ORIGINAL ARTICLE

Immunohistochemical Expression of Ki67 in Relation to Colposcopic Findings in Pateints with Cervical Intra Epithelial Neoplasia

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Abstract

Background: ***Cervical cancer develops from cervical intraepithelial neoplasia(CIN) grades I, II, and III, which are a defined set of preneoplastic lesions characterized by progressive cellular abnormalities. Over the past 20 years, numerous epidemiological studies have found that HPV types 16 and 18, which are considered high risk, are strongly associated with cervical cancer in as many as 95% of cases.***

Aim of the work: ***To study Immunohistochemical Expression of(Ki-67) in relation to colposcopic findings in patients with cervical intraepithelial neoplasia (CIN1, CIN2, and CIN3).***

Patient and method: ***This Prospective Cross-Section Interventional Study was conducted in colposcopy unit at Al-Zahraa University Hospital, data was collected from April 2021 till June 2023. Including 306-patients those attended to colposcopy unit. All of them subjected to Pap smear, colposcopic examination, cervical biopsy and Ki67 immunohistochimechal staining.***

Results: ***Researchers found a statistically significant correlation between CIN patients' levels of sexual activity and their Ki-67 expression scores. As a means of predicting CIN, this study found that colposcopy had a PPV of 52.2% and a sensitivity of 92.2% and a specificity of 30.1%. This study showed that sensitivity and specificity of Ki67 as immmunohistochemical marker in prediction of CIN were 84.4%, 100% respectively and its PPV is 100%.***

Conclusion: ***Sensitivity and specificity of colposcopy as method of prediction of CIN were 92.2%,30.1% respectively and its PPV is 52.2% comparing to immunohistochemestry sensitivity and specificity of Ki67 as immmunohistochemical marker in prediction of CIN were 84.4%, 100% respectively and its PPV is 100% which means that Ki67 improve accuracy of prediction of CIN.***

Keywords: CIN; Ki67; Colposcopy; Immunohistochemical Marker

1. Introduction

With an estimated 600,000 new cases and 340,000 fatalities in 2020, cervical cancer ranks as the fourth most frequent malignancy in women globally. Cervical cancer is more common and deadly in nations with low or medium socioeconomic levels. Major inequalities in access to cervical screening, treatment, and national HPV vaccination programs, as well as other social and economic factors, are to blame for this. [1]

Cervical intraepithelial neoplasia(CIN) grades I, II, and III are a sequence of preneoplastic lesions characterized by progressive cellular abnormalities that ultimately give rise to cervical cancer. Over the past 20 years, numerous epidemiological studies have found that HPV types 16 and 18, which are considered high risk, are strongly associated with cervical cancer in as many as 95% of case.[2]

The retinoblastoma protein(Rb) and the p53 transcription factor are two tumor suppressor genes that are severely impacted in cervical cancer cells. Cervical cancer develops due to the interplay of signaling pathways regulated by Rb and p53.[3]

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When cells divide and multiply, the Ki-67 protein is a key player. It has been utilized as a proliferation marker in multiple cancers, including cervical carcinoma, and its antigen is expressed throughout the cell cycle with the exception of the G0 phase.[4]

According to the description, the colposcopy machine is an upgraded version of the original device developed by Hinselmann. The addition of an ultraviolet light source and a camera made colpophotography possible, allowing for a magnified binocular study of the cervix. The Anglo-Saxon culture was hesitant to adopt colposcopy, even though it became prevalent in gynecological practice across Europe, Southern America, and Australia by the 1950s. This might have been due in part to the dearth of educational resources available at the time or to the fact that British gynecologists shunned the contentious Hinselmann because of his involvement in the war. The first colposcopy was performed in the British Isles thirty years after its development, and soon after, the procedure gained global acceptance as a diagnostic tool for cervical cancer screening programs.[5]

The method's acknowledged shortcomings, particularly inter-observer variability, are not surprising given that colposcopy is a visual diagnostic technique. Most clinicians now use Reid's Colposcopic Index, which was developed in the late 1980s and gives an objective score for grading the severity of cervical lesions. Compared to the former, the more recent Swede score, which takes lesion size into account, may be more applicable in contexts with limited resources.[6]

Colposcopic features in patients with cervical intraepithelial neoplasia(CIN1, CIN2, andCIN3) were correlated with immunohistochemical expression of(Ki-67).

