Submitted: 04 June, 2023 Accepted: 20 July, 2023 Published: 15 February, 2024 DOI:10.22514/ejgo.2024.020

SHORT COMMUNICATION

European Journal of Gynaecological Oncology

Evaluation of AI-assisted colposcopy for detecting high-risk subtypes of human papillomavirus in CIN2

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Abstract

Cervical cancer is the second most common cancer in women, and the role of human papillomavirus (HPV) testing in its etiology is becoming increasingly important. We aimed to evaluate the performance of an artificial intelligence (AI)-assisted colposcopy system in detecting high-risk human papillomavirus (HR-HPV) subtypes in cervical intraepithelial neoplasia (CIN) 2 patients. We conducted a *post-hoc* analysis of a previous observational study that developed an AI algorithm for colposcopic images of patients with CIN2. Out of 78 patients with HR-HPVs (HPV 16, 18, 31, 33, 35, 45, 52 and 58), 60 (76.9%) had positive AI colposcopy results. The accuracy, sensitivity and specificity of the AI-assisted colposcopy system in detecting HR-HPVs (16, 18, 31, 33, 35, 45, 52 and 58) were 0.689, 0.769 and 0.537, respectively. This study is the first to focus on using AI to detect high-risk subtypes. The AI algorithm accurately detects the characteristics of HR-HPVs. It can be used to detect high-risk CIN types in patients with cervical dysplasia based only on colposcopic imaging findings and is potentially a valuable tool for follow-up.

Keywords

Colposcopy; Artificial intelligence; Cervical intraepithelial neoplasia; Deep learning; Human papillomavirus

1. Introduction

Cervical cancer (CC) is a malignant tumor that affects many women; more than 600,000 new cases were reported worldwide in 2020, with 340,000 women dying from the disease [1]. CC and precancerous lesions (cervical intraepithelial neoplasia: CIN) are caused by chronic infection with high-risk human papillomavirus (HR-HPV) [2]. Among the HR-HPV types in Japanese women, eight types, including 16, 18, 31, 33, 35, 45, 52 and 58, all have difficulty spontaneously resolving. They are particularly susceptible to progression to CC and require more attention [3]. CC is averted by preventive HPV vaccination and screening [4]. Guidelines have suggested HPV testing as an effective screening method in recent decades; however, only approximately 10% of long-term HR-HPV infections cause CIN or lead to CC [5].

Pathological diagnosis is the gold standard for detecting CIN and CC, and colposcopy is a real-time technique for visualizing and evaluating the cervix to obtain specimens for biopsy [6]. Thus, the biopsy material obtained during colposcopy must be analyzed for an appropriate diagnosis. However, colposcopic biopsies are rarely repeatable and do not always yield samples from the most malignant tumors, resulting in many differences among colposcopists [7]. Therefore, qualified, knowledgeable colposcopists are required. Thus, the diagnostic accuracy of colposcopy must be improved to prevent the wastage of health resources due to overdiagnosis or missing patients [8]. Recently, we developed an artificial intelligence (AI)-assisted colposcopy system that can accurately detect high-grade lesions and predict the prognosis of CIN2 patients based solely on their colposcopy images [9].

HR-HPV testing is essential for managing CIN and determining the appropriate treatment strategies [4]. However, some drawbacks exist: not all facilities test for HR-HPV, several putative positive results exist, and the disease cannot be evaluated in real-time, necessitating follow-up. By contrast, in cases of CIN2, colposcopy should be performed according to guidelines [10]. Knowing the HR-HPV type and recognizing the lesion during colposcopy is beneficial for patient management. This would allow early intervention and prevent inappropriate testing and treatment.

Therefore, in this study, which is the first to focus on using AI to detect high-risk subtypes, we aimed to evaluate the performance of the AI-assisted colposcopy system in detecting high-risk subtypes of HR-HPVs in CIN2.

