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RESEARCH PAPER

Effectiveness of HPV E6/E7 mRNA Test to Triage Primary Screen Positive Women in Cervical Cancer Screening

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Abstract

Background: Marked advancements in molecular technology and better understanding of the natural history of Human Papillomavirus (HPV) have significantly contributed to the introduction of molecular biomarkers in cervical cancer screening in recent years. The detection of highly sensitive HPV DNA and the highly specific HPV E6/E7 mRNA are now widely utilized in developed countries for cervical cancer screening. Among these, the HPV E6/E7 mRNA test is considered more specific for identifying precancerous cervical lesions.

Objective: To evaluate the effectiveness of the HPV E6/E7 mRNA test as a triage tool for screening of cervical cancer in primary screen positive women by VIA (visual inspection with acetic acid) or Pap smear (cytology) or HPV DNA test.

Methods: This cross-sectional observational study was conducted in the colposcopy clinic of the National Centre for Cervical & Breast Cancer Screening & Training, Bangladesh Medical University (BMU) in collaboration with the Department of Virology, BMU, Dhaka, Bangladesh, from October 2023 to September 2024. This study included 150 women by consecutive sampling who tested positive on any primary cervical cancer screening method (VIA/Cytology/HPV DNA) and were referred to the colposcopy clinic of BMU. After collecting cervical sample from each enrolled subject, colposcopy and colposcopy directed biopsy was performed. HPV E6/E7 mRNA test was performed on cervical sample in virology department of BMU. Presence of E6/E7 mRNA predicts the precancerous & early invasive lesion. Colposcopy reported normal or precancerous lesion (CIN 1, 2, 3). Finally, histopathology on biopsy material confirmed it as normal (e.g cervicitis) or precancerous (CIN 1, 2, 3) or cancerous (e.g invasive carcinoma or carcinoma in situ). All data were processed and analysed using 26 version of SPSS. Diagnostic efficacy of HPV E6/E7 mRNA and colposcopy for detection of pre-cancerous/ cancerous cervical lesion were calculated taking histopathology as gold standard.

Results: The majority of participants were aged 30–39 years (45.3%) and multiparous (87.3%). Colposcopy revealed cervical intraepithelial neoplasia 1 (CIN I) in 60% of cases, while histopathology showed chronic cervicitis (54.67%) and CIN I (30.67%) as the most common findings. HPV E6/E7 mRNA was overexpressed in 15% of cases. Among E6/E7 mRNA-positive patients, 78.3% had biopsy-confirmed precancerous and cancerous lesions, compared to 39.37% in the mRNA-negative group. The E6/E7 mRNA test showed high specificity (93.9%), high PPV (78.3%) and overall accuracy 63.3% for detecting precancerous and early invasive lesions, with low sensitivity of 26.5%. Colposcopy showed higher sensitivity (94.12%) but very low specificity (8.54%) and low accuracy (47.33%) in this regard. Compared to colposcopy; the E6/E7 mRNA test provided more reliable diagnostic accuracy (63.3% vs 47.33%) for detecting precancerous and early invasive lesions of cervix.

Conclusion: The findings obtained from the study, emphasize the importance of integrating HPV E6/E7 mRNA molecular testing into routine cervical cancer screening programs as a triage test due to its high specificity, PPV and accuracy compared to colposcopy for identifying clinically significant precancerous and early invasive lesions of cervix. Therefore, the HPV E6/E7 mRNA test may serve as an effective triage tool before doing colposcopy for identifying clinically significant precancerous cervical lesions and contributing to the prevention of cervical cancer. Thus it also can minimize colposcopy referral and over treatment.

