Original Article

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Oncology Section

Detection of High Risk Human Papilloma Virus in Cervical Tissue, Urine and Plasma of Patients with Squamous Cell Carcinoma of Uterine Cervix Using Real-time Polymerase Chain Reaction: A Cross-sectional Study

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ABSTRACT

Introduction: Human Papillomavirus (HPV) has been detected in approximately 95% of cervical cancer cases, underscoring its role as the primary cause of the disease. Recent studies have demonstrated that HPV detection in urine samples is a highly effective, non invasive method for early cervical cancer screening, particularly among young women.

Aim: To detect High-risk HPV (HR-HPV) in cervical tissue, urine, and plasma samples from patients with Squamous Cell Carcinoma (SCC) of the cervix.

Materials and Methods: The present cross-sectional study was conducted in the Departments of Obstetrics and Gynaecology, Pathology, and Microbiology at Sri Devaraj Urs Medical College, Tamaka, Kolar, Karnataka, India over a period of 18 months from May 2023 to October 2024. The study included 75 newly diagnosed cases of primary SCC of the cervix, confirmed by cervical biopsy. For each case, cervical tissue, urine, and blood samples were collected. Deoxyribonucleic Acid (DNA) extraction was performed using the Truenat instrument, and Real-Time Polymerase Chain Reaction (RT-PCR) was employed to detect various high-risk HPV types. Statistical analysis was carried out using Statistical Packages of Social Sciences (SPSS) version 24.0. Descriptive statistics were used to summarise demographic and clinical variables. Sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) were calculated for different diagnostic tests using the area under the Receiver Operating Characteristic (ROC) curve. Confidence intervals were computed for these diagnostic measures. Optimal cut-off values were determined based on the highest combined sensitivity and specificity using ROC curve analysis. Likelihood ratios were also calculated.

Results: The mean age of study participants were 53.92±10.86 years. Among the 75 cervical cancer cases, high-risk HPV DNA was detected in 58 (77%) of cervical tissue samples, 41 (55%) of urine samples, and 8 (11%) of blood samples. Urine testing, being non invasive, showed a sensitivity of 68.96%, specificity of 94.11%, PPV of 97.56%, and NPV of 47.05%, making it a reliable diagnostic method. Plasma testing, in contrast, demonstrated limited sensitivity (13.79%) despite high specificity and PPV.

Conclusion: The present study highlights the significance of urine-based HR-HPV detection as a non invasive screening method for cervical cancer. It offers a promising avenue for future research, innovation, and development in cervical cancer screening, prevention, early detection, and treatment strategies.

Keywords: Cervical carcinoma, Cervical biopsy, Malignancy

INTRODUCTION

Cervical cancer is the third most common cancer among women globally [1]. In India, however, it ranks as the second most common cancer affecting women [2]. Specifically, in Kolar, cervical cancer accounts for 17.55% of all female cancers [3]. Human Papilloma Virus (HPV) is a primary risk factor, present in approximately 95% of cervical cancer cases [4]. Detection of HPV in urine samples has been reported as one of the most effective methods for early screening of cervical cancer in young women, as it can be collected non invasively [5]. Therefore, urine testing is highly preferred among women and offers the additional advantage of detecting both primary HR-HPV and biomarkers in the same sample. The use of urine samples also provides opportunities to reduce non adherence to screening and loss to follow-up. Moreover, since HPV detection by cervical biopsy or scrap samples can be difficult in certain subgroups, urine testing should be regarded as an acceptable alternative [6,7].

The prognosis of HPV infection depends on the viral strain, whether low-risk or high-risk. Low-risk strains (such as HPV 6 and HPV 11) are associated with a good prognosis and typically cause genital warts, while high-risk strains (such as HPV 16 and HPV 18) have high malignant potential.

In the present study, HR-HPV was detected in cervical tissues, urine samples, and plasma from cases of squamous cell carcinoma (SCC) of the cervix. The diagnostic utility of HPV detection in urine and plasma was assessed by considering detection in cervical tissue as the reference standard. The present study investigates the potential of urine and plasma testing as non invasive screening tools for cervical cancer, aiming to reduce the need for invasive procedures such as cervical biopsy. To the best of knowledge, very few studies in India have examined HR-HPV detection in cervical tissue, urine, and plasma (triple samples) in SCC cases. The objective of present study was to detect HR-HPV in cervical tissue, urine, and plasma in SCC of the cervix, and to determine

the association of HR-HPV in cervical tissue with its detection in urine and plasma.