The goal is to improve the accuracy of CIN prediction and decrease the number of false negative results from colposcopy in order to lower the number of missed cases of CIN.

2. Patients and methods

This prospective cross-sectional study was conducted in Al-Zahraa University Hospital(unit of colposcopy) during the period from April 2021 to 2023.

Selection criteria:

The study was included 70-attendances of unite of colposcopy at Obstetrics and Gynecology Department of Al-Zahraa HospitalAl-Azhar University. All candidate women were subjected to informed consent after explaining the aim of the search for every Patient.

Inclusion criteria:

Any patient selected for a subject colposcopic examination at the Obstetrics and Gynecology Department of Al-Zahraa Hospital, Al-Azhar University.

Exclusion criteria:

Patient diagnosed with cervical cancer, Patient with cervical surgery, Patient with normal biopsy, and Patient with general condition not suitable for examination.

Methodology:

After an informed written consent, the participants were subjected to the following:

Full history taking including: Personal, history of the Patient, Personal, history of her husband: Menstrual history, Contraceptive history, Obstetric history, Past medical history, Past surgical history(cervical surgery or D&C), and Family history: history of malignancy or similar condition. Analysis of the Patient's complaint, which varied from contact bleeding to Masses felt. Chronic pelvic pain. Dyspareunia. And Recurrent vaginal discharge. The Patient's complaints (onset, course, duration, and associated symptoms) were analyzed. Patient preparation(precautions): If the Patient is known to have an active lower genital tract infection at the time of examination, an antimicrobial agent is prescribed to her according to analysis of her complaint at least 7 days before cervical examination. The Patient was informed that she must avoid menstruating at the time of examination, vaginal douching, intercourse, vaginal Medication, vaginal contraception for a minimum of 24-48 hours before examination.

Pap smear: Procedure was performed without anesthesia in the lithotomy position. The Cusco speculum is applied for full visualization of the cervix. Ayres spatula was positioned to best fit the ectocervix, straddle the SCJ, and sample the distal endocervical canal as it firmly scraped the cervical surface at least one full rotation. Applied to two slides, one for the ectocervical specimen and one for the endocervical specimen. Fixation of the specimens obtained by 95% alcohol.

Colposcopy: Procedure was performed without anesthesia in the lithotomy position. The Cusco speculum is applied to explore the cervix and upper vagina. The cervix was washed with normal saline to remove the mucus. General look for any growth pathology(hypertrophy, papillomatosis, ectopia, erosion, ulcer), surface contours, and vascular pattern. The cervix is washed with acetic acid 3-5% and immediate observation of any aceto-white areas is considered a positive finding(due to reversible denaturation of cellular proteins). Under colposcopic vision, a single punch biopsy was taken from the most suspicious lesions(positive aceto-white and /or positive Schiller's iodine).

Biopsy: At the same setting and after visualization of the cervix and vagina, 210 of the patients with grossly and colposcopically suspicious cervices, a single punch biopsy was taken from the most suspicious area of each cervix, preserved in 10% formaline, and sent for histopathological examination at the pathology Department in Al-Zahraa University Hospital at once. Histopathological diagnosis was performed by expert pathologists.

Immunohistochemistry (IHC): Patients with CIN were referred to immunohistochemistry for Ki67 staining(77 patients represent our study group), using the automated Ventana staining machine; Before being placed in an endogenous peroxide block for 10 minutes, sections that had been paraffin-embedded and formalin-fixed were dewaxed in xylene and rehydrated using graded alcohol. Microwave antigen retrieval was carried out for a duration of fifteen minutes. Applying 1% horse normal serum in buffered saline to slices for 5 minutes prevented non-specific staining. The sections were incubated at room temperature for 1 hour after being coated with Anti-Ki-67(1:300; mouse monoclonal, MIB-1; DAKO, Glostrup, Denmark) antibody. An Ultravision LP kit from Lab Vision, which contains a horseradish peroxidase polymer, was used for 10 minutes to detect antibody binding. The chromogen employed was a solution of diaminobenzidine tetrahydrochloride(Kit HK153-5K; Biogenex, San Ramon, CA).

