



DIAGNOSTIC ACCURACY OF P16INK4A IN LIQUID BASED CYTOLOGY CELL BLOCK IN DETECTING PRE-INVASIVE AND INVASIVE LESIONS OF CERVIX IN CASES POSITIVE BY VISUALS METHODS

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ABSTRACT

Background: Cervical cancer remains a major public health concern, particularly in low-resource settings. Visual Inspection with Acetic Acid (VIA) is widely used for screening, but its high false positivity necessitates effective triaging methods. Biomarkers such as p16INK4a may improve diagnostic accuracy when applied to liquid-based cytology (LBC). **Aim:** diagnostic accuracy of p16INK4a immunostaining in LBC for detecting pre-invasive and invasive cervical lesions in VIA-positive women. **Methods:** This prospective study included premenopausal women aged 30–50 years attending the gynecology OPD who underwent opportunistic screening using VIA. Out of 700 women screened, 70 VIA-positive cases were enrolled. LBC samples were collected prior to colposcopy for cytology and immunostaining (p16INK4a). **Results:** The mean age of participants was 42.7 ± 4.99 years, with most women belonging to lower socioeconomic groups. Common presenting complaints included vaginal discharge (45.7%) and lower abdominal pain (24.3%). VIA showed limited diagnostic accuracy with high false positivity rates. LBC demonstrated high sensitivity and specificity for detecting CIN1+ and CIN2+ lesions. Among VIA-positive women, 30% were positive for p16INK4a. **Conclusion:** p16INK4a and immunostaining on LBC samples is a promising and effective method for triaging VIA-positive women. It improves detection of high-grade cervical lesions, reduces unnecessary referrals, and can be implemented in low-resource settings to enhance cervical cancer screening programs.

INTRODUCTION

Cervical cancer is a major health concern worldwide, especially in low- and middle-income countries, with Asia contributing to about half of the global burden. Infection with Human Papillomavirus (HPV), particularly high-risk types 16 and 18, is the main cause of cervical cancer. Screening methods such as conventional Pap smear, liquid-based cytology (LBC), HPV testing, and visual inspection (VIA/VILI) help in early detection and prevention. While HPV testing and LBC offer higher sensitivity, VIA remains a cost-effective option in low-resource settings but requires further evaluation of positive cases.^[1,2,3]

Newer biomarkers like p16INK4a and Ki-67 are being studied for their role in identifying high-risk cases. p16INK4a is associated with HPV-related cellular changes, while Ki-67 indicates cell proliferation.^[4] Using

these markers on LBC samples may help triage VIA-positive patients more effectively, especially in resource-limited settings. This proposed study aims to evaluate the diagnostic usefulness of p16INK4a for improving cervical cancer screening and management.^[5]

AIM

To study the accuracy of p16INK4a staining in Liquid based cytology cell block in detecting pre-invasive and invasive lesion of cervix in cases positive by visual methods.

OBJECTIVES

1. To study the accuracy of VIA in detecting pre-invasive and invasive lesions of cervix.
2. To study the accuracy of LBC in detecting pre-invasive and invasive lesions of cervix.

3. To compare p16INK4a immunostaining with colposcopy for detecting pre-invasive and invasive lesions of cervix.

MATERIAL AND METHODS

This study was conducted in the Department of Obstetrics & Gynecology and Department of Pathology

in VMMC & Safdarjung Hospital from October 2019 and March 2021 (18 months).

STUDY DESIGN: Cross-Sectional Study

To get a total of 70 VIA positive women, 700 premenopausal women attending the Gynaecology OPD of Safdarjung hospital were screened, the prevalence of VIA positivity in women attending gynae OPD.

RESULTS

Table 1: Distribution of the Participants in Terms of VIA (n = 70).

VIA	Frequency	Percentage	95% CI
Positive	70	100.0%	93.5% - 100.0%

Table 1: In present study 100.0% of the participants had VIA positive. 0.0% of the participants had VIA Negative.

