Research Article

Concordance and Acceptability of HPV DNA Genotyping Test by Patient's Self-Sampling Against Clinician Sampling

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Abstract

Objectives: To determine the effectiveness of self-sampling method, especially during the COVID-19 pandemic and considering Indonesia's cultural context.

Methods: This study utilized a cross-sectional design, and involved patients at the Gynecology and Colposcopy Clinic of Dr. Cipto Mangunkusumo General Hospital. The estimated sample size was 48, determined using a diagnostic test formula. The sample population consisted of female patients with positive VIA or abnormal Pap smear results. Each patient underwent HPV DNA self-sampling and clinician sampling tests using the GenoFlow HPV Array technique and continued with colposcopy. All patients were also administered a questionnaire consisting of eight questions about their perspective on the self-sampling HPV DNA test. The data analysis employed a 2 × 2 table using SPSS version 20, and Cohen's kappa coefficient was calculated to measure the agreement between the sampling results of patients' and clinicians'.

Results: Among the examinations conducted by clinicians, there were 33 patients with positive HPV results, whereas through self-sampling, there were 28 patients with positive HPV (p=0.00). High risk HPV was the most commonly observed, with HPV type 16 appearing the most (15%). Based on these data, the self-sampling sensitivity, specificity, positive predictive value, and negative predictive value were 85%, 100%, 100%, and 75%, respectively, with a concordance rate of 89.6%. The Cohen's Kappa coefficient between samples taken by the clinician and self-sampling resulted in K=0.778, which is considered a good agreement (K=0.61-0.80). All patients concluded that the procedure was easy (100%), and the majority (60.5%) expressed a preference for the self-sampling method.

Conclusion: There is a good agreement between the results of self-sampling and clinician sampling for detecting HPV DNA, with patients positively accepting the self-sampling method, indicating its potential as an effective cervical cancer screening method.

Keywords: Cervical Cancer Screening, Clinician Sampling, Human Papillomavirus, Self-Sampling.

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INTRODUCTION

Cervical cancer is a malignancy that is commonly experienced by women. Globally, cervical cancer ranks fourth after breast, lung, and colorectum cancers.[1] According to the International Agency for Research on Cancer, there were 660,000 new cases of cervical cancer worldwide in 2022, with 94% occurring in developing countries. Approximately 350,000 deaths were attributed to cervical cancer, accounting for 14.1% of cancer-related deaths among women.[2] In Indonesia, Globocan reported that there was an increase in the incidence and mortality rates due to cervical cancer with 36,964 cases (23.3 per 100,000 women) and 20,708 deaths (13.2 per 100,000 women).[2]

High-risk Human Papillomavirus (HPV) infections, particularly types 16 and 18, are the primary causes of cervical cancer. The disease often shows no clear signs or symptoms until it reaches an advanced stage, leading to delayed diagnosis and treatment. Therefore, the World Health Organization (WHO) recommends HPV

vaccination before individuals become sexually active as a means of cervical cancer prevention. Early detection methods such as Visual Inspection with Acetic Acid (VIA), Pap smears, and testing for high-risk HPV strains are also suggested.[3]

HPV DNA examination is an early detection method for cervical cancer that uses amplification techniques. The GenoFlow HPV Array (DiagCor) is a recognized tool for HPV DNA genotyping, capable of detecting high-risk HPV strains, which can significantly impact patient management. Patients with negative test results have a very low likelihood of developing cervical cancer, with the test showing a sensitivity of up to 90% and a specificity of 84.61%.[4] The combined use of HPV DNA examination and Pap smear achieves a sensitivity of 93.7% for detecting cervical intraepithelial neoplasia grades 2 and 3 (CIN 2/3). In contrast, a Pap smear alone has a sensitivity of 60%, while HPV DNA examination alone has a sensitivity of 85% for detecting high-grade lesions.[3]

