithelial Neoplasia (CIN), and invasive carcinoma.[3] CIN harbors a window of opportunity for early detection and intervention.It is histologically categorized into grades I, II, and III based on the dysplastic changes. Cervical cancer is preventable at this stage and 5-year survival rates for localized lesions are greater than 90%.[4] Human papillomaviruses (HPVs) are small, non-enveloped, double-stranded DNA viruses belonging to the family Papillomaviridae. Over 200 genotypes have been identified, with more than 15 of them found to be high-risk genotypes with strong association with oncogenesis, especially types 16 and 18, which are associated with 70% and more of all cervical cancer cases.[5] HPV16 is the most prevalent genotype worldwide, and HPV 18 ranks second, being of oncogenic potential. The viral DNA integration into the host genome and the subsequent E6 and E7 oncogene overexpression is the hrHPV oncogenic mechanism. Additionally, these viral proteins render

the host tumor suppressors retinoblastoma protein (pRb) and p53 inactive, which results in apoptosis inhibition, genomic instability, and cell cycle dysregulation.[6] Genomic integration is not the only way in which E6 and E7 modulate the pathways of host DNA methylation, in addition to genomic integration they also stimulate host DNA methyltransferases (such as DNMT1) to upregulate the host DNA methylation pathway, which further aids in the malignant transformation.[7] Current screening strategies mainly rely on cervical cytology or HPV DNA testing of cervical samples. The methods are effective, but they have some disadvantages including cytology is not very sensitive, presupposes the personnel, and sample adequacy can be varied. The invasive sample collection lowers the rates of compliance, especially among rural or conservative cultural groups.[8] The interest in alternative, minimally invasive means of detecting and monitoring cervical disease related to HPV has been growing. Liquid biopsy or the examination of circulating biomarkers such as cell-free DNA (cfDNA), circulating tumor DNA (ctDNA), or RNA has revolutionized cancer diagnoses. This approach is becoming a reliable, real-time, noninvasive modality to detect tumor-specific DNA fragments including viral DNA in HPV-associated malignancies.[9] Based on studies, ctDNA might be secreted from HPV-infected cells by active secretion, or shed into the bloodstream via apoptosis or necrosis and hence be detected in the plasma of affected people.[10] There have been several investigations that have shown the feasibility of detecting HPV DNA in the plasma of patients with invasive cervical cancer. For example, a study detected the presence of HPV DNA in both plasma and cervical samples with high concordance between the two sample types.[11] The HPV DNA was also detected in the plasma of patients with low-grade and high-grade dysplasia, which suggests that viral DNAemia may occur at the early stages of neoplastic transformation.[12] While the global interest in liquid biopsy-based screening exists, there are few studies on the role of liquid biopsy in CIN in particular in the Indian population. As India has a high cervical cancer burden, and there are regional disparities in access to Pap testing and HPV vaccination, there is an imperative to explore and validate such novel biomarkers as plasma-based HPV DNA for early diagnosis and disease monitoring.[13] Such biomarkers could complement existing screening programs, from a public health perspective. Additionally, plasma-based detection could be useful in post-treatment surveillance reducing the requirement for repeat cervical sampling and ensuring patient compliance. HPV vaccines (e.g. Cervarix™, Gardasil™) protect against HPV types 16 and 18, and are not universally available in India, as these are not affordable.[14] This study was undertaken to detect high-risk HPV DNA type 16 in the plasma of patients with histologically proven cervical CIN grades I, II, and III, and to evaluate its prognostic significance by correlation of its presence with the severity of the cervical preneoplastic lesions.

MATERIALS AND METHODS

Study Design and Ethical Approval: A two-year cross-sectional observational study was done in the Department of Pathology and Medical Research Unit of Tirunelveli Medical College in the period from 2020 to 2022. After Institutional Ethical Committee approval, samples were collected with informed consent from all participants.

Study Population: In this study, 50 women with histopathologically confirmed CIN (I, II, or III) were enrolled. Only the patients with newly diagnosed CIN were included in this study. To eliminate potential confounding factors and to minimize variation in the diagnosis across the study sample, patients with a prior history of invasive cervical carcinoma or oral carcinoma were excluded.