2. Materials and methods

2.1 Targets for analysis

In this *post-hoc* study, we used 593 images from 119 patients who visited our clinic between 2012 and 2020 and

were diagnosed with CIN2. The results of cytology, colposcopy, targeted histology and HPV examinations were obtained from medical records. We performed colposcopy according to the American Society for Colposcopy and Cervical Pathology (ASCCP) Colposcopy Standards and stratified 593 images. In this study, all patients diagnosed with CIN2 were identified based on pathological findings. To ensure consistent and reliable results, a skilled pathologist, with extensive experience, made these diagnoses.

2.2 HPV testing

We performed HPV typing with the PGMY line blot assay, as previously described [11]. We selected eight HR-HPV subtypes (HPV 16, 18, 31, 33, 35, 45, 52 and 58) most likely to be involved in CIN1,2 progression as HR-HPV positive group in the present analysis [12]. Previous studies have shown a substantial agreement rate of 88.7% between the PGMY line blot assay and the traditionally used MY09/11 assay [13]. This concordance suggests that the PGMY line blot assay can accurately detect HR-HPV subtypes.

2.3 Colposcopy

During the colposcopic examination, 5% acetic acid was applied to the cervix. Colposcopy findings were classified as normal, benign or abnormal (including low-grade, high-grade and cancerous). After applying acetic acid, a punch biopsy was performed if acetowhitening epithelium was observed. A colposcopy-directed biopsy was performed for each suspected lesion area.

2.4 AI system

We used the AI algorithm developed in our previous study [9]. The colposcopic impression of a high-grade lesion of CIN2 was detected by applying explainable AI techniques.

2.5 Statistical analysis

The detection of abnormal colposcopy findings based on the AI system was compared with HR-HPV results. Accuracy, sensitivity, specificity and precision were evaluated.

3. Results

This AI model was trained to associate specific colposcopic image features with HR-HPV infection. The results of a model trained to distinguish between positive and negative outcomes are presented in Fig. 1. The model was trained to differentiate between positive and negative outcomes. The regions highlighted in white or decolorized in the figure represent the regions identified by the model as critical in differentiating these outcomes. A positive AI result predicts infection with one or more specific HR-HPV types (16 or 18) or (16, 18, 31, 33, 35, 45, 52 or 58). Conversely, a negative AI result implies that infection with any of these HR-HPV types is not predicted by the AI model.

Of the 119 CIN2 patients, 73 (61.3%) were positive for HPV16 or 18. Of these 73 cases, 37 (50.7%) were determined to be positive by AI colposcopy. Overall, the diagnostic accuracies of AI colposcopy for detecting HR-HPV (16 or 18) were 0.647, 0.507 and 0.870 in terms of accuracy, sensitivity and specificity, respectively.

Of the 119 CIN2 patients, 78 (65.5%) were positive for HPV16, 18, 31, 33, 35, 45, 52 or 58. Of these 78 cases, 60 (76.9%) were determined to be positive by using AI colposcopy. The diagnostic accuracy of AI colposcopy for detecting HR-HPV (16, 18, 31, 33, 35, 45, 52 or 58) was 0.689, 0.769 and 0.537 in terms of accuracy, sensitivity and specificity, respectively.

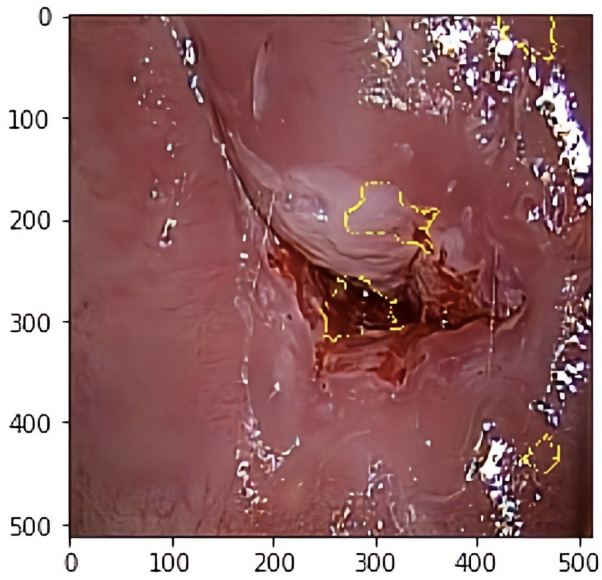

FIGURE 1. Visualization results by Lime based on our learning. The locations of the colposcopic lesions detected by the constructed AI algorithm are circled in yellow.