Sample collection for the GenoFlow HPV Array (DiagCor) examination can be performed by clinicians or independently by the patient. Self-sampling for HPV DNA testing involves using vaginal specimens and is considered more acceptable for women who are reluctant to undergo VIA or a Pap smear due to cultural reasons or discomfort. This method allows women to perform the test at home, offering greater convenience. It also reduces logistical and financial burdens while enhancing privacy and comfort.[6]

The Directorate of Diseases Prevention and Control of the Indonesian Ministry of Health reported that the screening coverage in 2021 was still around 6.8%.[7] Indonesia, with its diverse educational levels and habits, adds another layer of complexity. Cultural and normative differences also influence the acceptance rates of this examination. Self-sampling of the HPV DNA test presents as an alternative to cervical cancer screening. This is expected to enhance the cervical cancer screening coverage in Indonesia, thus reducing the incidence of cervical cancer. Therefore, this study aimed to determine the accuracy and patient perspective of a self-sampling HPV DNA genotyping test for cervical cancer detection.

METHODS

This study was a diagnostic test utilizing a cross-sectional design to determine the accuracy of self-sampling HPV DNA examination in women with positive VIA or Pap smear results at Dr. Cipto Mangunkusumo General Hospital (RSCM). The approach of this research was qualitative, as the information or data to be presented consisted of statements of both positive and negative outcomes, both from the self-sampling results of patients and direct examinations conducted by clinicians. This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was granted by the Ethics Committee of the Faculty of Medicine, University of Indonesia (KET-280/UN2.F1/ETIK/PPM.00.02/2022).

The sample population consisted of female patients who visited the Gynecology and Colposcopy Clinic at the RSCM with positive VIA or abnormal Pap smear results. Each patient underwent HPV DNA self-sampling using cervical sampling brush and clinician sampling, and continued with colposcopy. The population consideration was based on the population with positive VIA results, as the likelihood of obtaining a positive HPV DNA result was higher than that of normal patients, and adding a normal population results in higher costs. The sample size in this study was estimated using two diagnostic test formulas. We reviewed both these calculations and obtained an estimated sample size of 48.

The data collection technique used in this study employed a limited consecutive sampling from March 1st to August 31, 2022. All patients fulfilled the inclusion criteria, and no exclusion criteria were requested for their willingness to participate. The data underwent analysis using SPSS version 20. In order to ascertain sensitivity, specificity, positive predictive value, and negative predictive value, a diagnostic test employing a 2 × 2 table was employed. Cohen's Kappa coefficient was also calculated to measure the agreement between the patients' and Clinicians' sampling results. The interpretation of the Cohen's kappa coefficient as following <0.20 = poor, 0.21-0.40 = fair, 0.41-0.60 = moderate, 0.61-0.80 = good, >0.80 = very good.[8]

Patient perspectives were assessed using a questionnaire to evaluate concerns when taking samples independently, perceived concerns, ease of use of self-sampling, preferred sampling method, problems encountered in screening, affordable and reasonable price for self-examination of HPV DNA, interest in routine HPV DNA testing every 1-3 years, and the desire to convey the subject of independent HPV DNA

testing to friends and relatives. The questionnaire will be presented in the form of a descriptive table, using percentages.

RESULTS

The research subjects were selected based on inclusion criteria and were conducted at Gynecology and Colposcopy Clinic in RSCM from March 1st to August 31, 2022, resulting in a total of 48 subjects. As shown in **Table 1**, among the examinations conducted by clinicians, 33 patients (68.75%) had positive HPV results, whereas 28 patients (58.33%) had positive HPV results through self-sampling. The p-values comparing the two examination methods were p= 0.00 (p<0.05).

Table 1. Comparison between Examinations Conducted by Clinician and Self-sampling

Variable	Positive HPV		Negative HPV		P-value
	N	%	N	%	
Clinician Sampling	33	68.75	15	31.25	0.00
Self-Sampling	28	58.33	20	41.67	

Self-sampling sensitivity, specificity, positive predictive value, and negative predictive value were 85%, 100%, 100%, and 75%, respectively. We also calculated Cohen's Kappa coefficient between samples taken by clinicians and samples taken by patients, resulting in a kappa value of 0.778. From this kappa value, it can be concluded that the level of agreement between patients and clinician's sampling results is good agreement (*K*=0.61-0.80).