47.1% for $\geq$ CIN1. And diagnostic accuracy of VIA positive 27.1%, PPV 27.1% and False positivity rate 72.9% for $\geq$ CIN2.

In present study results were diagnostic accuracy of VIA positive 52.9%, PPV 52.9% and false positivity rate

Table 2: Association Between Liquid Based Cytology and p16 (n = 70).

p16	Liquid Based Cytology					Fisher's Exact Test	
	NILM	ASCUS/ASC-H	LSIL	HSIL	Total	χ^2	P Value
Positive	0 (0.0%)	9 (47.4%)	6 (85.7%)	6 (100.0%)	21 (30.0%)	43.362	<0.001
Negative	38 (100.0%)	10 (52.6%)	1 (14.3%)	0 (0.0%)	49 (70.0%)		

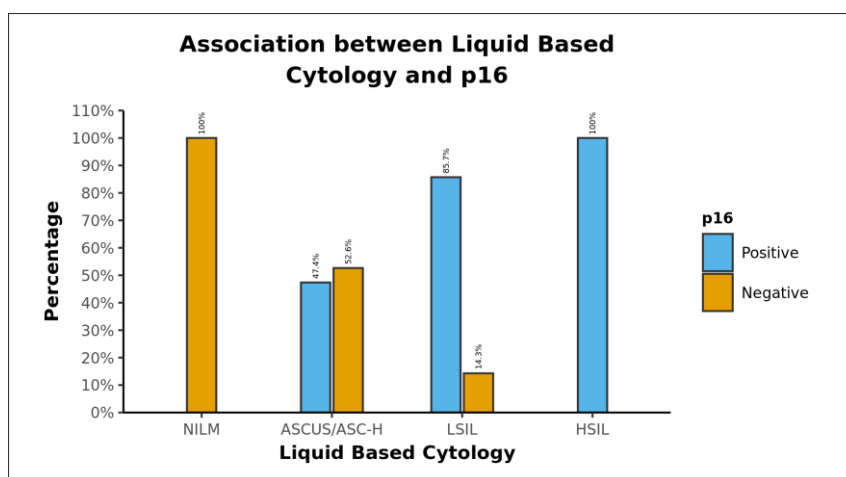


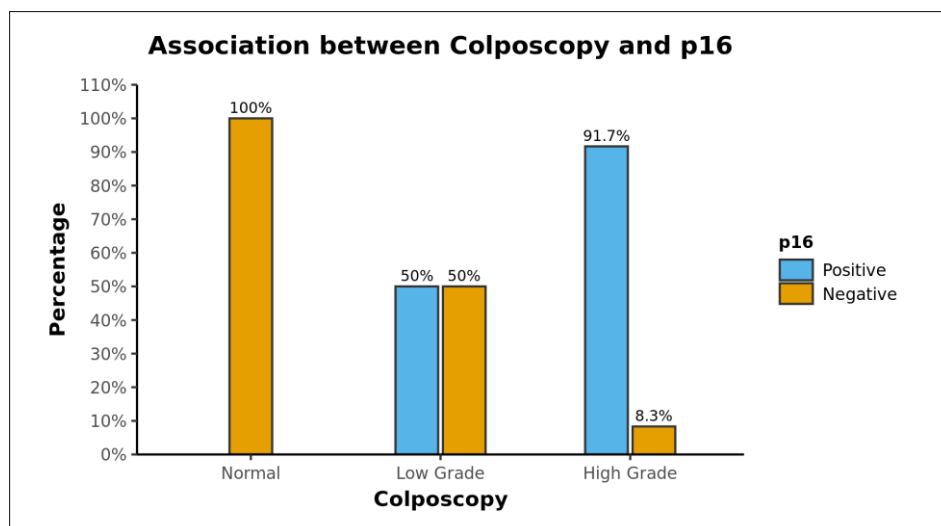
Table 3: Distribution of the Participants in Terms of p16 (n = 70).

p16	Frequency	Percentage	95% CI
Positive	21	30.0%	19.9% - 42.3%
Negative	49	70.0%	57.7% - 80.1%

Table 3: Our of total 70 VIA positive women 21 (30%) were positive and 49(70%) were negative.