Data Collection: Demographic data including age, residence (urban/rural), socioeconomic status (Modified Kuppuswamy Scale), parity, menstrual status, and age at first sexual intercourse were recorded. Obstetric and gynecological history, symptoms, cervical cytology findings, and histopathological CIN grading were also documented using a pre-validated structured proforma.[15]

Sample Collection and Preparation: Peripheral venous blood (5 ml) was collected in sterile EDTA vacutainers from histologically confirmed CIN patients. Plasma was separated by centrifugation at 2500 rpm for 10 minutes and stored at −80°C until DNA extraction. Standardized preanalytical conditions for cfDNA stabilization were followed, in line with guidelines for high-risk HPV liquid biopsy studies.[16]

Extraction of Viral DNA from Plasma: Viral nucleic acid extraction from plasma was done using the HELINI PureFast Viral Nucleic Acid Mini Spin Prep Kit which is based on silica membrane spin column system for high-yield, inhibitor-free viral DNA. It also included lysis with Proteinase K, addition of carrier RNAandprecipitation with ethanol. Binding and purification were performed by centrifugation at >12,000×g. With 60µL elution buffer, the elution was performed to obtain the eluted nucleic acid. All steps were carried out at room temperature to obtain DNA for PCR analysis. The eluted Nucleic acid was then stored at -80ºC.

Real-Time PCR Amplification for HPV DNA Detection: Real-time Polymerase Chain Reaction (PCR) amplification of high-risk HPV type was performed using HELINI HPV16 and 18 High-Risk Viruses Real-Time PCR kit. A qualitative detection of HPV 16 DNA was done using TaqMan™ hydrolysis probe chemistry. The probe PCR reactions contained 10 µL of Probe PCR MasterMix, 5 µL of HPV-specific primer probe mix, and 10 µL of purified viral DNA extracted from samples. To increase the coverage area of detection, parallel

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amplification was conducted using a 12 high-risk HPV primer probe mix and internal endogenous control to assess sample integrity. Validation of PCR reactions was performed by performing PCR reactions with proper inclusion of positive and negative controls. Initial activation-related data is mentioned in [Table 1]. The HPV 16 signals were detected on the FAM (6-Carboxyfluorescein) channel and the endogenous control on the HEX (Hexachloro-Fluorescein) channel and were detected as fluorescent signals. Those amplification curves for the respective genotype were considered to be positive andcrossed the threshold before 40 cycles if internal control validation was adequate. This method was comparable to current molecular diagnostic practice for monitoring HPV-associated cervical disease with high specificity and sensitivity for the detection of HPV DNA in plasma.

Table 1: Thermal Cycling Conditions for Real-Time PCR

Step	Temperature	Duration
Initial Activation	95°C	15 minutes
Denaturation (×45cycles)	95°C	20 seconds
Annealing/Data Collection	56°C	20 seconds
Extension	72°C	20 seconds"

Validation with Positive Controls and Visualization
The valid assay was confirmed using validated positive and negative controls in each PCR run. End-point fluorescence analysis was used to confirm the integrity of the sample and concurrent visualization of real-time amplification curves ensured amplification specificity. Only samples with valid internal controls that crossed the threshold cycle (Ct) prior to 40 were interpreted as positive. Color Plates show documented and archived representative amplification plots from HPV-positive plasma samples.

Statistical Analysis: Microsoft Excel (Windows 10, Version 2010) was used to compiledata. The SPSS for Windows, Version 20.0 (SPSS Inc., Chicago, IL) was used to perform statistical analysis. The continuous variables were expressed as mean ± standard deviation and categorical variables were summarized as frequency and percentages. The Chi-square test was used to examine associations between categorical variables such as HPV DNA status, CIN grade, socioeconomic class, or cytological findings. p-value of less than 0.05 were considered statistically significant.

RESULTS

HPV 16 DNA was most commonly detected in the 40-60 age group. 11 cases (55%) were detected in adults aged 40-49 and 8 cases (57%) in 50-59 age group. Noneof the patient below the age of 30 tested positive. Although the trend of increased HPV detection with advancing age did not show statistical significance ($\chi^2 = 1.82$, $p = 0.76$), age alone may not be sufficient to predict whether the plasma sample is positive for HPV DNA. The association of age and HPV16 DNA detection is mentioned in [Table 2]."