Keywords: HPV E6/E7 mRNA, Screening, Triage, Cervical Cancer, CIN

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Introduction

Cervical cancer (CC) is the fourth most common cancer and a leading cause of cancer-related deaths among women globally. According to global cancer statistics 2022, Bangladesh recorded 9,540 new cervical cancer

cases and 5,826 deaths. Globally, there were 662,301 new cases and 348,874 deaths. In Bangladesh, cervical cancer is the second most common malignancy in women, comprising 13.3% of female cancers, with a 5-year prevalence of 32.1 per 100,000 women. [1]

Persistent infection with high-risk human papillomavirus (HPV) types is recognized as the primary cause of cervical cancer.[2,3] Although most HPV infections are transient and are cleared by the immune system within months, certain high-risk subtypes, particularly HPV 16 and 18, may persist and lead to malignant transformation. The HPV genome contains an early (E) region that encodes proteins essential for viral replication.[4] High-risk HPV types express E6 and E7 oncogenes, which disrupt key tumor suppressor pathways, resulting in genomic instability, accumulation of mutations, and eventual integration of HPV DNA into the host genome.[5] Specifically, the E6 protein promotes degradation of the tumor suppressor protein p53, while E7 binds to the retinoblastoma protein (pRb), leading to its degradation via the ubiquitin–proteasome pathway.[6-10]

Cervical intraepithelial neoplasia (CIN) represents a spectrum of premalignant lesions graded as CIN 1 (low-grade), CIN 2 (high-grade), and CIN 3 (high-grade). While the majority of CIN lesions regress spontaneously, approximately 70% of CIN 1 lesions within one year and 90% within two years, some progress to carcinoma in situ (CIS) or invasive cancer. CIS may develop in 11% of CIN 1 and 22% of CIN 2 cases, while invasive cancer may emerge in approximately 1% of CIN 1, 5% of CIN 2, and at least 12% of CIN 3 lesions.[11]

In Bangladesh, the government has implemented visual inspection with acetic acid (VIA) as the primary screening method for cervical cancer. VIA offers advantages such as simplicity, low cost, feasibility in low-resource settings, and the potential for immediate treatment linkage. However, its specificity is relatively low (52.1%), leading to high false-positive rates and increased burden on colposcopy clinics, potentially contributing to overtreatment.[12] Although VIA has shown promise in cross-sectional studies, randomized controlled trials have demonstrated its limited efficacy in reducing cervical cancer incidence and its precursors. [13]

Cytology-based screening (Pap smear), supported by robust healthcare infrastructure, has significantly reduced CC incidence in high-resource countries. Nonetheless, the World Health Organization (WHO) now recommends HPV DNA testing as the primary screening method, given its superior sensitivity. In 2018, the WHO launched a global call to eliminate cervical cancer, culminating in the 2020 Global Strategy with targets for 2030: (1) vaccinate 90% of eligible girls against HPV, (2) screen 70% of women at least twice in their lifetime, and (3) effectively treat 90% of screen-positive women, including access to palliative care.[14]

In Bangladesh, the prevalence of HPV infection is estimated at 7.7%, with no significant difference between urban and rural populations. Globally, the prevalence of high-risk HPV (HR-HPV) is 21%, and for any HPV type, it is 31%.[15,16] A randomized controlled trial demonstrated that HPV-based screening is more effective than cytology in preventing invasive cervical cancer by detecting persistent high-grade lesions earlier and enabling longer screening intervals.[17] With a sensitivity of approximately 95%, HPV testing is well-suited for primary screening, providing greater reassurance following a negative result and better detection of glandular lesions and precursors of adenocarcinoma.[18] It is also more appropriate for populations vaccinated against HPV.[19]

Despite its high sensitivity, HPV DNA testing has lower specificity, which may lead to overdiagnosis and overtreatment, particularly in younger women. Therefore, effective triage strategies are essential when using HPV DNA as the primary screening tool.[20] One promising approach involves detecting HPV E6/E7 mRNA transcripts, which reflect active viral oncogene expression and correlate more strongly with lesion severity compared to HPV DNA detection.[21,22] Evidence suggests that E6/E7 mRNA testing offers higher specificity and better predictive value, making it a potentially valuable biomarker in cervical cancer screening.

Therefore, this study aims to evaluate the effectiveness of the E6/E7 mRNA test in triaging women who test positive on primary cervical cancer screening, using histopathological findings as the gold standard.