MATERIALS AND METHODS

The present cross-sectional observational study was conducted in collaboration between the Departments of Pathology, Microbiology, and Obstetrics and Gynaecology (OBG) at Sri Devaraj Urs Medical College, Tamaka, Kolar, Karnataka, India over a period of 18 months from May 2023 to October 2024. The study was approved by the Institutional Ethics Committee (IEC number: DMC/KLR/IEC/5/2023-24) and conducted from May 2023 to October 2024. Patient information sheets were provided to all participants, and informed consent was obtained after explaining the details of the study.

Sample size clculation: Sample size was 75, based on the sensitivity and specificity of HPV detection in urine (87% and 94%, respectively, with cervical samples as the reference), as reported by Van Keer S et al., with an absolute error of 5% and a 95% confidence interval [7].

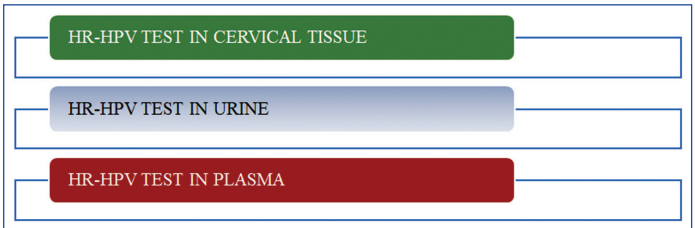
A total of 75 newly diagnosed cases of SCC of the cervix were included and staged according to the International Federation of Obstetrics and Gynaecology 2019 (FIGO) criteria and the 8th American Joint Committee on Cancer (AJCC) 2017 guidelines.

Inclusion and exclusion criteria: All fresh cases of primary SCC of the cervix confirmed by cervical biopsy were included in the study. Exclusion criteria were: post-chemotherapy and post-radiotherapy cases, recurrent cases, secondary metastasis to the cervix, or presence of any other malignancy in the patient.

Study Procedure

Sample Collection and Processing

Patient data such as age, parity, and clinical features were collected through interviews and case file reviews. For each case of cervical carcinoma, three types of samples were collected [Table/Fig-1]:



[Table/Fig-1]: Triple samples collected in SCC cervix cases.

Cervical tissue: Urine samples (first-void sample, or a sample collected after a 2-hour gap from the last urination)

Blood samples {collected in Ethylenediaminetetraacetic Acid (EDTA) vacutainers}: Blood samples were centrifuged at 1500 rpm for 5 minutes to separate plasma, and all samples were stored at -20°C until testing.

The Truenat instrument was used for DNA extraction and analysis, employing real-time PCR with the Truemix™ HPV-HR Genotyping Kit (Molbio Diagnostics). Truemix™ HPV-HR Genotyping (16/18/33/35, 31/39/45, 51/52/56/58, 59/66/68) is a freeze-dried, ready-to-use open-format test based on TaqMan chemistry. The assay targets the L1 and E7 genes and includes an internal control to verify sample collection, extraction, and PCR validity. Real-time detection was enabled using target-specific fluorescent hydrolytic probes.

The test involves two processes in a single tube: PCR amplification of targets and internal control, and simultaneous real-time detection using dual-labelled fluorescent probes. Primers (forward and reverse) and fluorescence detectors (FAM, Cy5, Texas Red, and VIC) were used.

The Truelab workstation, comprising the Trueprep Auto sample processing device and a real-time quantitative micro-PCR analyser, enabled rapid and automated DNA extraction and analysis. HR-HPV subtypes were identified in all three sample types from each patient. Results from urine and plasma were compared with cervical tissue results, with cervical biopsy serving as the gold standard for cervical cancer diagnosis.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS version 24.0 software. Descriptive statistics, including mean, standard deviation, and percentages, were used to summarise demographic and clinical variables. The sensitivity, specificity, PPV and NPV were calculated for the different diagnostic tests using the area under the ROC curve. Confidence intervals were computed for these diagnostic measures. Optimal cut-off values were determined based on the highest combined sensitivity and specificity using ROC curve analysis. The Likelihood Ratio (LR) was also calculated.