Table 4: Association Between Colposcopy and p16 (n = 70)

p16	Colposcopy				Chi-Squared Test	
	Normal	Low Grade	High Grade	Total	χ^2	P Value
Positive	0 (0.0%)	10 (50.0%)	11 (91.7%)	21 (30.0%)	41.825	<0.001
Negative	38 (100.0%)	10 (50.0%)	1 (8.3%)	49 (70.0%)		
Total	38 (100.0%)	20 (100.0%)	12 (100.0%)	70 (100.0%)		



By applying chi square test, p value obtained was <0.001 which implies there is significant relation between p16 positivity and colposcopy findings.

Table 4: Out of 21 p16 positive cases 10 showed in low grade lesion on colposcopy and 11 positive cases in high grade on colposcopy lesion. Out of 49 p16 negative cases 38 in normal on colposcopy, 10 negative cases in low grade on colposcopy lesion and 1 case negative on high grade lesion on colposcopy.

Table 5: Association Between Biopsy Impression and p16 (n = 70).

p16	Biopsy Impression			Chi-Squared Test	
	Positive	Negative	Total	χ^2	P Value
Positive	21 (100.0%)	0 (0.0%)	21 (100.0%)	26.757	<0.001
Negative	16 (32.7%)	33 (67.3%)	49 (100.0%)		
Total	37 (52.9%)	33 (47.1%)	70 (100.0%)		

Table 5: By applying chi square test, p value obtained was <0.001 which implies there is significant relation between p16 positivity and biopsy findings.

Table 6: Association Between p16 and Biopsy (n = 70)

Biopsy	p16			Fisher's Exact Test	
	Positive	Negative	Total	χ^2	P Value
Chronic Cervicitis	0 (0.0%)	1 (2.0%)	1 (1.4%)	53.766	<0.001
Squamous Metaplasia	0 (0.0%)	32 (65.3%)	32 (45.7%)		
CIN 1	3 (14.3%)	15 (30.6%)	18 (25.7%)		
CIN 2	10 (47.6%)	1 (2.0%)	11 (15.7%)		
CIN 3	5 (23.8%)	0 (0.0%)	5 (7.1%)		
SCC	3 (14.3%)	0 (0.0%)	3 (4.3%)		
Total	21 (100.0%)	49 (100.0%)	70 (100.0%)		

By applying chi square test, p value obtained was <0.001 which implies there is significant relation between p16 positivity and biopsy findings.

Table 6: P16 showed linear relation with increasing grade of squamous dysplasia. Also p16 positivity was seen in 16.6% cases of CIN1, 90.9% cases of CIN2, 100% cases of CIN3 and 100% cases of SCC.

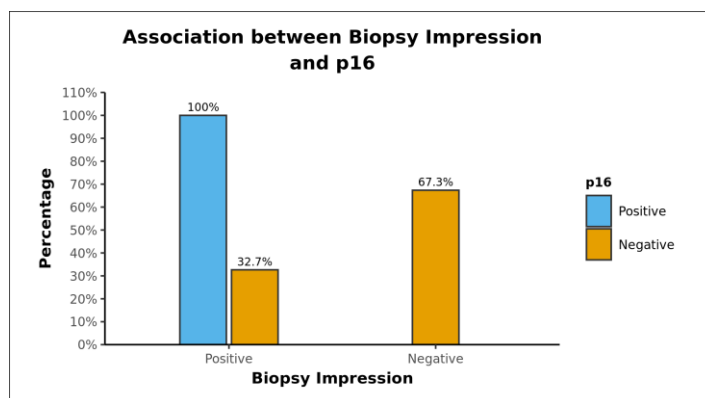


Table 7: Comparison of Sensitivity, Specificity, PPV and NPV CIN1+ and CIN2+ Vs P16.