Materials and Methods

This cross-sectional observational study was conducted in the colposcopy clinic of the National Centre for Cervical & Breast Cancer Screening & Training, at Bangladesh Medical University (BMU) in collaboration with the Department of Virology, BMU,

Dhaka, Bangladesh, from October 2023 to September 2024. Total 150 women who tested positive on any primary cervical cancer screening method (VIA, cytology/pap smear, HPV DNA) were subsequently referred to the colposcopy clinic at BMU were enrolled in the study.

Participants were 30–65 years, married or sexually active for at least 10 years, with a healthy-looking cervix, no history of therapeutic procedures involving the cervix (e.g., LEEP, conization, cryotherapy). Women younger than 30 years with less than 10 years of sexual activity, or older than 65 years, known cases of cervical cancer or precancerous lesions, pregnant or lactating women, women who were not willing to participate in the study were excluded from the study.

Data were collected using a predesigned data collection sheet specifically for this study. After obtaining informed written consent, data collection was carried out through face-to-face interviews using structured questionnaires. The data collection sheet was designed to capture comprehensive information, including demographic details, reproductive and sexual history, menopausal status, and contraceptive practices. Clinical examination was performed and colposcopy evaluation was done by trained gynecologists following standard protocols. Colposcopy findings were documented and categorized as normal or pre-cancerous (CIN 1, CIN 2, CIN 3). Colposcopy guided cervical biopsies were taken from suspicious lesions for histopathological confirmation. Histopathological outcomes are categorized as precancerous/cancerous vs normal (chronic cervicitis). Histo-pathologically precancerous/ cancerous lesion includes CIN 1, 2, 3; carcinoma in situ (CIS) and invasive carcinoma. In addition to colposcopy and biopsy, cervical samples were collected for HPV E6/E7 mRNA testing using an established molecular assay. The expression status (positive or negative) of HPV E6/E7 mRNA was recorded for each participant. Positive expression of HPV E6/E7 mRNA predicts the precancerous and early invasive lesion.

Quantitative data were expressed as mean and standard deviation, and qualitative data were expressed as frequency distribution and percentage. Diagnostic performance of colposcopy and HPV E6/E7 mRNA for detection of precancerous and cancerous cervical lesion was done with respect to the histopathology report as gold standard. To evaluate the diagnostic performance of both colposcopy and the HPV E6/E7 mRNA test, standard diagnostic metrics were calculated, including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy. Statistical analysis was performed by using SPSS 26 (Statistical Package for Social Sciences).

Results

The majority of participants were aged between 30–39 years (45.3%), Most participants had a primary level of education (44.7%) and a mean BMI of 18.4 ± 1.5 kg/m². In contrast, the highest prevalence of HPV among women aged 55–64 years (12.2%) compared to those aged 35–44 and 45–54 years. Most participants in this study were multiparous (87.3%), with a mean duration of marriage of 21.3 years. Additionally, 27.3% were postmenopausal, and 62% had a history of oral contraceptive pill (OCP) use. Regarding education levels, the largest group had a primary education (44.7%), followed by those with a secondary school certificate (SSC) (28%), and postgraduates (16%) (table-I).

Table I: Distribution of the participants according to sociodemographic characteristics (N=150)

Characteristics	Frequency (n)	Percentage
Age group (years)		
<30	13	8.7
30–39	68	45.3
40–49	49	32.7
50-59	20	13.3
Education level		
Primary	67	44.7
SSC	42	28
HSC	4	2.7
Graduate	13	8.7
Post graduate	24	16
Parity		
Nulliparous	4	2.7
Primipara	15	10.0
Multipara	131	87.3
Menopause		
Yes	41	27.3
No	109	72.7
Methods of contraception used		
Oral Contraceptive Pill (OCP)	93	62.0
Implant	7	4.7
Intrauterine Device (IUD)	6	4.0
Others	34	22.7
Mean BMI (kg/m²)	18.4 ± 1.5	
Duration of marriage (years)	21.3 ± 8.6	

Table II: Comparison of colposcopy and histopathology findings for detection of precancerous and early invasive cancerous cervical lesions (N=150)

Colposcopy findings	Histopathological findings Precancerous & Cancerous Lesions (n=68)	Normal (n=82)
Precancerous lesions (n=139) [CIN 1, 2, 3]	64 (46%)	75 (54%)
Normal(n=11)	4 (36.4%)	7(63.6%)

The distribution of colposcopy findings revealed that CIN I was the most common, identified in 60% of cases. CIN II followed with 25.3% of cases. Both normal findings and CIN III were observed in 7.3% of cases each (figure-1).

