Original Article

Diagnostic Efficacy of Enhanced Visual Assessment [Visual Check] for Triaging Cervical Cancer Screen Positive Women

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Abstract

Introduction: Colposcopy is important for triaging any abnormal cervical screening test. Scarcity of trained colposcopists and colposcopy centers is a big hurdle to screening programs in low- and middle-income countries. **Objectives of the Study:** The objective was to assess the performance of the artificial intelligence incorporated into the mobile optical device technologies (ODT) Enhanced Visual Assessment (EVA visual check) against physician colposcopic diagnosis and the gold standard of histopathology. **Materials and Methods:** It was a cross-sectional observational study conducted on women referred to a colposcopy clinic following an abnormal screening test. Colposcopic examination was performed by colposcopists using the MobileODT EVA system. Physician's impression and Visual Check analysis were compared with the final histopathological analysis or cytology. Cases with normal cytology and normal colposcopy did not undergo biopsy, and these were considered normal. **Results:** A total of 2050 women were screened, and 147 screen-positive women were recruited in the study. EVA Visual Check had a sensitivity of 86.8% (75–95), specificity of 28.7% (20–39), positive predictive value (PPV) of 40.7% (32–50), negative predictive value (NPV) of 79.4% (62–91), and diagnostic accuracy of 49.7% (41–58) for diagnosing cervical intraepithelial neoplasia (CIN) 1+ lesions. EVA Visual Check has a sensitivity of 89.3% (72–98), specificity of 26.1% (18–35), PPV of 22.1% (15–31), NPV of 91.2% (76–98), and diagnostic accuracy of 38.1% (30–46) for CIN 2+ lesions. **Conclusion:** MobileODT EVA colposcope with AI has sensitivity comparable to physician's diagnosis, whereas specificity, PPV, and NPV were less than that of physician's diagnosis. It could prove valuable for triage of screen-positive women for further management.

Keywords: *Artificial intelligence technology, enhanced visual assessment, cervical cancer screening, visual check*

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Introduction

In the year 2020, an estimated 604,127 new cases of cervical cancer were diagnosed worldwide and about 341,831 women died from the disease (GLOBOCAN 2020).[1] Incidence and mortality vary widely with geographic location, and ~ 90% of cervical cancers occur in low- and middle-income countries (LMICs) that lack organized screening and human papillomavirus (HPV) vaccination programs.[2,3]

Colposcopy which is commonly used for triage of screen-positive women has its own limitations in LMICs as it is expensive, sophisticated, requiring high maintenance and a skilled colposcopist, all of which are scarce in LMICs.[4] There is an urgent need for point-of-care tests where screening, triage, and treatment could be done in the same sitting as it may be the woman's only opportunity to contact the health-care

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system. A triaging system is needed for screen-positive women which has good diagnostic accuracy, is cost-effective, simple, is user-friendly, and can be used by any health personnel with minimal training.

Incorporation of artificial intelligence (AI) in digital colposcopy has generated a lot of interest in recent years to overcome these challenges.[5,6] Enhanced Visual Assessment (EVA) is one such system in which use of an inbuilt deep leaning algorithm (EVA Visual Check) in a mobile colposcopy device allows health personnel with minimal training to make a diagnosis and help in managing these patients effectively. It is based on the reviews of highly qualified colposcopists in various countries.

Visual Check combines high-quality image capture with secure online data management and services. It allows providers to visualize the cervix, document examination, and add annotations for appropriate site of biopsy. An added advantage is an option of further review, collaboration with fellow colposcopists for quality assurance, remote consultation, and continued education.[7-9] The present study is an effort to assess the diagnostic accuracy of EVA Visual Check compared to physician diagnosis and histopathology.

Aims and objectives

The objective was to compare the performance of EVA Visual Check with physician colposcopic diagnosis using histopathology as the gold standard.