P16 immunostaining	CIN1+ or more	CIN2+ or more
Sensitivity	56.8% (39-73)	94.7% (74-100)
Specificity	100.0% (89-100)	94.1% (84-99)
PPV	100.0% (84-100)	85.7% (64-97)
NPV	67.3% (52-80)	98.0% (89-100)

Table 7: By comparing p16 immunostaining results with biopsy finding Sensitivity, Specificity, PPV and NPV for CIN 1 or more was 56.8%, 100%, 100% and 67.3% respectively and for CIN2 or more 94.7%, 94.1%, 85.7% and 98% respectively.

DISCUSSION

India has the highest number of cervical cancer deaths, and although Pap smear screening is effective, it is difficult to implement widely due to limited infrastructure and shortage of skilled professionals. Therefore, the Government of India recommends a low-cost “screen and treat” approach using VIA, which can be performed by paramedical staff in resource-limited settings. VIA-positive women are referred for further management at higher health facilities, where treatment such as cryotherapy may be provided.

However, VIA has limitations, including high false-positive rates leading to unnecessary referrals, risk of overtreatment, and missed high-grade lesions. Due to a shortage of trained colposcopists, effective triaging of VIA-positive women is essential. HPV testing is not always practical because of cost and limited availability.

Immunostaining with biomarkers p16INK4a and Ki-67 has emerged as a promising triaging method. These markers help identify women with high-grade cervical lesions more accurately and can be analyzed even by trained healthcare workers with minimal resources. The study proposes a novel approach of using p16 and Ki-67 immunostaining on LBC cell block samples from VIA-positive women. This single-sample method can support cytology, HPV testing, and immunohistochemistry, potentially reducing unnecessary referrals and easing the burden on healthcare systems while improving detection of serious cases.

Age distribution

The women in present study were recruited from reproductive age group, 30-50 years. Mean age was 42.71 years and standard deviation (± 4.99). Majority were in the group of 40-45 years age interval.

One big study done by Luthra et al screened 68,436 women and result showed that the mean age of mild, moderate and cervical dysplasia was 33.8%, 35.2% and 40.2% years respectively.^[7]

Oster AG et al studied in South Indian population and found that the average age of mild dysplasia was 31.4 years, severe dysplasia 34.7 years and invasive carcinoma 42.2 years.^[8] Thus the prevalence of invasive cancer seems to increase with age, though all grades of dysplasia can be seen at all ages.

Accuracy of VIA in present study

In present study results were diagnostic accuracy of VIA positive 52.9%, PPV 52.9% and false positivity rate 47.1% for $\geq$ CIN1. And diagnostic accuracy of VIA positive 27.1%, PPV 27.1% and False positivity rate 72.9% for $\geq$ CIN2.

Landy R, Castanon A, et al in 2015 reported at first cytology 259 precancerous lesions and squamous cell carcinoma diagnosed in women aged 40–69 and 78 in women aged ≥ 70 . The sensitivity of cytology $\geq$ HSIL for was 89% and 83% respectively, and the number of women needed to test to identify one cancer was 404 (95% confidence interval [CI]: 355–462) and 226 (95% CI: 177–292) respectively. There was 17–22% reduction in case fatality with early detection of preinvasive and invasive lesion in women > 66 years of age.^[9]

Lim AW, Landy R et al in 2016 concluded cervical cytology as well established screening test to detect pre-invasive cervical lesions (high-grade cervical

intraepithelial neoplasia). They estimated prevalence of cervical cancer among symptomatic women was between 0.4% and 0.9%. They found sensitivity of cytology for moderate dyskaryosis (high-grade squamous intraepithelial lesion [HSIL]) or worse in women aged 20–29 years was 90.9% to 96.2% and the PPV was estimated to be between 10.0% and 30.0%.^[10]

P16^{INK4a} in cytology

Various studies have evaluated the usefulness of the immunocytochemical detection of the biomarkers as potential markers of dysplasia in cervical cytology preparation.

Results showed in present study Sensitivity, Specificity, PPV and NPV of p16ink4a in CIN1+ lesions as 56.8%, 100%, 100% and 67.3% respectively and for CIN2+ lesions as 94.7%, 94.1%, 85.7% and 98% respectively.