4. Discussion

CC is the second most common cancer among women worldwide; nevertheless, it is a type of genital cancer that can be prevented by early diagnosis and screening tests [14]. The benefits of primary HPV screening include identifying precancerous lesions, determining the need for biopsy, and the safe lengthening of screening intervals [15]. Current treatment for CIN2 is centered on regular surveillance based on tests for HR-HPV subtypes and colposcopy [16].

The precision rate of the detection of HR-HPV subtypes in this study was 75.9%. This AI algorithm that can extract HR-HPV groups from colposcopy images of CIN2 patients could be of great clinical significance in patient management. For example, real-time evaluation of HR-HPV groups could enable more rapid diagnosis and earlier therapeutic intervention. It could also facilitate follow-up, especially in facilities with limited medical resources. With continuous advancements and further refinement of the AI algorithm, there is potential for it to make valuable contributions to the management of CIN2 patients in the future. These advancements could reduce the dependence on biopsies and enable more personalized observation or treatment approaches.

We noted a substantial increase in sensitivity from 0.507

(Table 1) to 0.769 (Table 2) when incorporating five additional HPV-positive patients. This notable enhancement can be attributed to the introduction of variation through these extra images. Despite their limited quantity, they depicted scenarios not adequately represented in the original dataset. Consequently, these new images expanded the model's training coverage, enhancing its ability to recognize diverse situations. The improved sensitivity, therefore, signifies the model's heightened capacity to accurately identify true positive cases, emphasizing the significance of diverse and comprehensive training data in constructing effective AI models.

TABLE 1. Diagnostic accuracy of differentiating HR-HPV (HPV 16, 18) positive group by AI colposcopy.

	HPV (HPV 16/18)	
	Negative	Positive
AI Colposcopy		
Negative	40	36
Positive	6	37

HPV: human papillomavirus; AI: artificial intelligence.

TABLE 2. Diagnostic accuracy of differentiating HR-HPV (HPV 16, 18, 31, 33, 35, 45, 52, 58) positive group by AI colposcopy.

	HPV (HPV 16/18/31/33/35/45/52/58)	
	Negative	Positive
AI Colposcopy		
Negative	22	18
Positive	19	60

The precision rate for detecting HR-HPVs (16, 18, 31, 33, 35, 45, 52 or 58) in our study was 75.9%. HPV: human papillomavirus; AI: artificial intelligence.

Upon examining the colposcopic images processed by the AI algorithm developed in this study, we observed its recognition of image findings associated with HPV infection, including white lesions (Fig. 1). Previous research indicates that the detection of HPV16, particularly, is associated with high-grade findings, irrespective of the histological diagnosis [17, 18]. Furthermore, HPV16 is understood to cause more extensive lesions than other HPV types, often presenting more pronounced colposcopic abnormalities. Conversely, precancerous lesions associated with HPV18/45 are reported to be more challenging to detect using conventional cytology and colposcopy techniques than those linked with HPV16. Moreover, various studies have highlighted distinctive connections between specific HPV subtypes and the colposcopic findings of CIN [19, 20]. This indicates that although HPV 16 and 18 receive significant attention, other high-risk HPV types are equally important in clinical follow-up. The correlation between colposcopic findings identified by our AI algorithm and HPV subtypes remains not fully explored. However, we anticipate that distinctive imaging patterns corresponding to specific HR-HPV subtypes will emerge. While HPV 16 and 18 are indeed associated with a higher risk of progression, our AI model's increased sensitivity to a wider range of genotypes does not contradict this fact.