Materials and Methods

This was a cross-sectional observational study conducted at a tertiary care teaching hospital in North India after approval by the institutional review board and institutional ethical committee. The study was conducted for 9 months starting from January 2021, and 2050 women were screened in the outpatient department during this duration. Women aged 25–65 years with an abnormal cervical screening test (Pap, HPV, or visual inspection with acetic acid [VIA]) referred for colposcopy were included in the study. Informed consent was obtained from all the subjects and/or their legal guardians. Pregnant women and women who were treated for cervical intraepithelial neoplasia (CIN) or cervical cancer were excluded from the study. A sample for cytology was taken for all women who did not have a Pap smear earlier. All Colposcopic examination were carried out by four trained colposcopists using the EVA [Visual check] system. EVA colposcope with artificial intelligence incorporated in the form of Visual Check is manufactured by MobileODT, Digital Health Femtech company, Tel Aviv, Israel in collaboration with Genworks, India. All colposcopists were qualified colposcopist from the Indian Society of Colposcopy and Cervical Pathology and had at least 5-year experience in colposcopy. All images were reviewed by the senior most colposcopist of the team. Images were taken serially after applying normal saline, 5% acetic acid, and Lugol's iodine. Standard methodology was followed in all the cases. Acetic acid image was taken after a wait of 1 min after application of 5% acetic acid. Scoring of the lesion was done according to Swede score. A colposcopic impression of Minor-grade lesion or Major-grade cervical intraepithelial lesion (CIN) was made by the colposcopist according to International Federation for Cervical Pathology and Colposcopy nomenclature;[10] guided biopsy was taken from any acetowhite lesion and sent for histopathological examination. We performed biopsy of 97 women, 3 women denied biopsy in spite of positive triage test and were excluded from the study, and in 50 women, Pap smear that is surface biopsy was taken as a surrogate of cervical biopsy. We did not perform biopsy of women who had negative Pap smear and negative colposcopic examination by physicians due to ethical reasons. Images taken with the EVA system were automatically uploaded to a cloud with the AI algorithm (EVA Visual Check) at the end of examination. "Run Visual Check" needs to be clicked to start the process of evaluation. In less than a minute, a message was received whether the images were likely to specify abnormal (suspected positive findings) or normal (no suspected positive findings). Colposcopic correlation of "physician diagnosis" using EVA digital colposcope was compared with Visual Check analysis. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of physician diagnosis and EVA Visual Check were compared with the final histopathology or cytology.

Statistical analysis

SPSS v23 (IBM Corp.) was used for data analysis. Descriptive statistics for categorical variables (physician, PAPS, histopathological evaluation diagnosis, etc.) were elaborated in the form of frequencies, percentages, and the 95% CI for these percentages. Chi-squared test was used to explore the association between EVA Visual Check impression and diagnoses by different modalities. Fisher's exact test was where > 20% of the cells contained an expected count of < 5. Sensitivity, specificity, PPV, NPV, and diagnostic accuracy for various modalities were calculated by taking histopathological evaluation or cytology as the gold standard. Statistical significance was kept at $P < 0.05$.

Results

We screened 2050 women, out of which 150 women were found to be screen positive. Visual inspection after application of acetic acid was done as a primary

screening test in 113 women, smear in 33 women, and HPV testing in 1 case.

Ultimately, 147 women were considered for analysis; three women were dropped from the analysis since they did not consent for biopsy. A total of 97 women had a biopsy and histologically proven diagnosis. Following are the results of the study.

The mean age of the participants was 38.81 ± 10.78 years. Table 1 depicts the association between EVA Visual Check impression and physician's diagnosis in 147 women. EVA Visual Check perceived more abnormal in images diagnosed as normal by an experienced colposcopist. Out of 50 cases which were normal according to physician diagnosis, EVA Visual Check reported 27 (79.4%) as normal and 23 (20.4%) as abnormal. All cases of ectropion, squamous metaplasia, and cervicitis were diagnosed as abnormal on EVA Visual Check which emphasizes the need for further training in automated visual evaluation (AVE) for these benign conditions. Out of 33 (22.4%) minor-grade lesions as per physician diagnosis, 7 (20.6%) were diagnosed as normal on EVA Visual Check. However, most of major-grade lesions and cancer were diagnosed as abnormal by EVA Visual Check. It shows that Visual Check is less specific for minor-grade lesions but 100% specific for high grade and cancer.