Jane L Meyer et al in 2007 performed a study for evaluation of p16 expression in Pap smear and demonstrated that out of 47 women with CIN1 and 26 women with CIN2, 29 and 25 were positive for p16

respectively concluding that the sensitivity and specificity of p16 for detecting CIN2 or more was 62% and 96% respectively.^[11]

N Wentzensen et al in 2012 concluded in their study on 625 women referred for colposcopy that sensitivity and specificity of p16/ki67 for detecting CIN2 or more was 85.5% and 59.4% respectively. P16/ki67 for triage of LSIL and HPV+ve ASCUS could decrease the colposcopy referrals by 54.5%.^[12]

Sun L et al in 2018 reported that some contradictory results declaring p16 IHC lacks utility in cases of morphologically obvious CIN2, as the stain is positive in a majority of cases. The LAST recommendation to use p16 IHC to support all diagnosis of CIN2 will result in performing the immunostain in many circumstances where it is not medically necessary. Among cases that are p16 negative, many have compelling high-grade morphology. The LAST perspective that the stain trumps histology may allow false-negative IHC results to prevail.^[13]

Other studies on diagnostic performance of p16ink4a by different authors

Table 8: Diagnostic performance of p16ink4a.

STUDY	Year	Population studied	SENSITIVITY	SPECIFICITY	PPV	NPV
Present study for CIN1+	2021	70 VIA POSITIVE	56.8%	100%	100%	67.3%
Present study for CIN2+	2021	70 VIA POSITIVE	94.7%	94.1%	85.7%	98%
Lalita V et al ¹⁴	2020	50 VIA Positive	87.5%	97.06%	93.3%	94.2%
Desai F et al ¹⁵	2019	350	100%	93.7%	-	-
Ding L et al ⁵	2019	6257	75%	67.1%	32.4%	92.7%
Hebbbar A et al ⁶	2017	50	76.2%	87.5%	96.9%	41%

Thus p16 immunostaining allowed precise identification of CIN1 lesions that are associated with HR-HPV types, CIN2, CIN3 and cervical cancers in biopsy sections. This helped to reduce false positivity and negativity thereby significantly improving the cervical cancer and pre cancer detection in tissue specimen and conventional Pap smear.

However, studies reported that P16 was rarely detected in benign squamous mucosa or CIN 1 lesions that are associated with LR-HPV.^[16]

Advantage of p16 over Pap cytology

- p16ink4a immunostaining can differentiate transient HPV infection from persistent HPV infection that have already initiated neoplastic transformation and may overcome the current limitations of VIA triage.
- p16ink4a immunostaining is based on morphological evaluation of cervical smears and can be performed with a higher interobserver agreement than with Pap cytology and may detect high grade CIN with high sensitivity and specificity.
- p16ink4a/Ki-67 dual-staining cytology is of great significance in screening and triaging VIA positive in camp setting and in remote areas for cervical cancer and precancerous lesions.

- It provides a good risk marker for the stratification of HPV-positive women, including normal cytological patients, and for the identification of high-grade CIN from women diagnosed as ASCUS or LSIL.
- Compared with Pap cytology and HPV detection, it has higher sensitivity and specificity in detecting cervical precancerous lesions and cervical cancer.
- This is also helpful for the diagnosis of cervical glandular lesions.
- The combination of p16/Ki-67 dual-staining and HP-HPV detection is recommended as a strategy for monitoring women treated for high-grade CIN.
- It is believed that p16/Ki-67 dual-staining cytology has broad application prospects in the diagnosis and treatment of cervical cancer.
- Same LBC sample can be sent for HPV testing which is the latest recommendation by WHO. It will also help in co-testing in further follow up and test of cure.

SUMMARY

- The present study was carried out in Department of Obstetrics and Gynaecology, VMMC and Safdarjung Hospital, New Delhi in Collaboration with the Department of Pathology from May 2019 to

March 2021.

