**Concordance of Cervical Cancer Screening Methods in a Low-Resource Setting**

Abstract:

Background: Cervical cancer remains a significant public health challenge, particularly in low-resource settings where access to advanced screening technologies is limited. Visual Inspection with Acetic Acid (VIA) and Visual Inspection with Lugol’s Iodine (VILI) are often employed as feasible alternatives to HPV testing. Understanding the concordance between these methods and HPV testing is essential for optimizing screening strategies.

Objective: This study aims to evaluate the concordance of VIA and VILI with HPV testing for cervical cancer screening in the low-resource setting of Imo State, Nigeria.

Materials and Methods: A cross-sectional study was conducted from February to June 2023 across three geopolitical zones of Imo State, Nigeria. A total of 257 women underwent screening using VIA, VILI, and HPV DNA testing. Statistical measures, including sensitivity, specificity, Cohen’s kappa value, and Youden’s Index, were employed to assess concordance.

Results: Among the 257 participants, HPV positivity was 43.6%, while VIA and VILI positivity rates were 11.3% and 28.8%, respectively. VIA demonstrated a sensitivity of 18.8%, specificity of 94.5%, positive predictive value (PPV) of 72.4%, and negative predictive value (NPV) of 60.1%. VILI showed higher sensitivity (42.0%) but lower specificity (81.4%), with a PPV of 63.5% and NPV of 64.5%. Cohen’s kappa values for VIA and VILI were 0.142 and 0.243, respectively, indicating slight to fair agreement with HPV testing. Youden’s Index values were 0.133 for VIA and 0.234 for VILI, reflecting low overall diagnostic performance.

Conclusion: VIA and VILI demonstrated limited sensitivity and low concordance with HPV testing. While VILI showed relatively better performance, both methods exhibited poor agreement with HPV testing, underscoring the need for improved screening approaches. Combining visual methods with more sensitive techniques may enhance diagnostic accuracy and effectiveness in low-resource settings. Further research is warranted to refine visual inspection methods and explore integrated screening strategies.

**Introduction:**

Cervical cancer is a significant public health issue and in 2022, contributed 660,000 new cases and 350,000 deaths globally1. Cervical cancer rates are worse in low resource countries with attendant high mortality2. This is due to limited access to high quality health care.

Cervical cancer screening with early detection and treatment has been shown to reduce the morbidity and mortality of cervical cancer in developed countries3. Unfortunately the availability of different screening methods varies greatly across the world. In low resource settings, screening and treatment with HPV with or without visual inspection with acetic acid has been prescribed by ACOG 4.

Visual Inspection with Acetic acid, a systematic application of acetic acid on the cervix with observation of the squamo-columnar junction under good light source, usually without magnification for aceto-white lesions. This test is popular in communities where capacity for cytology based tests are not readily accessible. Mid-level manpower can provide these services readily and under supervisionbut has a high negative predictive value of over 99%4. According to Goel et al, VIA remains a feasible alternative in the absence of HPV testing5. They concluded from their study that a single-visit or two-visit approach with the VIA method could reduce the lifetime risk of cervical cancer by 25% and HPV DNA testing could reduce it by 36%.

Screening is said to be optimal when the lowest resource is used to achieve greatest benefit5. HPV testing while being the preferred method of screening for cervical cancer , has the drawback of detecting many infections that may not progress to pre-cancer lesions or even cancer especially in women below 30 years of age. Up to 86.7% of HPV positive women did not develop cervical cancer or pre cancer after follow over 10 years6.

Evaluating the concordance (agreement) between different cervical cancer screening methods in such environments is vital to ensure effective, accessible, and reliable screening options. Existing methods for cervical cancer screening include Pap Smear (Cytology), Visual Inspection with Acetic Acid (VIA), Visual Inspection with Lugols Iodine (VILI), and Human Papillomavirus (HPV) Testing. The effectiveness of several screening methods available for detecting cervical cancer precursors may vary based on the context of the healthcare system. The concordance between screening methods is crucial in determining the reliability and utility of a screening program. Some key factors that influence the concordance of cervical cancer screening methods in low-resource settings include Accuracy and Sensitivity, Infrastructure and Equipment Availability, Training and Expertise, Cost and Feasibility, Screening Frequency and Access, Community Acceptance. This study focuses on accuracy and sensitivity.