Table 2 describes the association between histopathological diagnosis with EVA Visual Check and physician impression.

Table 3 summarizes the prediction of CIN 1+ lesions by various modalities.

Table 4 summarizes the prediction of CIN 2+ lesions by various modalities.

Table 5 evaluates the diagnostic parameters in the form of likelihood ratio and the Youden index for diagnosing CIN lesions. The Youden index of Visual Check is 15.5%, physician impression is 68.7%, and Pap's impression is 18.4%.

However, EVA Visual Check was found to be noninferior to physician colposcopic diagnosis as it was able to detect 17 out of 23 of histologically proven CIN 1 (73.91%), 16 out of 18 (88.88%) histologically proven CIN II, 11 out of 12 (91.6%) histologically proven CIN III, 4 out of 4 (100%) histologically proven carcinoma cervix, and 1 out of 1 (100%) case of VIN3.

Discussion

In recent years, AI has been utilized in various fields for phonetic recognition, image recognition, face recognition, automated driving, etc.[9] Many medical disciplines are also successfully utilizing AI including detection of skin cancer, diabetic retinopathy, predicting stroke, assessing bone health, and diagnostic mammograms.[11-14] Most of the methods of cervical cancer screening such as cytology, VIA, and colposcopy depend on visual interpretation by a trained health-care provider which is subjective and depends on the level of training. AI is a proposed method to mitigate such subjective variations in visual interpretation.[15] Digital colposcopy built around a smartphone with incorporated AI has the potential to revolutionize the cervical screening program.[6]

Visual Check is not a replacement for clinical judgment instead it provides a clinical decision support tool using both a quality classifier and a predictive algorithm. The results of the present study reveal that MobileODT EVA colposcope with an inbuilt AVE algorithm "EVA Visual Check" has sensitivity and negative predictive value comparable to physician diagnosis though having a lower specificity and diagnostic accuracy for CIN.

CIN 2+ lesions are true precursors for cervical cancer, and we found that EVA Visual Check had better

Table 1: Association between Enhanced Visual Assessment Visual Check impression and physician diagnosis (*n*=147)

Physician diagnosis	EVA Visual Check impression			Chi-squared test	
	Normal, *n* (%)	Abnormal, *n* (%)	Total, *n* (%)	χ^2	*P*
Normal	27 (54)	23 (46)	50 (100)	46.125	<0.001
Ectropion	0	22 (100)	22 (100)		
Squamous metaplasia	0	5 (100)	5 (100)		
Cervicitis	0	7 (100)	7 (100)		
Minor-grade lesion	7 (21.21)	26 (78.78)	33 (100)		
Major-grade lesion	0	27 (100)	27 (100)		
Cancer	0	3 (100)	3 (100)		
Total	34 (23.12)	113 (76.87)	147 (100.0)		

The difference is findings of EVA Visual Check and physician diagnosis was significant. Visual Check made significantly higher diagnoses of abnormal in benign variations such as ectropion, squamous metaplasia, and cervicitis. However, 21.21% of low-grade lesions were also diagnosed as normal by Visual Check. However, Visual Check was 100% accurate in the diagnosis of high-grade lesions and cervical cancer. EVA: Enhanced Visual Assessment

Table 2: Association between histopathological diagnosis with Enhanced Visual Assessment Visual Check and physician impression