Statistical analysis:

The data was input into the Statistical Package for the Social Sciences(IBM SPSS) version 23 after it had been edited, coded, and gathered. If the quantitative data were parametric, it was shown as mean, standard deviation, and range; if it was non-parametric, it was shown as median, inter-quartile range(IQR). Quantitative and qualitative characteristics were also displayed using percentages and numbers. The Chi-square test was used to compare the groups using qualitative data. Using the One-Way ANOVA test, we compared more than two groups using quantitative data and a parametric distribution. The Kruskal-Wallis test was used for comparisons involving more than two groups, where the data were quantitative and did not follow a normal distribution. To evaluate sensitivity, specificity, PPV, NPV, and the accuracy of colposcopy and KI67, a qualitative version of the receiver operating characteristic curve(ROC) was utilized. We allowed a 5% margin of error and put the confidence interval at 95%. Accordingly, the following is why the p-value was deemed significant: "Highly significant"(HS) is denoted by a P-value less than 0.01, while "nonsignificant"(NS) is denoted by a P-value greater than 0.05.

		CIN	
		Negative	Positive
X/X	Negative	TN	FN
	Positive	FP	TP

The following formulas can be used to calculate values:PPV=TP/Total positive(TP+FP) and NPV=TN/Total Negative(TN+FN). The accuracy formula is (TP+TN)/Total number of patients. We used these equations to determine the sensitivity, specificity, net present value(NPV), and positive predictive value(PPV) of Ki67 expression and colposcopy in patients with chronic cervicitis(negative CIN) and as a control group in patients without CIN.

3. Results

Table 1 showed that, the mean of the age of CIN patients was 41.68-years and ranged between 18-69-years with 8.17 SD, the median of parity of our study group was3 and ranged between 0-9.

Table 1. Demographic data of CIN patients.

		No=77
Age(Years)	Mean±SD	41.68±8.17
	Range	18-69
Parity	Median(IQR)	3(2-4)
	Range	0-9
BMI(kg\m^2)	Mean±SD	32.25±5.34
	Range	22.04-48.83

Table 2 showed that, there was statistically highly significant difference between grading groups of CIN as regard colposcopic finding with p-value 0.000 which mean increase suspicion of colposcpic findings associated with prediction of high grade of CIN

Table 2. Relation between CIN grading and colposcopic finding.

Colposcopy	CIN 1		CIN 2		CIN 3		Test value*	P-value	Sig.
	No.	%	No.	%	No.	%			
No	6	10.0%	0	0.0%	0	0.0%	24.473	0.000	HS
Suspicious cervix and +ve lugols iodine and -ve acitowhite area	44	73.3%	7	50.0%	1	33.3%			
Suspicious cervix and -ve lugols iodine	8	13.3%	1	7.1%	0	0.0%			

and +ve acitowhite area :suspicius cervix and +ve lugols iodine and +ve acitowhite area	2	3.3%	6	42.9%	2	66.7%

* P-value<0.05 indicates significance(S); P-value<0.05 indicates non-significant(NS); and P-value<0.01 indicates highly significant(HS).Chi-square analysis

With a P-value of 0.00, Table 3 demonstrated, a statistically significant difference between the groups with Ki67 expression scores and the colposcopic results. This indicates that an increase in Ki67 expression corresponds to a higher suspicion of colposcopic findings.

Table 3. Relation between Ki67 expression score and colposcopic findings.