RESULTS

The study population exhibited a wide age distribution for cervical cancer diagnosis, ranging from 33 to 87 years, with a mean age of 53.92±10.86 years. The peak incidence occurred in the 50 to 59 years age group, and 29 (72%) of cases were noted in post menopausal women.

HR-HPV analysis: High-risk Human Papillomavirus (HR-HPV) DNA was analysed in cervical tissue, urine, and plasma samples using PCR [Table/Fig-2]. Cervical tissue was used as the reference standard for determining HR-HPV status.

HPV	n (%)	
Cervical tissue		
Positive	58 (77%)	
Negative	17 (23%)	
Urine		
Positive	41 (55%)	
Negative	34 (45%)	
Plasma		
Positive	8 (11%)	
Negative	67 (89%)	
Total	75	100.0

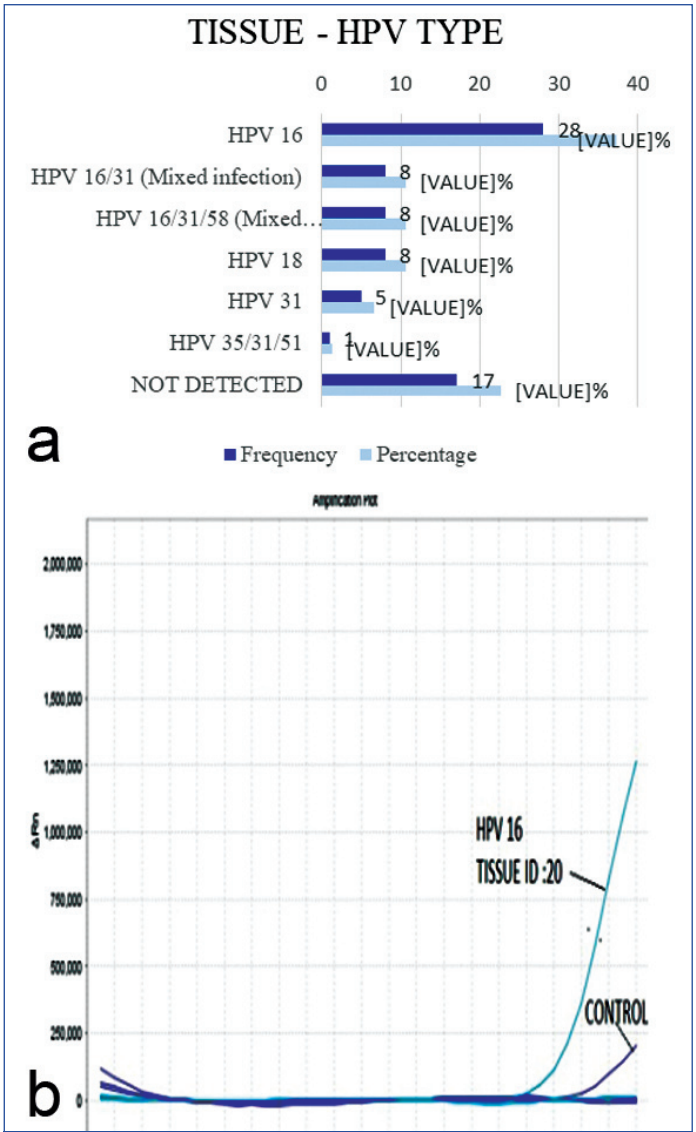
[Table/Fig-2]: HR-HPV proportion detected in cervical tissue, urine and plasma.

In cervical tissue, HR-HPV DNA was detected in 58 (77.33%) samples, with HPV 16 being the most prevalent genotype, while 17 (22.66%) samples tested negative. Urine analysis revealed HPV positivity in 41 (54.66%) cases, primarily HPV 16, with 34 (45.33%) cases testing negative. Plasma samples showed significantly lower HPV detection rates, with only 8 (10.66%) cases testing positive (mostly HPV 16) and 67 (89.33%) cases testing negative.