Concordance studies compare the results of two or more screening methods to determine how well they agree in detecting cervical cancer precursors. In low-resource settings, studies have shown that VIA has shown moderate to good concordance with Pap smears, particularly in settings where infrastructure is limited. However, VIA tends to have lower sensitivity than Pap smears, which could lead to missed cases of precancerous lesions 7. For VIA and HPV testing, VIA tends to have lower sensitivity than HPV testing but may still be a viable alternative in low-resource settings. Concordance between VIA and HPV testing can vary, with some studies showing reasonable agreement, while others show significant discrepancies8. HPV testing generally has a higher sensitivity for detecting high-grade cervical lesions than Pap smears. In studies where both tests are available, concordance tends to be high, but there are still concerns about HPV testing’s cost and access limitations9. Simpler, low-cost methods like VIA and VILI, although having slightly lower accuracy, can still play an essential role in cervical cancer prevention, particularly when combined with other strategies like self-sampling for HPV10. This study is an excerpt from a component of a larger study.

Objectives:

To determine the concordance of visual screening methods with HPV testing in screening for cervical cancer in low resource setting of Imo state, Nigeria.

## Material & Methods

This was a cross-sectional study carried out in the community outreaches in the three geopolitical zones of Imo state Nigeria from February, 2023 to June, 2023. A total of 257 women were screened following a convenience sampling. The exclusion criteria included being pregnant, having had a hysterectomy, having a cancer diagnosis or treatment, active bleeding and never being sexually active.

Ethical approval of the study protocol was obtained from the Institutional Review Board of Federal Medical Centre, Owerri. Bulk and individual consent was obtained and in privacy, the cervix was carefully examined. Dry cervical swab was collected for HPV DNA testing. Thereafter, the cervix was painted with 5% acetic acid and the squamocolumnar junction and transformation zone were carefully observed for aceto white lesions. This was followed with painting with Lugol’s Iodine and inspection for areas of poor uptake of the Lugol’s Iodine / mustard yellow on the cervix which is taken as VILI positive.

The dry cervical swabs were stored in a refrigerator at 2-8oC in waiting for HPV DNA/ viral studies at the Infectious Disease and Molecular Epidemiology laboratory of the Department of Public Health, Federal University of Technology*,* Owerri, Imo State, Nigeria.

The high risk HPV DNA test of the Atila biosystems was used for the assay. The Atila AmpFire HPV High-risk genotyping assay is an isothermal nucleic acid amplification assay for qualitative genotyping of high-risk types of human papillomavirus (HPV).The assay genotypes HPV 16,18,31,33,35,39,45,51,52,53,56,58,59,66,68. Detection of any of the hr HPVs was taken as a HPV positive status11.

Data analyses

Data analysis was done with SPSS version 27. The sensitivity, specificity, positive and negative predictive values of the visual screening tests described above (VIA and VILI) were analyzed using DNA test result as the reference standard. The Cohen’s kappa value and **Youden’s Index were further determined.**

**RESULT**

A total of 257 women were screened using VIA and VILI screening as well as HPV testing which served as the reference standard. The results were as follows: 29 out of 257 women tested positive with VIA (11.3%), 74 out of 257 tested positive for VILI (28.8%) while 112 out of 257 women tested positive for HPV DNA. (43.6%).

**Diagnostic Accuracy of VIA Screening Compared to HPV Testing as the reference Standard for Cervical Cancer Screening.**

When VIA was compared with HPV DNA testing for screening of these women, the following observations were made: True Positives (TP): 21; False Positives (FP): 8; False Negatives (FN): 91; True Negatives (TN): 137; Total HPV-positive cases (reference standard): 112; Total HPV-negative cases (reference standard): 145. These resulted in the diagnostic accuracy metrics of VIA as follows: Sensitivity: 18.8%; Specificity: 94.5%; Positive Predictive Value (PPV): 72.4% and Negative Predictive Value (NPV): 60.1% (Table 1) The Cohen’s kappa value was 0.142 and **Youden’s Index was 0.133**