Table 2: Association of Age with HPV 16 Detection

Age Group	HPV16 Detected	HPV16 Not Detected
<30	0	1
30-39	3	4
40-49	11	9
50-59	8	6
≥60	5	3

HPV 16 was detected in 34.4% of rural women among 58% of rural participants and 9.5% of urban women among 42% urban participants. The chi-square between HPV 16 detection was statistically significant ($\chi^2 = 6.22$, $p = 0.012$). This higher burden in rural women may probably due to lower access to vaccination, later screening, and sociocultural barriers. [Figure 1] show the disparities in HPV detection between rural and urban areas.

56% of postmenopausal women were positive for HPV 16DNA. Premenopausal women were less likely to detect HPV 16 DNA. This trend may mean that hormonal and immunological changes associated with menopause help viruses persist longer in women. The detected variations were not statistically significant(p=0.69),suggesting that several interacting factors apart from menstrual status alone play a role and these differences are mentioned in [Table 3].

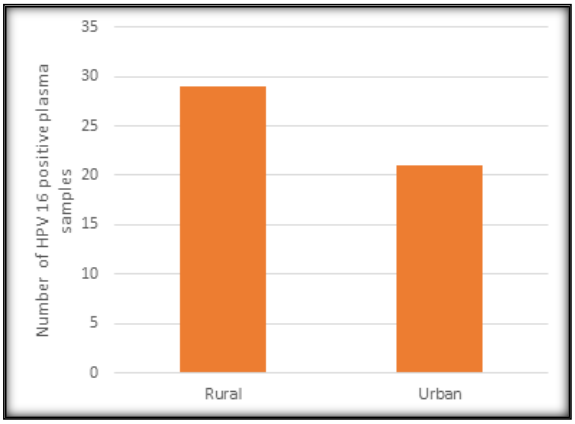

Figure 1: HPV 16 Detection by Residence

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Table 3: Association of Menstrual Status with HPV DNA Detection

Menstrual Status	HPV16 Detected	HPV16 Not Detected
Premenopausal	8	8
Postmenopausal	19	15

The prevalence of HPV 16 DNA was significantly higher among women from lower and lower-middle socioeconomic groups. In the lower socioeconomic group (38% of the study population), 37% were positive for HPV 16. This indicates high susceptibility due to limited health literacy, less screening and inadequate access to preventive services. However, these trends were not statistically significant (p = 0.81) and are mentioned in [Figure 2].

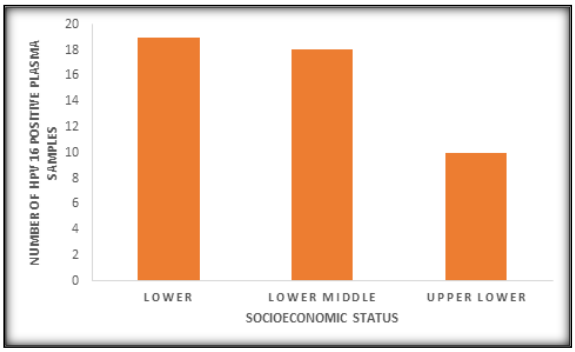

Figure 2: HPV 16 Detection by Socioeconomic Status

It was observed that HPV 16 DNA has been detected in 75% of HSIL casesas shown in Figure 3. Presentations of cervical cytology has been depicted Figure 4.These results emphasized the prognostic value of high-risk HPV detection on cytological lesions. The associations did not reach statistical significance (p = 0.58), although they can help direct surveillance strategies for early cytological changes." All nulliparous women (n = 3) were also positive for HPV 16. Of women who were multiparous and had 1-3 children, 52.5% had HPV 16 DNA. In women with more than 3 children, 42.8% showed HPV 16 positivity. Statistical testing did not show significant relationships, these patterns were consistent with the hormonal changes that accompany parity and a potential etiological role of cervical trauma in HPV persistence (p=0.22). The distribution of HPV 16 detection by parity status is mentioned in [Table 4].

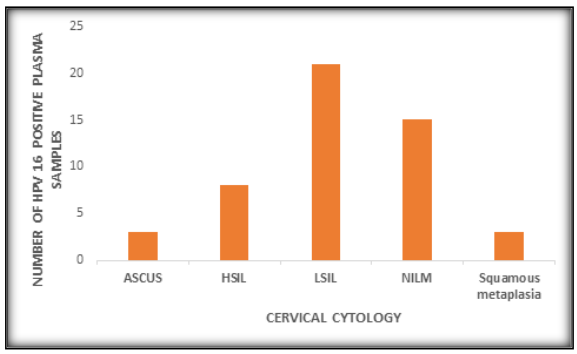

Figure 3: HPV 16 Detection by Cervical Cytology.