Colposcopy	Ki67 score 0		Ki67 score 1		Ki67 score 2		Ki67 score 3		Test value	P-value	Sig.
	No.	%	No.	%	No.	%	No.	%			
No	2	16.7%	3	6.8%	1	6.7%	0	0.0%	29.684	0.000	HS
Suspicious cervix and +ve lugols iodine and -ve acitowhite area	8	66.7%	34	77.3%	8	53.3%	2	33.3%			
Suspicious cervix and -ve lugols iodine and +ve acitowhite area	1	8.3%	7	15.9%	1	6.7%	0	0.0%			
Suspicious cervix and +ve lugols iodine and +ve acitowhite area	1	8.3%	0	0.0%	5	33.3%	4	66.7%			

P-value>0.05:Non-significant (NS);P-value<0.05:Significant (S); P-value<0.01:highly significant(HS)
*:Chi-square test

Table 4 showed that, there was statistically highly significant difference between CIN groups and expression of Ki67 with p-value 0.000 which mean increase grades of CIN corresponding to increase expression of Ki67 score.

Table 4. Relation between CIN grades in biopsy and Ki67 score.

Ki67 score	CIN 1		CIN 2		CIN 3		Test value*	P-value	Sig.
	No.	%	No.	%	No.	%			
Score 0	12	20.0%	0	0.0%	0	0.0%	78.010	0.000	HS
Score 1	43	71.7%	1	7.1%	0	0.0%			
Score 2	5	8.3%	10	71.4%	0	0.0%			
Score 3	0	0.0%	3	21.4%	3	100.0%			
Total	*60*	*100.0%*	*14*	*100.0%*	*3*	*100.0%*			

*P-value<0.05 indicates significance(S);P-value<0.05 indicates non-significant (NS); and P-value<0.01 indicates highly significant(HS).Chi-square analysis

To calculate Sensitivity, Specificity, NPV, PPV and accuracy of Ki67 expression and colposcopy patients with CIN considered(positive CIN) as case group and patients with chronic cervicitis(negative CIN) considered as control group.

Table 5 showed negative (true and false) and positive(true and false) values of Ki67 expression.

Table 5. Comparison of Ki67 expression in positive and negative(chronic cervicitis) patients.

KI67 score	CIN				Test value*	P-value	Sig.
	Negative(chronic cervicitis)		Positive				
	No.	%	No.	%			
Negative(Score 0)	93	100.0%	12	15.6%	127.106	0.000	HS
Positive(Score >0)	0	0.0%	65	84.4%			

*P-value>0.05 indicates non-significant(NS);P-value<0.05 indicates significant(S);and P-value<0.01 indicates highly significant(HS).chi-squared analysis

Table 6 showed that, sensitivity and specificity of Ki67 as immmunohistochemical marker in prediction of CIN were 84.4%, 100% respectively and its PPV is 100%.

Table 6. Predictive value of Ki67 expression in patient with CIN lesions.

PARAMETER	TP	TN	FP	FN	ACCURACY	SENSITIVITY	SPECIFICITY	PPV	NPV
KI67 SCORE	65	93	0	12	92.9%	84.4%	100.0%	100 %	88.6 %

TP:true positive, TN:true negative, FP:false positive, FN:false negative, PPV positive predictive value, NPV:negative predictive value.

Table 7 showed that, sensitivity and specificity of colposcopy as method of prediction of CIN were 92.2%, 30.1% respectively and its PPV is 52.2%.

Table 7. Predictive value of colposcopy in patient with CIN lesions.

PARAMETER	TP	TN	FP	FN	ACCURACY	SENSITIVITY	SPECIFICITY	PPV	NPV
COLPOSCOPY	65	28	71	6	58.2%	92.2%	30.1%	52.2%	82.3%

TP:true positive, TN:true negative, FP:false positive, FN:false negative, PPV positive predictive value, NPV:negative predictive value.