**Table 1: Diagnostic Accuracy of VIA Screening Compared to HPV Testing as the Gold Standard for Cervical Cancer Screening**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **VIA SCREENING** | **HPV POSITIVE** | **HPV NEGATIVE** | **TOTAL** | **PERFORMANCE** | **METRICS** |
| **RESULT** | **(RS)** | **(RS)** |  | **PPV** | **NPV** |
| **VIA ABNORMAL** | 21 (TP) | 8 (FP) | 29 | 72.4% |  |
| **VIA NORMAL** | 91 (FN) | 137 (TN) | 228 |  | 60.1% |
| **TOTAL** | 112 | 145 | 257 |  |  |
| **PERFORMANCE METRICS** |  |  |  |  |  |
| **SENSITIVITY** | 18.8% |  |  |  |  |
| **SPECIFICITY** |  | 94.5% |  |  |  |

*RS (REFERENCE STANDARD)*

*TP (TRUE POSITIVE); FP (FALSE POSITIVE); TN (TRUE NEGATIVE); FN (FALSE NEGATIVE)*

*Sensitivity = TP / (TP + FN) × 100*

*Specificity = TN / (TN + FP) × 100*

*Positive Predictive Value (PPV) = TP / (TP + FP) × 100*

*Negative Predictive Value (NPV) = TN / (TN + FN) × 10*

**Diagnostic Accuracy of VILI Screening Compared to HPV Testing as the reference Standard for Cervical Cancer Screening**

A total of 257 women were screened using VILI screening and HPV testing (reference standard). True Positives (TP) were 47; False Positives (FP): 27; False Negatives (FN): 65; True Negatives (TN): 118. Total HPV-positive cases (reference standard) were 112 while 145 participants tested negative using the HPV testing. The Diagnostic Accuracy Metrics of VILI compared to HPV testing were: Sensitivity: 42.0%; Specificity: 81.4%; Positive Predictive Value (PPV): 63.5% and Negative Predictive Value (NPV): 64.5% (Table 2). The Cohen’s kappa for the VILI screening compared to HPV testing is **0.243**, while the Youden’s Index was 0.234

**Table 2: Diagnostic Accuracy of VILI Screening Compared to HPV Testing as the Gold Standard for Cervical Cancer Screening**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **VILI SCREENING** | **HPV POSITIVE** | **HPV NEGATIVE** | **TOTAL** | **PERFORMANCE** | **METRICS** |
| **RESULT** | **(RS)** | **(RS)** |  | **PPV** | **NPV** |
| **VILI ABNORMAL** | 47 (TP) | 27 (FP) | 74 | 63.5% |  |
| **VILI NORMAL** | 65 (FN) | 118 (TN) | 183 |  | 64.5% |
| **TOTAL** | 112 | 145 | 257 |  |  |
| **PERFORMANCE METRICS** |  |  |  |  |  |
| **SENSITIVITY** | 42.0% |  |  |  |  |
| **SPECIFICITY** |  | 81.4% |  |  |  |

*RS (REFERENCE STANDARD)*

*TP (TRUE POSITIVE); FP (FALSE POSITIVE); TN (TRUE NEGATIVE); FN (FALSE NEGATIVE)*

*Sensitivity = TP / (TP + FN) × 100*

*Specificity = TN / (TN + FP) × 100*

*Positive Predictive Value (PPV) = TP / (TP + FP) × 100*

*Negative Predictive Value (NPV) = TN / (TN + FN) × 100*

Discussion

This study examines the diagnostic accuracy of Visual Inspection with Acetic Acid (VIA) and Visual Inspection with Lugol’s Iodine (VILI) in screening for cervical cancer when compared to HPV testing, which is considered the reference standard in this study. Note that the HPV test seeks evidence of the virus in samples from the cervix. When the performance of VIA screening was compared to HPV testing (used as the reference standard), in 21 cases where VIA identified HPV-positive women, 8 cases where VIA incorrectly identified HPV-negative women as positive, while in 91 cases where VIA did not identify HPV-positive women (i.e., missed cases). 137 cases where VIA correctly identified HPV-negative women.