- Aim of present study was “Diagnostic accuracy of p16 ink4a staining in liquid-based cytology in detecting pre-invasive and invasive lesions of cervix in cases positive by visual methods”.
- Premenopausal women between age group 30-50 years coming to Gynaecology OPD with any complaint had opportunistic screening for cancer cervix by visual inspection using acetic acid (VIA). Screen positive women who gave consent for the study were asked to come for colposcopy. Prior to colposcopy, liquid based cytology was taken for cytology, p16ink4a and ki67 immunostaining. We have screened 700 women attending Gynaecology OPD out of which 70 VIA positive. However, the calculated sample size 43.
- Women in our study population ranged between 30-50 years. The mean age was 42.71 year and standard deviation was ± 4.99 years. It was observed that majority of women screened positive were aged between 40-45 years.
- Majority of women belonged to upper lower and lower middle socioeconomic class according to Modified Kuppuswamy Scale.
- Age at marriage was 18-20 years in 42.9%, 21-25 years in 55.7% and 26-30 years in 1.4% of women screened VIA positive.
- In present study 14.3% women were para 1, 40% women were para 2, 31.4% women were para 3 and 14.3% women were more $\geq$ para 4.
- In present study commonest presenting symptoms was discharge per vagina in 45.7% women followed by lower pain abdomen in 24.3% women.
- In present study results were diagnostic accuracy of VIA positive 52.9%, PPV 52.9% and false positivity rate 47.1% for $\geq$ CIN1. And diagnostic accuracy of VIA positive 27.1%, PPV 27.1% and False positivity rate 72.9% for $\geq$ CIN2.
- Liquid Based Cytology results were compared with biopsy findings Sensitivity, Specificity, PPV and NPV for CIN 1 or higher lesions was 86.5%, 100%, 100% and 86.8% respectively and for CIN2 or higher lesions was 100%, 74.5%, 59.4% and 100% respectively.
- Out of total 70 VIA positive women 21 were p16ink4a and ki67 positive and 49 were negative p16ink4a and ki67. Percentage of IHC positivity in VIA positive patients was 30%
- Out of 70 VIA positive 20 (28.6%) showed low grade lesion on colposcopy, 12 (17.1%) showed high grade lesion on colposcopy and 38 (54.3) showed in normal on colposcopy.
- The histopathological diagnosis of 70 women in our study were benign (squamous metaplasia and chronic cervicitis) in 33 women (47%). CIN 1 in 18 women (25.7%), CIN 2 in 11 women (15.7%), CIN 3 in 5 women (7.1%) and squamous cell carcinoma in 3 women (4.3%).
- p16ink4a immunostaining results were compared

with biopsy findings Sensitivity, Specificity, PPV and NPV for CIN 1 or higher lesions was 56.8%, 100%, 100% and 67.3% respectively and for CIN2 or higher lesions was 94.7%, 94.1%, 85.7% and 98% respectively.

CONCLUSION

We concluded that p16ink4a in LBC cell block are accurate pre-invasive and invasive lesion of cervix with Sensitivity, Specificity, PPV, NPV of combined p16ink4a for CIN1+ or higher lesions was 56.8%, 100%, 100%, and 67.3% and for CIN2+ or higher lesions was 94.7%, 94.1%, 85.7% and 98.0%.

Hence, we recommended immunostaining of p16ink4a to be used of larger scale for triaging women who were screened positive by VIA (visual inspection acetic acid).

Table 9: Comparison of Sensitivity, Specificity, PPV and NPV CIN1+ and CIN2+ Vs P16.

P16 immunostaining	CIN1+ or more	CIN2+ or more
Sensitivity	56.8% (39-73)	94.7% (74-100)
Specificity	100.0% (89-100)	94.1% (84-99)
PPV	100.0% (84-100)	85.7% (64-97)
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Table 9: By comparing p16 immunostaining results with biopsy finding Sensitivity, Specificity, PPV and NPV for CIN 1 or more was 56.8%, 100%, 100% and 67.3% respectively and for CIN2 or more 94.7%, 94.1%, 85.7% and 98% respectively.

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