The types of HPV detected by either method of sampling are presented on **Table 2**. High-risk HPV was the most commonly observed, with HPV type 16 appearing the most frequently (15%). Identification of two low-risk HPV types were also found in both samples. Concordance was observed in 43 pairs (28 positive for the same HPV types and 15 negative). In general, there was an 89.6% agreement rate (43 out of 48 pairs) between the outcomes acquired through HPV DNA testing via self-sampling and clinician sampling.

Table 2. HPV Type in Clinician and self-sampling results

HPV Type	Clinician Sampling (N)	Self-Sampling (N)
HR 16	5	4
HR 16, 18	1	1
HR 16, 59	1	1
HR 18	2	2
HR 18, 58	1	1
HR 33	2	2
HR 39	1	-
HR 39, 56	1	-
HR 45	2	2
HR 51	3	3
HR 52	1	-
HR 52, 53	1	1
HR 52, LR 44	1	1
HR 53	1	1
HR 56	1	1
HR 56, 58	1	1
HR 58	3	3
HR 66	1	-
HR 66, LR 43	1	1
HR 68, LR 43	1	1
LR 42, 81	1	1
LR 81	1	1
Negative	15	20

Table 3. Patient Perspective on HPV DNA Self-Sampling Test

Question	Number of Patients (N)	(%)
Concerns when taking samples independently		
Yes	20	41.7
No	28	58.3
Perceived concerns		
Painfull	10	21
The sample taken is not good	7	15
The sampling tool falls	7	7
Others	1	2.1
Ease of use of self-sampling		
Easy	48	100
Difficult	0	0
Do not know	0	0
Preferred sampling method		
By clinician	19	39.5
Self-sampling	29	60.5
Problems encountered in screening		
Fear of precancerous or cancerous results	42	87.5
Facilities (Hospital) away from home or office	4	8.4
Feeling unnecessary because there are no symptoms/pain	5	10.5
Transport issues	2	4.2
The cost of the examination is quite expensive	18	37.5
If the result is positive, it is feared that the cost will be expensive	25	52.1
Not approved by the husband/spouse	5	10.5
Affordable and reasonable price for self-examination of HPV DNA		
<500,000 rupiah	37	77
500,000-1,000,000 rupiah	9	18.7
>1,000,000 rupiah	2	4.3
Interest in routine HPV DNA testing every 1-3 years		
Yes	46	95.8
No	2	4.2
Desire to convey the subject of independent HPV DNA testing to friends and relatives		
Yes	48	100
No	0	0

In **Table 3**, where questionnaire responses were collected from patients after undergoing the examination, 28 patients (58.3%) expressed concerns about conducting self-sampling. The greatest concern was related to pain during the examination, with 10 patients (21%) mentioning it. After self-sampling, all patients concluded that the procedure was easy (100%), and the majority of patients (29 patients, 60.5%) expressed a preference for the self-sampling method. A significant proportion of patients (42 patients, 87.5%) were admitted to being fearful of undergoing screening, as a positive result might lead to worries. According to the questionnaire, the anticipated cost of the self-sampling method was <500,000 rupiah (37 patients, 77%).

DISCUSSION

In developing countries, cervical cancer is often detected at advanced stages, leading to high mortality rates. According to Globocan data from 2022, there were 36,964 new cases of cervical cancer in Indonesia, out of a total of 69,886 cases in Southeast Asia. The estimated number of deaths due to cervical cancer was 20,708 out of 38,703 cases in the same region. This makes Indonesia the highest-ranking country in Southeast Asia in terms of new case detection and cervical cancer-related deaths. Cervical cancer is prioritized in Indonesia due to the low coverage of screening and early detection efforts.