HPE diagnosis	Total, *n* (%)	EVA Visual Check		Physician impression	
		Normal, *n* (%)	Abnormal, *n* (%)	Normal, *n* (%)	Abnormal, *n* (%)
Normal	83 (56.5)	26 (31.32)	57 (68.67)	44 (53.01)	39 (46.98)
Cervicitis	11 (7.5)	1 (9.09)	10 (90.9)	1 (9.09)	10 (90.9)
CIN-I	25 (17.0)	4 (16)	21 (84)	4 (16)	21 (84)
CIN-II	14 (9.5)	2 (14.28)	12 (85.71)	1 (7.14)	13 (92.8)
CIN-III	8 (5.4)	1 (12.5)	7 (87.5)	0	8 (100)
Carcinoma	6 (4.1)	0	6 (100)	0	6 (100)
Total	147 (100.0)	34 (23.12)	113 (76.87)	50 (34.01)	97 (65.98)

For EVA Visual Check, strength of association between the two variables that is histopathological diagnosis and EVA Visual Check diagnosis is low (Cramer's V=0.23) (bias-corrected Cramer's V=0.14). For physician diagnosis, strength of association between the two variables that is physician impression and histopathological diagnosis is moderate (Cramer's V=0.45) (moderate association) (bias corrected Cramer's V=0.41). EVA: Enhanced Visual Assessment

Table 3: Summary of prediction of cervical intraepithelial neoplasia 1+ lesions

Variable	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
Physician impression	86.8% (75–95)	81.9% (73–89)	73.0% (60–83)	91.7% (84–97)	83.7% (77–89)
Pap's impression	22.6% (12–36)	95.7% (89–99)	75.0% (48–93)	68.7% (60–77)	69.4% (61–77)
EVA Visual Check impression	86.8% (75–95)	28.7% (20–39)	40.7% (32–50)	79.4% (62–91)	49.7% (41–58)

PPV: Positive predictive value, NPV: Negative predictive value, EVA: Enhanced Visual Assessment

Table 4: Summary of prediction of cervical intraepithelial neoplasia 2+ lesions

Variable	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
Physician impression	92.9% (76–99)	68.9% (60–77)	41.3% (29–54)	97.6% (92–100)	73.5% (66–80)
Pap's impression	35.7% (19–56)	95.0% (89–98)	62.5% (35–85)	86.3% (79–92)	83.7% (77–89)
EVA Visual Check impression	89.3% (72–98)	26.1% (18–35)	22.1% (15–31)	91.2% (76–98)	38.1% (30–46)

PPV: Positive predictive value, NPV: Negative predictive value, EVA: Enhanced Visual Assessment

Table 5: Diagnostic parameters: Likelihood ratio and Youden index for diagnosis of cervical intraepithelial neoplasia

Variable	LR+	LR−	Youden index
Physician impression	4.80 (3.08–7.47)	0.16 (0.08–0.32)	68.7
Pap's impression	5.32 (1.81–15.67)	0.81 (0.69–0.94)	18.4
EVA Visual Check impression	1.22 (1.03–1.44)	0.46 (0.22–0.98)	15.5

EVA: Enhanced Visual Assessment, LR: Likelihood ration

sensitivity, specificity, PPV, NPV, and diagnostic accuracy for CIN 2+ lesions as compared to CIN 1+ lesions. EVA Visual Check falsely diagnosed 20.4% of normal cervices, 19.5% of ectropion, 4.4% of squamous metaplasia, and 6.2% of cervicitis in the present study. A similar observation was made in another multinational study which noted a high prevalence of cervicitis in images collected from India which interfered with decision-making of AVE algorithm and commented that AVE algorithm needs to be trained to deal with such regional variations.[6,16]

In another study, AVE algorithms on images taken by MobileODT EVA were found to be at par with human evaluation by a gynecologist in predicting the precancerous lesions.[6] AVE algorithms strongly predicted CIN 2+ or worse lesions proven on histopathology. We second their suggestion that it is essential to train AVE algorithms for broader use with larger sample-sized studies with rigorously defined cases of histologically proven CIN 2+ lesions in association with HPV testing.[6]

A large prospective epidemiological study was done in Guanacaste Cohort, Costa Rica where another AVE detection algorithm was developed from 9406 subjects. It compared cytology, VIA, and HPV testing with trained algorithm using data with a long natural history dating from 1990 and reported that trained algorithm using digitalized cervicogram had excellent sensitivity for detection of CIN 2+ lesions. This performance was found to be better than colposcopist's interpretation of the same image and had high agreement with cytology and HPV testing. The sensitivity and specificity of AVE

were found to be 97.7% and 84% for the age group of 25–49 years.[17] However, this study used archived then digitized cervical images from screening, taken with a fixed-focus camera ("cervicography") instead of much upgraded mobile digital camera used now.