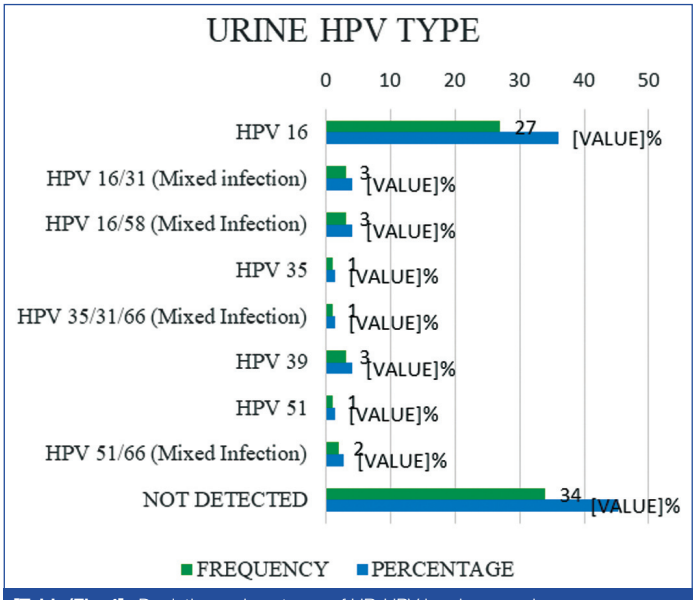
Across all sample types, HPV 16 was the most frequently detected genotype. In cervical tissue, HPV 16 accounted for 37.33% of cases, followed by mixed infections of HPV 16/31/58 (10.66%), HPV 18 (10.66%), and HPV 31 (6.66%) [Table/Fig-3]. In urine samples, HPV 16 was the most prevalent genotype (36.00%), followed by mixed infections (12.00%), HPV 35 (1.33%), HPV 39 (4.00%), and HPV 51 (3.00%) [Table/Fig-4]. Plasma testing showed HPV 16 in 7 (9.33%) of cases, followed by HPV 39 in 1 (1.33%) [Table/Fig-5].

Diagnostic Performance of Urine and Plasma HPV Testing Compared to Cervical Tissue

Comparative analysis of HPV testing in urine and plasma revealed significant differences in diagnostic performance. Urine testing demonstrated a sensitivity of 68.96%, specificity of 94.11%, PPV of 97.56%, and overall diagnostic accuracy of 74.61%. Plasma testing showed a much lower sensitivity (13.79%) despite high specificity



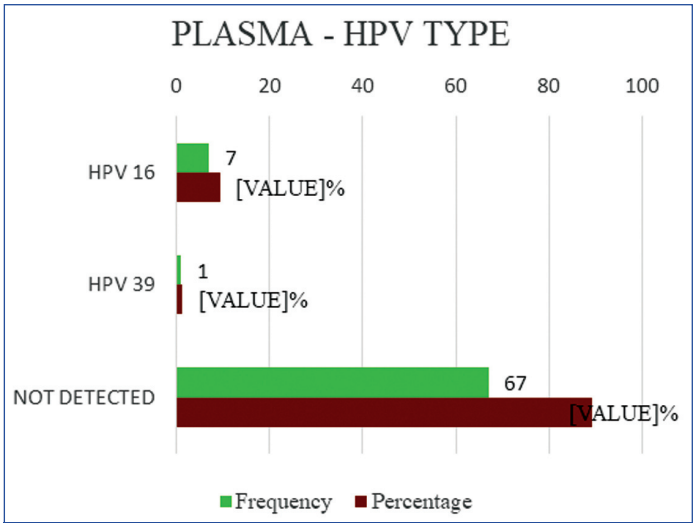
[Table/Fig-3]: Demonstrating HR-HPV types (a) real-time PCR graph of HPV types shows a clear amplification curve with a Cycle threshold (Ct) value of approximately 25-35. This indicates the presence of HPV 16 DNA in the sample, the negative control did not show any amplification, indicating the absence of contamination (b).



[Table/Fig-4]: Depicting various types of HR-HPV in urine samples.