Our study found that high-risk HPV type 16 was the most frequent (15%). This was consistent with the study which reported HPV 16 (18.4%) as the most prevalent type among the 61 HPV DNA genotypes.[9] Chan et al. also demonstrated HPV type 16 to be the most detected virus worldwide, with it being responsible for around 32% of all infections in South Asia alone.[10]

The self-sampling tests in this study generated a sensitivity, specificity, positive predictive value, and negative predictive value of 85%, 100%, 100%, and 75%, respectively. Several studies have examined the accuracy of self-sampling HPV DNA tests compared to those obtained by clinicians. A study conducted in India found that the diagnostic values between self-sampling and clinician sampling did not significantly differ. In self-sampling, the sensitivity, specificity, positive predictive value, and negative predictive value were 66.7%, 98.1%, 83.3%, and 95.3%, respectively.[11] In a study which investigated the effectiveness of self-sampling for HPV DNA testing in Ghana, the results were highly promising. Self-sampling exhibited a sensitivity and specificity of 92.6% and 95.9%, respectively. The concordance with samples collected by clinicians was also high, at 94.2% with a kappa value of 0.88.[12]

Our study also observed a high concordance rate between the self-sampling and clinician sampling results. Overall, a 89.6% concordance rate was observed between the tests for combined high- and low-risk types. This percentage is consistent with other studies, such as those conducted in Netherlands showed concordance rates of 96.8%.[13] A study conducted in Brazil also revealed that 88% of self-collected HPV DNA test results matched samples collected by clinicians.[14] A study in Singapore showed sensitivity 83.3%, specificity 94.6%, positive predictive value 79.4%, negative predictive value 95.8%, accuracy 93.3% and kappa value of 0.77.[15]

Cohen's kappa coefficient was also calculated to assess the agreement between samples collected by clinicians and those taken by patients. The resulting kappa value of 0.778 falls within the range indicative of good agreement (K=0.61-0.80). A study conducted in India also found that HPV DNA testing with self-sampling yielded diagnostic values equivalent to those obtained with clinician-collected samples at 94.1% with a kappa of 0.73.[11] This value would further increase when combined with other screenings, such as VIA or Pap smear. A study in

Hongkong showed a kappa value of 0.652.[16] This signifies a robust level of consistency between the two sampling methods employed by patients and clinicians. Our findings suggest reliable and good agreement in the sampled data, highlighting the strong concordance between the samples obtained from both clinicians and patients during the study. These values led to the conclusion that self-sampling can be performed when there is a limited availability of human resources in particular area.

Based on questionnaires administered to patient samples, there is a reluctance to undergo early detection of cervical cancer due to the fear of receiving a positive diagnosis and discomfort with examinations. However, they preferred screening by self-sampling in future tests because of their ease of use. This finding is consistent with other research conducted in Argentina, a middle-income country, which 85.8% accepted self-sampling as a screening method.[17] Another study in Malaysia, 84.5% also found that self-sampling was easy and 81.7% good experience about it.[18] A study in Thailand showed 91.5% women felt comfort and 80.8% rated very good to excellent for overall experience compared to clinician collected method.[19] Other study in USA showed that 59.1% preferred self HPV testing with 82.7% said the reason more convenient, easier, and time saving.[20] In a study conducted in Norway, the majority of respondents concluded that self-sampling was easy to perform (94.5%), painless (90.7%), and devoid of embarrassment (89.7%), as it was performed independently.[21] These findings align with the results of the study

CONCLUSION

There is a good agreement between the results of self-sampling and clinician sampling for detecting HPV DNA, with patients positively accepting the self-sampling method, indicating its potential as an effective cervical cancer screening method.

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CONFLICT of INTEREST

There is no conflict of interest associated with this article.

DATA AVAILABILITY STATEMENT

The authors affirm that the data supporting the findings of this research are accessible within the article and its supplementary resources.

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