The capability of our AI algorithm to identify a subgroup of high-risk HPV types (16, 18, 31, 33, 35, 45, 52 or 58) in this study indicates a promising avenue for utilizing common imaging findings in lesion detection through colposcopic imaging. It also holds potential for risk stratification in CIN patients. Although the preliminary results are encouraging, we acknowledge the need for further refinement to enhance the model's specificity and ultimately fulfill the rigorous criteria required for clinical adoption.

Further investigation is needed to clarify the mechanisms behind the association of colposcopic findings, identified by our AI algorithm, with HPV subtypes and their respective pathological features. Despite these future research needs, this study holds significant value as the first to establish a correlation between colposcopy findings and HPV subtypes in CIN2 patients using an AI algorithm. Furthermore, applying AI-driven colposcopy technology as a real-time monitoring tool offers the potential for innovative strategies for early diagnosis and appropriate therapeutic management of CIN patients.

The use of AI in oncology has increased over the past decade [21]. Colposcopy is a real-time visualization and assessment technique of the cervix for detecting CIN and invasive cancer; the results showed the possibility of detecting HPV subtypes using colposcopy by using an AI algorithm. It has been reported that specific HPV subtypes, such as white lesions, can be detected on high-risk imaging [8], thus confirming the hypothesis that AI can infer HPV subtypes *via* learning from these findings.

A limitation of this study is that many images used have small pixel counts, and the number of training images was minimal; however, improving these aspects would improve the accuracy of the constructed AI algorithm. Another limitation of this study is the relatively small sample size and the single-source nature of the samples. These factors may hinder the generalizability and robustness of the AI model developed in this study. To achieve a more accurate and reliable model, extensive case training, multicenter external validation, and a comparison between human and machine predictions are necessary.

In conclusion, our results indicate that AI-based analysis of colposcopic images can identify HR-HPV groups.

AVAILABILITY OF DATA AND MATERIALS

The data underlying this article will be shared on reasonable request to the corresponding author.

AUTHOR CONTRIBUTIONS

TT—conceptualized the research study and curated the data. HM—performed the formal analysis; designed the software. GT—helped with the funding acquisition; validated the results. TT and GT—performed the research; were the project administrators. TT and HM—designed the methodology; visualized

the results; wrote the original draft. TI, KB, GT and WY—supervised the research. YK, HM, TI and GT—reviewed and edited the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Clinical Research Ethics Review Committee of Keio University Hospital guidelines for clinical research (approval number: 20190165, approval date: 30 September 2019), and was conducted according to the principles of the Declaration of Helsinki. In this retrospective observational study, we adopted an opt-out approach.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2021; 71: 209–249.

[2] Chu D, Liu T, Yao Y. Implications of viral infections and oncogenesis in uterine cervical carcinoma etiology and pathogenesis. Frontiers in Microbiology. 2023; 14: 1194431.

[3] Onuki M, Matsumoto K, Iwata T, Yamamoto K, Aoki Y, Maenohara S, *et al*. Human papillomavirus genotype contribution to cervical cancer and precancer: implications for screening and vaccination in Japan. Cancer Science. 2020; 111: 2546–2557.

[4] Lukic A, De Vincenzo R, Ciavattini A, Ricci C, Senatori R, Ruscito I, *et al*. Are we facing a new colposcopic practice in the HPV vaccination era? Opportunities, challenges, and new perspectives. Vaccines. 2021; 9: 1081.

[5] Hoste G, Vossaert K, Poppe WAJ. The clinical role of HPV testing in primary and secondary cervical cancer screening. Obstetrics and Gynecology International. 2013; 2013: 610373.

[6] Singer A, Monaghan JM, Quek SC, Deery ARS. Human papillomaviruses in pathogenesis of lower genital tract neoplasia. In Singer A, Monaghan JM, Quek SC, Deery ARS (eds.) Lower Genital Tract Precancer: Colposcopy, Pathology and Treatment (pp. 15–33). 2nd edn. Blackwell Publishing: London. 2000.

[7] Wu A, Xue P, Abulizi G, Tuerxun D, Rezhake R, Qiao Y. Artificial intelligence in colposcopic examination: a promising tool to assist junior colposcopists. Frontiers in Medicine. 2023; 10: 1060451.