(100%) and PPV (100%), resulting in an overall diagnostic accuracy of 33.33%.

The positive Likelihood Ratio (+LR) for both urine and plasma testing was greater than one, suggesting their utility for ruling in the diagnosis of cervical carcinoma. Plasma testing showed a +LR of



[Table/Fig-5]: Demonstrating different types of HR-HPV in plasma.

infinity, which is farther from one, and thus theoretically stronger for ruling in cervical carcinoma.

However, the negative Likelihood Ratio (–LR) for both urine and plasma testing was not less than 0.1, indicating that neither test can be used to reliably rule out cervical carcinoma.

When comparing HPV status in cervical tissue (the reference standard) with urine samples, 40/58 (69%) of HPV-positive cases in tissue were also positive in urine. Plasma testing, in contrast, detected only 8/58 (13.8%) of HPV-positive cases. Notably, 75% of plasma-detected cases were in advanced stages of disease (Stage IIIB or higher), while only 2/8 (25%) were in early stages. This suggests that plasma HPV positivity may be associated with advanced disease, although its diagnostic value is limited compared to urine testing [Table/Fig-6a,b].

ROC curve analysis: ROC curve analysis demonstrated that urine testing is a reliable diagnostic tool (AUC=0.815, $p<0.05$), effectively distinguishing between positive and negative cases [Table/Fig-7]. In contrast, plasma testing performed poorly (AUC=0.569, not significant), with results only marginally better than random chance.

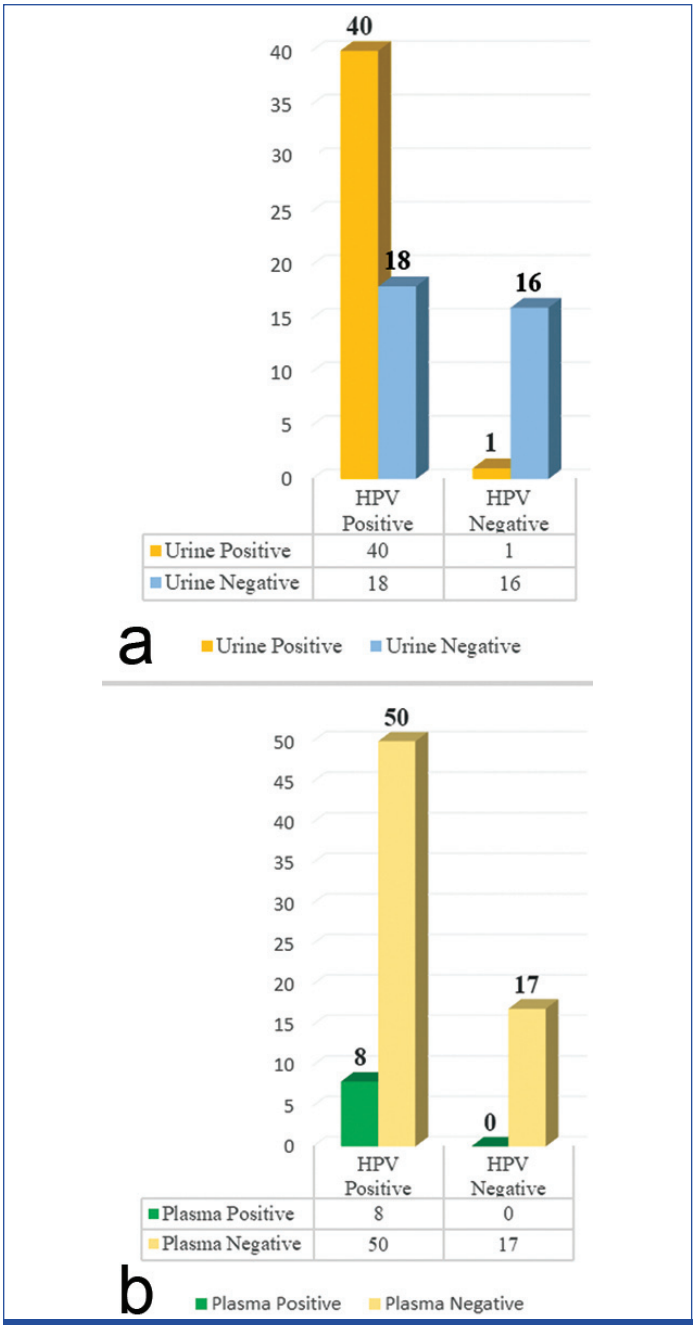
Based on these findings, urine testing emerges as the preferred diagnostic option. Plasma testing, due to its low sensitivity and poor overall accuracy, should not be relied upon as a standalone diagnostic tool.