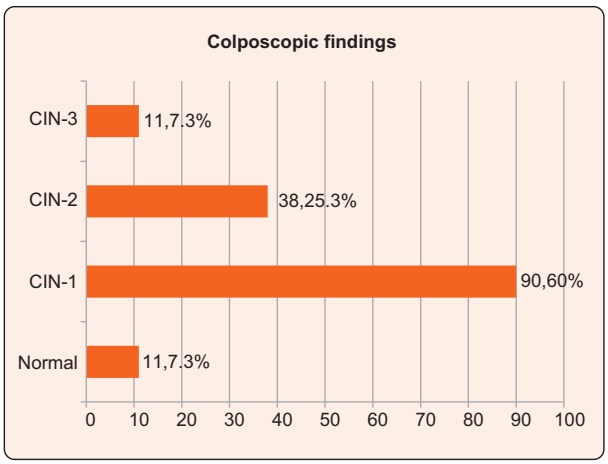

Figure 1: Distribution of the participants according to colposcopic findings

The histopathological findings showed that chronic cervicitis was the most frequent condition, observed in 82 (54.67%) cases. CIN 1 was the next most common, with 46 (30.67%) cases. CIN 2 and CIN 3 were each found in 8 (5.33%) cases. Carcinoma in situ (CIS) was present in 2 (1.33%) cases, and invasive cancer was observed in 4 (2.66%) cases (figure-2).

The pie chart demonstrates that among 150 patients, HPV E6/7 mRNA was overexpressed in 23 cases (15%) and not expressed in 127 cases (85%) (figure-3).

Among the 23 participants who tested positive for E6/7 mRNA, 78.3% (n = 18) had biopsy-confirmed precancerous or cancerous lesions, while 21.7% (n = 5) had normal biopsy findings. In contrast, among the 127 participants who were negative for E6/7 mRNA, 39.4% (n = 50) had precancerous or cancerous lesions,

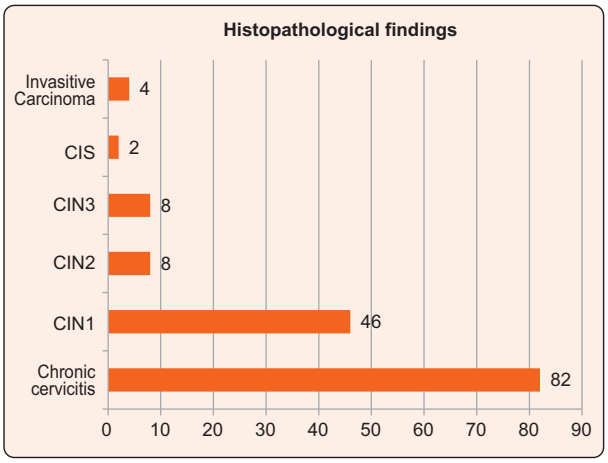

Figure 2: Distribution of the Participants According to Histopathological Findings