In a recent study, a set of researchers compared impression of 100 images of colposcopy by a panel of 32 colposcopists versus artificial intelligence supported diagnosis (AISD). AI was found to have accuracy of 57.8% for normal, 35.4% for CIN 1, 40.5% for CIN 2 and 3, and 44.5% for invasive cancer as compared to colposcopist's diagnosis of 54.4% for CIN 1, CIN 2, and CIN 3 and 38.9% for invasive cancer. After learning from AISD, even diagnosis of gynecologists improved to 58.0% for CIN 2 and 3 lesions and 48.5% for invasive cancer. They reported that assistance from AI significantly improves the diagnostic accuracy of gynecologists for invasive cancer ($P < 0.1$) and for CIN 2 and 3 ($P = 0.14$).[18]

In the present study, MobileODT EVA Visual Check had good sensitivity and NPV but lower specificity, PPV, and diagnostic accuracy as compared to physician diagnosis. However, it can help in quicker triage of screen-positive women by health-care workers who can apply this algorithm at the peripheral centers. Moreover, the sensitivity, specificity, and diagnostic accuracy of EVA Visual Check are higher for CIN 2+ lesions as compared to all CIN 1+ lesions. Trainees in colposcopy could also use it for triage of screen-positive women before colposcopy by an expert. The images marked abnormal could be reviewed by an expert even situated remotely. This can reduce the load on expert colposcopists who can review only the "abnormal ones," thereby reducing waiting times for colposcopy and treatment. Quicker triage can also reduce loss to follow-up and help in achieving the 90% treatment goal of the World Health Organization (WHO). Efficient data collection by incorporation of AI will pave the way for an organized cancer registry as well as deep learning and evidence-based care for health-care providers.[18]

Conclusion

The present study revealed that MobileODT EVA Visual Check helps quicker triage of abnormal screening as it has good sensitivity comparable to physician diagnosis for precancerous lesions and invasive cancer. Although it cannot replace an expert colposcopist, it has great potential as a point-of-care triage. The results of this study suggest that potential modifications are needed in the AI system to improve the specificity and larger multicentric studies including different levels of health-care workers.

Limitations of the present study

It was a single-center study, and the population was hospital based instead of community screening. The sample size was random, so the number of CIN 2+ lesions is small; the diagnostic accuracy of Visual Check for CIN 2+ lesions cannot be fully evaluated. We recommend future multicenter studies on triage incorporating WHO-recommended primary HPV testing in all participants. To evaluate its diagnostic accuracy for CIN 2+ lesions, AVE should be trained and evaluated on a larger cohort of colposcopic images of histologically proven CIN 2+ lesions. It was beyond the purview of the present study. Another limitation of the study was that we did not perform biopsy of Pap smear-negative and physician colposcopic impression-negative cases due to ethical reasons, so there is a possibility of missing some histologically positive cases. To the best of our knowledge, no guideline directs to perform biopsy in such cases. We took Pap smear that is surface biopsy as a surrogate to biopsy in such cases.

Strength of the present study

As compared to most retrospective studies, our study was a cross-sectional study which provided the results of physician's diagnosis, EVA Visual Check, and histopathology which paves the way for future follow-up and review of EVA Visual Check's performance. The study was performed on a random sample of women who were screened for the first time, and our definition of precancer was robust as it was proven by histopathology.

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Conflicts of interest

There are no conflicts of interest.

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