The positivity for HPV, VIA and VILI were 43.6%, 18% and 28.8% respectively. This compares with the study in Kenya were the overall positivity were 32.5% and 7.1% for HPV and VIA respectively. In that study, the agreement between HPV status and VIA diagnosis had a Kappa of − 0.002 (95%CI − 0.053 to + 0.049). This implied little or no agreement in both tests and the two will provide inconsistent results12. In this study The Cohen’s kappa value was 0.142 and suggests slight agreement between the HPV and VIA tests while the **Youden’s Index of 0.133** indicates that **VIA has poor overall diagnostic performance** in detecting HPV-positive cases. The low sensitivity significantly reduces the test's effectiveness, despite a high specificity.

The most concerning result from this study is VIA's low sensitivity (18.8%). This means that VIA misses a large proportion of HPV-positive women who might be at risk for cervical cancer. In practice, this could result in women who are actually HPV-positive not receiving timely follow-up or treatment. The high specificity of VIA (94.5%) is a positive aspect. It means that when the test is negative, it is quite reliable in identifying women who do not have HPV, reducing the likelihood of false-positive results. The PPV and NPV values suggest that VIA can be somewhat reliable in identifying women who are HPV-positive (72.4% chance) and HPV-negative (60.1% chance), but these values still indicate that there is room for improvement, especially in ruling out HPV-negative women as false negatives are still a concern.

Visual Inspection with Lugol’s Iodine (VILI) on the other hand had a sensitivity of 42.0% which is relatively low, meaning that VILI missed a significant portion of women who actually had HPV infections (False Negatives = 65). VILI, therefore is not as effective in detecting HPV-positive cases, and there is a substantial risk of failing to identify women who may need further investigation or treatment. A specificity of 81.4% is relatively high, meaning that VILI is good at ruling out women who do not have HPV infections (or cervical abnormalities). However, there is still an 18.6% chance that VILI incorrectly classified HPV-negative women as positive (False Positives = 27). The PPV of 64.5% is moderate and implies that further confirmation is needed for women who test positive for VILI. The Cohen’s kappa for the VILI screening compared to HPV testing is **0.243,** which indicates **fair agreement** between the two tests. The Youden’s Index (JJJ) a summary measure of the diagnostic test performance, was 0.234 and suggests that the VILI test has **low discriminatory power** in distinguishing between HPV-positive and HPV-negative cases.

# Many HPV tests are adjudged to by up to 99% accurate with a sensitivity of 100% and specificity (90.6%) compared to VIA with sensitivity of  31.6% and specificity = 87.5%). sensitivity = 31.6%; specificity = 87.5%).13 A Systematic reviews and meta-analyses of the accuracy of HPV tests, visual inspection with acetic acid, cytology, and colposcopy reported differences in sensitivity of HPV when compared with VIA to be 95% compared to 60%.14

While VIA has a high specificity, its low sensitivity and moderate predictive values suggest that it is not a reliable alternative to HPV testing for cervical cancer screening. The low sensitivity means that VIA may fail to detect many women who are at risk of cervical cancer, making it less effective in preventing the disease compared to HPV testing. However, the HPV positive women who tested negative to VIA or VILI could be interpreted as not having cellular changes on their cervix. The HPV test looks for evidence of the virus in samples from the body

The findings indicate the need for further research into improving VIA or combining it with other screening methods to increase its diagnostic accuracy. VILI screening, although promising in low-resource settings, shows relatively low sensitivity compared to HPV testing. This means that while it may be helpful in ruling out disease (due to its relatively high specificity), it is less effective at detecting true positives, which could result in missed cases. Therefore, VILI may serve as a useful initial screening tool, but it should be combined with more sensitive tests like HPV testing to improve the overall diagnostic accuracy and reduce the risk of false negatives in cervical cancer screening programs.

These findings are however not completely out of place because VIA and VILI are detecting pre-cancer lesions whereas HPV testing will show both new and persistent infections of HPV, bearing in mind that the new HPV infections could be wiped out without progression to pre -cancer lesions detectable by visual methods.

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