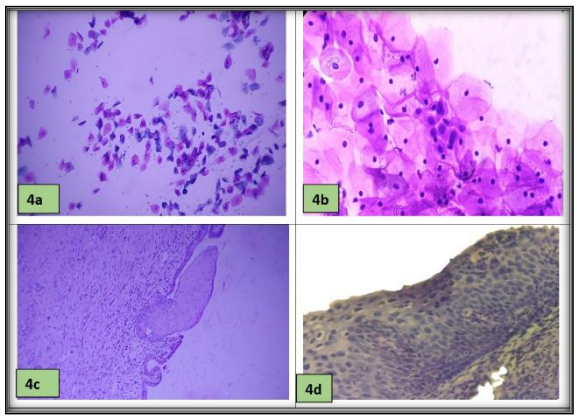

Figure 4: Image illustrations of Normal cervical cytology(4a), HSIL(4b), Histopathology image of endocervix showing squamous metaplasia(4c) and CIN II(4d) exhibiting koilocytocytic changes and dysplasia in upper two third of ectocervical epithelium.

Table 4. Distribution of HPV 16 Detection by Parity Status"

Parity	HPV 16 Detected	HPV 16 Not Detected
Nulliparous	3	0
Multiparous (1–3)	21	19
Multiparous (>3)	3	4
Total	27	23

Women who began sexual activity between 18 and 21 years of age were shown to have a marked predominance of HPV 16 DNA detection, over 85% of all positive cases. Biologically plausible, this trend was due to early sexual debut increases the exposure of the immature cervical transformation zone, a region highly susceptible to high-risk HPV integration. Following these positive findings, the chi-square analysis failed to reveal a statistically significant correlation (p = 0.65), suggesting that, in addition to other variables that influence HPV persistence and progression, age at first sexual contact was a significant risk factor. The age-based distribution of the participant's first sexual activity is illustrated in in [Figure 5].

A statistically significant correlation between plasma detection of high-risk HPV genotypes and CIN grade was found. HPV 16 DNA was found in 37.5% of CIN I, 42.3% of CIN II, and 81.2% of CIN III. Suggesting that HPV DNA may be a circulating biomarker of disease stratification and progression monitoring. These trends were confirmed by the statistical analysis which showed p-values of 0.028. The association of CIN with plasma HPV 16 DNA

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detectionis mentioned in [Table 5]. Histopathology images of CIN II has been shown in [Figure 4].

Table 5: Association of Cervical Intraepithelial Neoplasia Grade with Plasma HPV DNA Detection

CIN Grade	HPV 16 Detected	HPV 16 Not Detected
CIN I	3 (37.5%)	5
CIN II	11 (42.3%)	15
CIN III	13 (81.2%)	3
Total	27	23

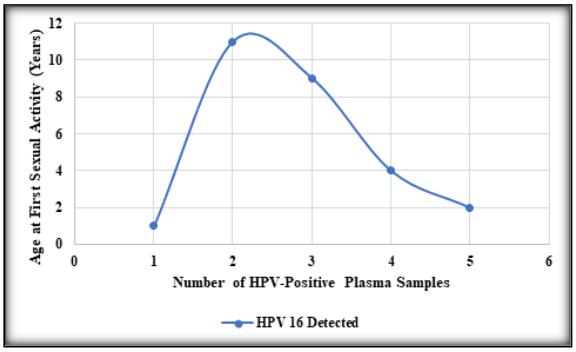

Figure 5: Distribution of HPV 16 detection by Age at First Sexual Activity

Visualization of Amplification Curves and End-Point Fluorescence: Standard positive and negative control template was used to validate the real-time PCR amplification outcomes for every assay run. Amplification curve kinetics and end-point fluorescence analysis verified that circulating DNA could be found in plasma.All samples had internal endogenous controls to ensure template quality and samples were processed on the FAM and HEX channels to detect HPV 16 DNA.