DISCUSSION

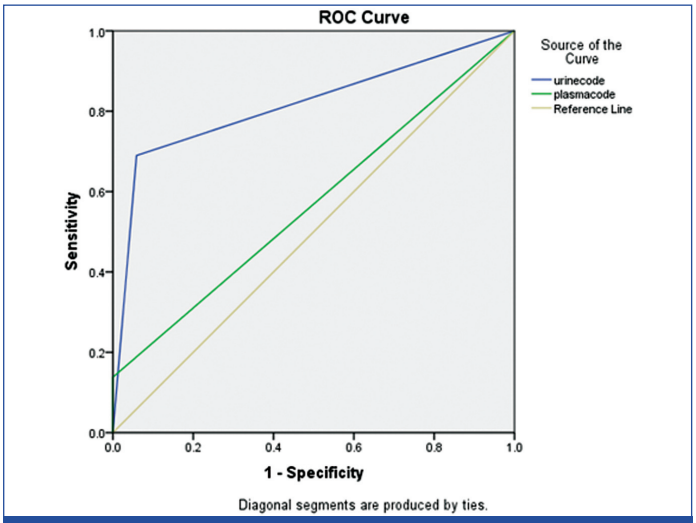
Despite being preventable, cervical cancer ranks fourth among cancers affecting women in terms of both incidence and mortality [8]. Of these cases, 21% of new diagnoses and 23% of cervical cancer–related deaths occur in India, highlighting the inadequacy of screening in the country [9].

To bridge this gap, it is essential to increase awareness, organise effective screening programs, and implement better strategies to combat cervical cancer in India. The pelvic examination required for Pap tests can be a significant deterrent for many Indian women due to concerns about modesty, privacy, and discomfort. A non invasive urine sample or minimally invasive plasma sample could help alleviate these concerns and increase participation in screening programs. The present study focuses on the potential of a less invasive test for HR-HPV that could increase cervical cancer screening uptake among Indian women, especially considering the cultural and social barriers that contribute to low screening rates. In addition, plasma samples were evaluated for HPV testing to assess disease severity and the possibility of HPV serving as an aetiological factor for cancers in other organs.

HPV in cervical cancer: The present study found a 77% positivity rate for HPV, with HPV 16 being the most common genotype detected (37.3%). These results are consistent with recent research, confirming HPV's significant role in cervical cancer and identifying



[Table/Fig-6]: Comparative analysis of HPV detection in (a) Urine and cervical tissue and (b) Plasma and cervical tissue.



[Table/Fig-7]: ROC curve analysis.

HPV 16 as the primary oncogenic strain associated with Squamous Cell Carcinoma (SCC) of the cervix. Globally, HPV 16 is the most common type, while HPV 18 is the second most frequent carcinogenic strain, although regional variations exist. The present study mirrors this global pattern, with HPV 16 as the most prevalent type.

Although HPV genotype does not significantly impact clinical outcomes or prognosis, the high prevalence of oncogenic types particularly HPV 16 underscores the importance of targeting these strains in vaccine development [10].

HPV testing in urine: Urine contains exfoliated cervical cells that can be analysed for HPV DNA using various amplification and hybridisation techniques [11]. Notably, the first-void urine sample contains a significantly higher concentration of epithelial cells and HPV DNA compared to later fractions [12].

In the present study, HPV DNA was detected in 55% of urine samples, compared to 77% in cervical tissue samples. This lower detection rate is consistent with previous studies, which have reported moderate under-detection of HPV DNA in urine compared to cervical tissue [13,14]. However, Tshomo et al., reported better HPV detection in urine than in cervical samples, attributing this to optimised urine collection protocols [15].