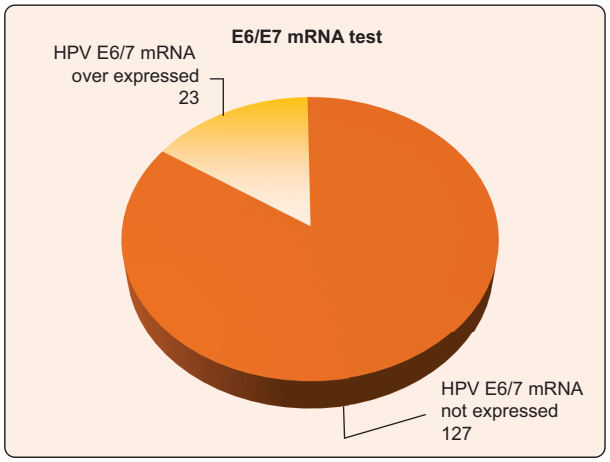

Figure 3: Distribution of the participants according to overexpression of E6/E7 mRNA

and 60.6% (n = 77) had normal findings. This difference was found to be statistically significant (p = 0.003, χ^2-test) (Table-II). The E6/7 mRNA test demonstrated a much higher specificity (93.9%) and PPV (78.3%), with sensitivity (26.5%), NPV (60.63%) resulting in a higher overall diagnostic accuracy 63.3% (table-IV).

Table III: Comparison of E6/7 mRNA test and histopathology findings for detection of precancerous and early invasive cancerous cervical lesions (N=150)

E6/7 mRNA Result	Histopathological findings Precancerous & Cancerous Lesions (n=68)	Normal (n=82)
Positive (n=23)(Precancerous and cancerous)	18 (78.3%)	5 (21.7%)
Negative (n=127)(Normal)	50 (39.4%)	77 (60.6%)

Table IV: Diagnostic performance of E6/7 mRNA test and colposcopy for detection of precancerous and early invasive cancerous cervical lesions (N=150)

	Sensitivity	Specificity	PPV	NPV	Accuracy
E6/7 mRNA	26.5	93.9	78.3	60.6	63.3
Colposcopy	94.1	8.5	46	63.6	47.3

Among the 139 participants who tested positive for colposcopy as precancerous lesions, 46% (n =64) had biopsy-confirmed precancerous or cancerous lesions, while 54% (n =75) had normal biopsy findings. In contrast, among the 11 participants who were normal for colposcopy 36.4% (n = 4) had precancerous or cancerous lesions, and 63.6% (n = 7) had normal findings (table-III). This shows greater discrepancies with no significant association. Colposcopy showed a high sensitivity (94.1%) but very low specificity (8.5%), with a positive predictive value (PPV) of 46.0%, negative predictive value (NPV) of 63.6%, and an overall accuracy of 47.3% (table-IV).

Discussion

The findings of this study provide valuable insights into the demographic, clinical, and pathological characteristics of the study population, as well as the diagnostic utility of E6/E7 mRNA testing in HPV-related cervical lesions. The majority of participants were aged between 30–39 years (45.3%), which corresponds to the period of heightened cervical transformation zone activity during reproductive years.

In contrast, the highest prevalence of HPV among women aged 55–64 years (12.2%) compared to those aged 35–44 and 45–54 years. However, they still recommended that screening should be prioritized in the 35–44 years age group.[23]

Most participants in this study were multiparous (87.3%), with a mean duration of marriage of 21.3 years, indicating long-term exposure to hormonal and mechanical changes of the cervix. Additionally, 27.3% were postmenopausal, and 62% had a history of oral contraceptive pill (OCP) use. Since OCP use is known to contribute to persistent HPV infection, this may explain the higher occurrence of cervical lesions observed in the population.[24,25]

Colposcopy examination identified Cervical Intraepithelial Neoplasia grade I (CIN-I) as the most common lesion (60%), followed by CIN-II (25.3%). CIN-III and normal findings were each observed in 7.3% of participants. Histologically, chronic cervicitis—considered a normal lesion—was found in 82 patients (54.7%). However, more concerning findings included carcinoma in situ (CIS) in 1.3% and invasive carcinoma in 2.6% of cases, suggesting the effectiveness of early detection practices. A total of 46 cases were confirmed as CIN-I.