One of the typical plasma samples contained HPV 16 DNA, as shown by the extremely strong exponential amplification curve in the FAM channel, which is shown in [Figure 5A]. Figure 5B depicts the marked amplification curve on the HEX channel and corroborates the detection of HPV 16 DNA as the amplification curve crosses the threshold before 40 cycles, indicating a valid and specific result. The fluorescence image of an HPV 16 positive sample in the FAM channel depicted in Figure 5C illustrates strong intensity indicating the presence of HPV 16 DNA in the sample.

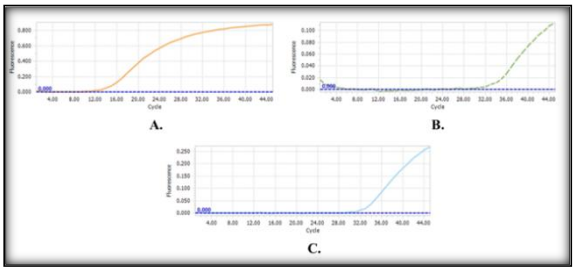

Figure 6: Real-Time PCR Amplification and Fluorescence Detection of HPV 16 DNA in Plasma Samples

The visual results confirmed the reproducible detection of HPV DNA in plasma, the integrity of the PCR procedureand the primer-probe performance. The use of circulating HPV DNA as a molecular biomarker for early diagnosis and prognosis monitoring of CIN was strengthened by such confirmation.

DISCUSSION

High-risk HPVplays a major role in the pathogenesis of cervical intraepithelial neoplasia. This study sought to ascertain whether HPV DNA could be used to identify the severity and course of the disease in plasma samples from women with histologically confirmed CIN grades I, II, and III. Results suggest that HPV DNA detection, may serve as a non-invasive tool to monitor CIN.HPV 16 DNA detection peaked in women aged 50–59 and was highest between 40 and 60 years [Table 2]. Study revealed that age could not serve as a reliable predictor of HPV positivity but scientific studies had previously established age as a contributing risk factor. The host immune response together with viral persistence serve as stronger determinants for detecting HPV DNA in plasma samples than other factors.[17] The participants younger than 30 years showed no HPV positivity, probably due to immunological clearance of HPV in younger women.[18] HPV 16 positivity was higher in rural (34.4%) than urban women (9.5%), likely due to limited access to screening and vaccination. This highlights the need to enhance HPV prevention efforts in underserved areas. Women with regular menstrual cycles were less likely to have HPV DNA (50%) than postmenopausal women (56%), though not statistically significant [Table 3]. Hormonal and immune changes during menopause may influence infection risk. HPV detection was higher in lower socioeconomic groups(Table 2), likely due to limited access to vaccination and screening, underscoring the need for targeted health programs.[19] HPV 16 was also more common in patients with HSIL, suggesting its potential as a biomarker for disease stratification and monitoring [Figure 3]. Nulliparous women showed higher HPV 16 prevalence, while multiparous women had a more even distribution, though not statistically significant [Table 4]. These findings support the idea that childbirth-related trauma and hormonal changes may influence HPV persistence, consistent with prior studies.[20] Women who began sexual activity between 18 and 21 were more likely to have HPV 16 DNA, though not statistically significant; early exposure increases risk in the cervical zone, highlighting the need for education and

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vaccination.[21] HPV 16 prevalence rose with CIN severity, supporting plasma HPV DNA as a non-invasive biomarker for monitoring disease progression and aiding risk stratification, as confirmed in [Table 5]. This method can complement conventional screening for early diagnosis and follow-up, and given India's high cervical cancer burden, its routine use is feasible.

CONCLUSION

This study emphasises that plasma HPV 16 DNA as a non-invasive biomarker for monitoring CIN progression. HPV 16 was detected in 37.5% of CIN I, 42.3% of CIN II, and 81.2% of CIN III cases. Detection was higher in the 40–49 (55%) and 50–59 (57%) age groups, rural women (34.4%) than urban (9.5%), and postmenopausal (56%) than premenopausal women. and these differences may be explained by differential access to healthcare and preventive services. Effective HPV vaccination and Plasma-based HPV DNA detection, complementing conventional screening offers a reliable, simple tool for early diagnosis and monitoringto reduce cervical cancer in India. However more research to be conducted to validate this approach.

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