The most common HPV genotype detected in urine was HPV 16, present in 36% of cases. This showed strong analytical agreement with cervical tissue samples, both in terms of HPV presence and genotype identification. This concordance supports earlier findings that urine samples are representative of the cervical cellular composition, reinforcing their potential for HPV-based screening [15].

HPV in plasma: Evidence suggests that tumour DNA can be detected in the circulation of patients with cervical cancer, though reported HPV DNA detection rates in serum or plasma vary widely, from 7% to 45% [16].

Although plasma-based HPV screening shows limited promise, studies indicate that detection rates increase with advancing disease stage. HPV detection in plasma has been reported as an indicator of disease progression and advanced cervical cancer. Furthermore, plasma HPV DNA may prove valuable for monitoring therapeutic response and tracking disease progression. However, additional studies are needed to clarify its role as a biomarker of tumour burden and metastasis in cervical cancer management [17,18].

In the present study, HPV DNA was detected in 8/75 (11%) of plasma samples. Of these, 75% were associated with advanced disease (Stage IIIB or higher), while 2/8 (25%) were detected in early-stage disease. This discrepancy in detection rates may be attributed to differences in sample type (serum vs. plasma), the number of HR-HPV types analysed, plasma volume used, DNA extraction techniques, analytical tools, and primer selection [16,19].

Diagnostic utility of non invasive samples: The study evaluated urine and plasma as alternative, less invasive samples for HPV detection, revealing notable differences in diagnostic accuracy.

Urine testing demonstrated a sensitivity of 69% and a specificity of 94.1%, with a Positive Predictive Value (PPV) of 97.6% and a Negative Predictive Value (NPV) of 47.1%. Its overall diagnostic accuracy was 74.6%, with a high AUC of 0.815, establishing urine as a promising non invasive sample for HPV testing [Table/Fig-8]. Its utility is particularly relevant in resource-limited settings, where access to cervical tissue sampling may be challenging.

Parameters	Urine	Plasma
Sensitivity	68.96%	13.8%
Specificity	94.11%	100%
PPV	97.56%	100%
NPV	47.05%	25.4%
Diagnostic accuracy	74.6%	33.3%
+LR	11.695	Infinity
-LR	0.329	0.862

[Table/Fig-8]: Demonstrating the accuracy of HPV testing.

Author name/year of study	Sensitivity			Specificity		
	Physician collected cervical tissue samples	Urine (%)	Plasma (%)	Physician collected cervical tissue samples	Urine (%)	Plasma (%)
Hsu KF et al., (2003) [20]	-	-	45.2%	-		88.6%
Wei YC et al., (2007) [21]	-	-	64.7%	-		100%
Jaberipour M et al., (2011) [22]	-	-	23.5%	-		90.91%
Pathak N et al., (2014) [23]	-	87%	-			
Sahasrabuddhe VV et al., (2014) [24]	96.2%	80.8%	-	35.6%	42.2%	-
Nilyanimit P et al., (2017) [25]	-	56.5%	-	-	70.6%	-
Tranberg M et al., (2020) [26]	-	63.9%	-	-	96.5%	-
Cho HW et al., (2020) [27]	93.13%	73.28%	-			
Ørnskov D et al., (2021) [28]	97%	95%	-			
Song J and Wang J (2025) [29]	96.7%	85.2%	-	20.2%	23.2%	-
Present study, 2025	Comparator test n=75	69%	13.8%	Comparator test n=75	94.1%	100%

[Table/Fig-9]: Sensitivity and specificity of HPV testing across different sample types in various studies [20-29].

In contrast, plasma testing showed limited efficacy, with a sensitivity of 13.8% and a diagnostic accuracy of 33.3% in the present study. Despite high specificity and PPV, plasma's poor sensitivity restricts its use as a standalone screening tool. This is consistent with previous findings suggesting that circulating HPV DNA often falls below detectable levels in plasma, particularly in early-stage disease [16] The sensitivity and specificity of HPV testing across different sample types in various studies has been depicted in [Table/Fig-9] [20-29].