[8] Fan A, Wang C, Zhang L, Yan Y, Han C, Xue F. Diagnostic value of the 2011 international federation for cervical pathology and colposcopy terminology in predicting cervical lesions. Oncotarget. 2018; 9: 9166–9176.

[9] Takahashi T, Matsuoka H, Sakurai R, Akatsuka J, Kobayashi Y, Nakamura M, *et al*. Development of a prognostic prediction support system for cervical intraepithelial neoplasia using artificial intelligence-based diagnosis. Journal of Gynecologic Oncology. 2022; 33: e57.

[10] Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, *et al*. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. Obstetrics & Gynecology. 2013; 121: 829–846.

[11] Kondo K, Uenoyama A, Kitagawa R, Tsunoda H, Kusumoto-Matsuo R, Mori S, *et al*. Genotype distribution of human papillomaviruses in Japanese women with abnormal cervical cytology. The Open Virology Journal. 2012; 6: 277–283.

[12] Matsumoto K, Oki A, Furuta R, Maeda H, Yasugi T, Takatsuka N, *et al*. Predicting the progression of cervical precursor lesions by human papillomavirus genotyping: a prospective cohort study. International Journal of Cancer. 2011; 128: 2898–2910.

[13] Gravitt PE, Peyton CL, Alessi TQ, Wheeler CM, Coutlée F, Hildesheim A, *et al*. Improved amplification of genital human papillomaviruses. Journal of Clinical Microbiology. 2000; 38: 357–361.

[14] Pimple SA, Mishra GA. Global strategies for cervical cancer prevention and screening. Minerva Ginecologica. 2019; 71: 313–320.

[15] Bhatla N, Singhal S. Primary HPV screening for cervical cancer. Best Practice & Research Clinical Obstetrics & Gynaecology. 2020; 65: 98–108.

[16] Bedell SL, Goldstein LS, Goldstein AR, Goldstein AT. Cervical cancer screening: past, present, and future. Sexual Medicine Reviews. 2020; 8: 28–37.

[17] Zhou Q, Gong Y, Qiu X, Sui L, Zhang H, Wang Y, *et al*. Visual appearance of the uterine cervix differs on the basis of HPV type status in high-grade squamous intraepithelial lesion: the results of a reliable method. BMC Women's Health. 2022; 22: 24.

[18] Rema PN, Mathew A, Thomas S. Performance of colposcopic scoring by modified international federation of cervical pathology and colposcopy terminology for diagnosing cervical intraepithelial neoplasia in a low-resource setting. South Asian Journal of Cancer. 2019; 08: 218–220.

[19] Scheungraber C, Koenig U, Fechtel B, Kuehne-Heid R, Duerst M, Schneider A. The colposcopic feature ridge sign is associated with the presence of cervical intraepithelial neoplasia 2/3 and human papillomavirus 16 in young women. Journal of Lower Genital Tract Disease. 2009; 13: 13–16.

[20] Zaal A, Louwers JA, Berkhof J, Kocken M, Ter Harmsel WA, Graziosi GC, *et al*. Agreement between colposcopic impression and histological diagnosis among human papillomavirus type 16-positive women: a clinical trial using dynamic spectral imaging colposcopy. BJOG: an International Journal of Obstetrics & Gynaecology. 2012; 119: 537–544.

[21] Sone K, Toyohara Y, Taguchi A, Miyamoto Y, Tanikawa M, Uchino-Mori M, *et al*. Application of artificial intelligence in gynecologic malignancies: a review. Journal of Obstetrics and Gynaecology Research. 2021; 47: 2577–2585.

How to cite this article: Takayuki Takahashi, Hikaru Matsuoka, Yusuke Kobayashi, Takashi Iwata, Kouji Banno, Wataru Yamagami, *et al*. Evaluation of AI-assisted colposcopy for detecting high-risk subtypes of human papillomavirus in CIN2. European Journal of Gynaecological Oncology. 2024; 45(1): 143-146. doi: 10.22514/ejgo.2024.020.