E6/E7 mRNA overexpression was detected in 23 cases (15.3%). The positive rate of E6/E7 mRNA was higher in high-grade squamous intraepithelial lesions (HSIL) than in low-grade (LSIL) or normal cases.[26] Higher positivity rate of 97.2% (962/990), while around 50% positivity in a hospital-based cohort.[27,28] HPV16 had the highest detection rate (8.49%) for oncoprotein expression.[29]

Importantly, biopsy findings showed a strong association with E6/E7 mRNA detection (p = 0.003), supporting the test's clinical relevance in identifying CIN-II and higher-grade lesions. In total, 60.63% of cases had both negative E6/E7 mRNA results and non-cancerous biopsy findings. Among the E6/E7 mRNA positive cases, 78.3% also had biopsy-confirmed precancerous or early invasive carcinoma.[30]

When comparing colposcopy and biopsy no significant associations were found for all precancerous and early invasive lesions; however, a significant correlation emerged specifically for CIN-II and higher lesions. Notably, colposcopy identified 92.7% of cases as precancerous or cancerous, yet 85.6% of these were negative for E6/E7 mRNA. This suggests that colposcopy may overestimate disease severity. The diagnostic parameters, specificity, positive predictive value (PPV), and accuracy, were all higher for E6/E7 mRNA than for colposcopy when benchmarked against biopsy results. It was found that 55.5% (534/962) had abnormal cytology (ASC-US+), 35.1% (338/962) had positive HPV mRNA results, and 13.9% (134/962) had CIN2+ lesions.[27]

There is strong association (p = 0.001) was observed between mRNA detection and biopsy findings in CIN-II and higher lesions. Among the 23 cases positive for E6/E7 mRNA, 69.6% were diagnosed with CIN-II or higher, while only 30.4% were classified as chronic cervicitis or CIN-I.

The diagnostic performance of E6/E7 mRNA testing was notable. For all cervical precancerous lesions, the test demonstrated a sensitivity of 26.5%, specificity of 93.9%, PPV of 78.3%, NPV of 60.63%, and accuracy of 63.3%. When narrowed to CIN-II and higher lesions, sensitivity improved significantly to 72.7%, specificity to 94.5%, PPV to 69.56%, NPV to 95.3%, and accuracy to 91.3%. These findings highlight the strong predictive value and specificity of the E6/E7 mRNA test, despite its lower sensitivity overall. The particularly high NPV for CIN-II+ lesions (95.3%) indicates that a negative E6/E7 mRNA result reliably rules out significant cervical pathology.

Overall sensitivity of 92.3% and specificity of 33.01%.[31] Similarly, it was found that mRNA test sensitivities for detecting CIN2 and CIN3 were 93.8% and 95.7%, respectively, comparable to those of HPV DNA testing.[28] Other studies also showed higher sensitivity for mRNA testing compared to DNA methods.[20,32] The number of colposcopies required per CIN2+ detection was lower with HPV-mRNA testing (3.1) than with cytology (5.2).[27]

On the other hand, the sensitivity and specificity of E7 mRNA testing did not significantly differ from those of cytology (sensitivity: 68.8% vs. 75.0%; specificity: 59.4% vs. 65.3%).[33]

The discrepancies observed between colposcopy, biopsy, and E6/E7 mRNA results underscore the complexity of cervical lesion diagnosis. While colposcopy remains a critical visual diagnostic tool, its subjectivity and inconsistent association with molecular findings limit its reliability. Biopsy continues to be the gold standard, but molecular tests like E6/E7 mRNA offer valuable insight, especially for identifying high-risk HPV infections. Given its high specificity and PPV, the E6/E7 mRNA test shows promise as an effective triage tool that could help reduce unnecessary colposcopies.

Conclusion

The findings obtained from the study, emphasize the importance of integrating HPV E6/E7 mRNA molecular testing into routine cervical cancer screening programs as a triage test due to its high specificity, PPV and accuracy compared to colposcopy for identifying clinically significant precancerous and early invasive lesions of cervix. Therefore, HPV E6/E7 mRNA test may serve as an effective triage tool before doing colposcopy for identifying clinically significant precancerous cervical lesions and contributing to the prevention of cervical cancer. Thus, it also can minimize colposcopy referral and over treatment.

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