Implications for screening and diagnosis: The findings of present study carry important implications for cervical cancer prevention and management. HPV-based screening has higher sensitivity compared to conventional cytological screening, allowing for longer intervals between tests [30]. Indian women, particularly in rural areas, often prefer self-collection of samples for screening [31]. This was further supported by an Indian survey, which revealed that 60% of women preferred self-collection over physician-collected samples, and 65% favoured urine over vaginal self-sampling [32].

The present study demonstrates that urine-based HPV testing is a promising alternative to tissue-based diagnostics, offering high sensitivity and specificity. Incorporating this method into screening programs could increase coverage, particularly in underserved populations with limited access to healthcare. Urine sampling offers multiple advantages: it is non invasive, easy to use, accessible, and well-suited for home-based collection, which is generally preferred by patients. This approach also reduces the need for hospital visits and technical assistance. However, challenges related to sample transportation, handling, and the risk of degradation or loss must be addressed to fully leverage the potential of urine-based HPV testing.

Given the low uptake of cervical cancer screening in India, introducing urinary HPV testing could be highly beneficial, as it is both non invasive and acceptable to the Indian population.[23,32-34] Furthermore, even a single round of HPV screening has been shown to reduce cervical cancer–related mortality [34].

Although urinary HPV detection has slightly lower sensitivity compared to cervical samples, this limitation can be offset by repeated screening throughout a woman's lifetime. Improving the accuracy of urinary HR-HPV detection can be achieved through standardised procedures for urine collection, transport, optimised HPV assays, self-collection devices, and the development of assays specifically modified for urine samples [15,34].

Limitation(s)

The present study has certain limitations. Firstly, the cross-sectional design restricts the ability to assess the longitudinal role of HPV in disease progression. Future research with larger, more diverse cohorts and longitudinal follow-up is needed to validate these findings and explore causal relationships. Additionally, the study focused exclusively on squamous cell carcinoma of the cervix, emphasising the need to evaluate other histological subtypes. Standardisation of HPV detection techniques in urine and plasma samples at a larger scale is also required.

Implications of the study: Plasma HPV testing demonstrated limited diagnostic value for screening due to its low sensitivity in present study. However, HPV detection in both cervical and plasma samples was shown to increase with disease severity or stage [17]. Circulating tumour DNA in plasma may also serve as an indicator of recurrence or disease progression [18,19]. Importantly, present study showed high specificity for plasma HPV detection, suggesting that plasma viremia may be a useful tool for monitoring treatment response and prognosis. Future research should focus on optimising plasma-based HPV detection, potentially through advanced molecular techniques such as digital PCR or next-generation sequencing. Additionally, plasma viremia may contribute to HPV-associated cancers in other organs.

Vaccine monitoring: The distribution of HPV subtypes in a specific geographical region influences the effectiveness of HPV vaccines currently available. As vaccine coverage expands nationwide, supported by increasing awareness, there is a growing need for a convenient and non invasive method to monitor HPV antibody levels. Urine-based HPV detection, using specialised molecular assays for anti-HPV antibody measurement, is likely to emerge as a vital tool for vaccine surveillance in the near future [15,34]. Further research will be crucial to evaluate its feasibility and applications.

Future directions: Future research should focus on adapting urine-based HPV testing for integration into primary screening programs, especially in low-resource settings, to strengthen cervical cancer prevention strategies. Additionally, efforts should be directed toward improving plasma-based HPV detection for potential use in liquid biopsy. Molecular studies examining the correlation between HPV genotyping, treatment response, and prognosis could support the development of personalised approaches to cervical cancer management. Furthermore, urinary HPV detection holds potential for use in vaccine surveillance, offering a promising tool for monitoring vaccine effectiveness and population-level immunity.

CONCLUSION(S)

The present study highlights the potential of urine-based HR-HPV detection as a non invasive screening method for cervical cancer. The non invasive nature of urine testing may help overcome cultural, social, and religious barriers associated with traditional Pap tests, which require pelvic examinations. Urine-based HPV

testing therefore presents a promising avenue for future research, development, and innovation in cervical cancer prevention, early detection, and treatment strategies. Its implementation could contribute to achieving the World Health Organisation (WHO) goal of 70% screening coverage among women by 2030.

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