CIN, Ki67;Colposcopy;Immunohistochemical Marker

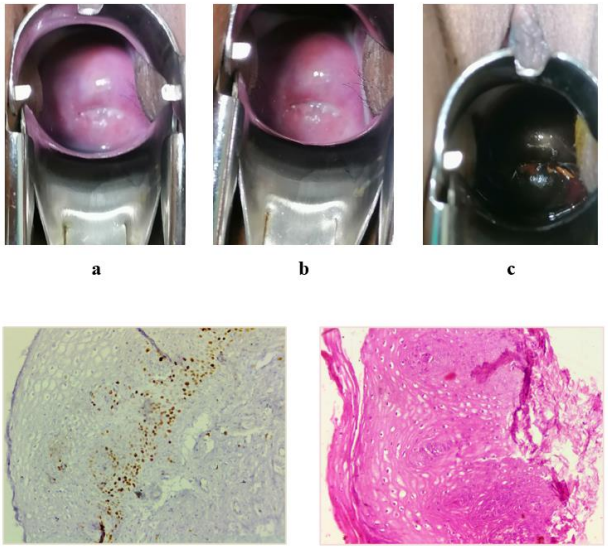

Figure 1. a-Gross picture of the cervix.b-Cervix after application of acetic acid(normal appearance).c-cervix after application of lugols iodine (normal appearance).d-Ki67 expression(score-1). e-H&E histopathological results(CIN1).

Case (2):CIN 1 with Ki67 score(2).

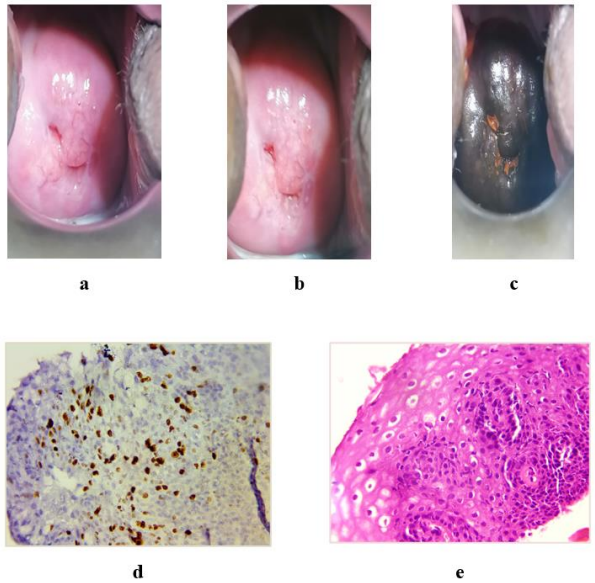

Figure 2. a-Gross picture of the cervix.b-Cervix after application of acetic acid (positive acetowhite areas).c-Cervix after application of lugols iodine (negative lugols iodine).d-Ki67 expression (score-2).e-H&E histopathological results(CIN1)

Case (4):CIN2 with Ki67 score(3).

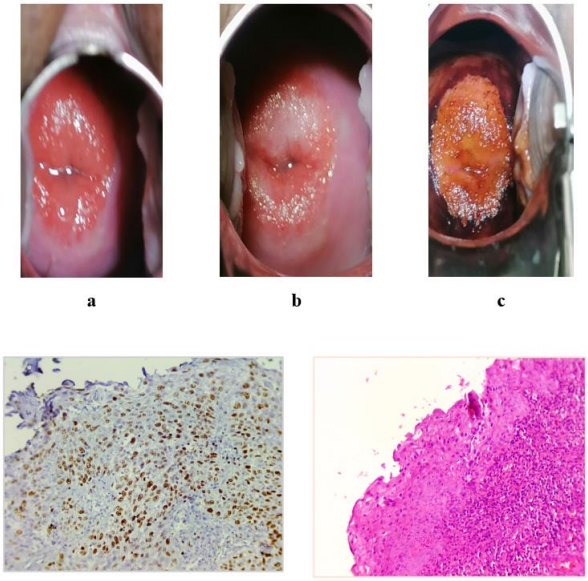

Figure 4. a-Gross picture of the cervix.b-Cervix after application of acetic acid (positive acetowhite areas).c-cervix after application of lugols iodine (positive lugols iodine).D-Ki67 expression (score-3).e-H&E histopathological results(CIN2).

Case (5):CIN3 with Ki67 score(3).

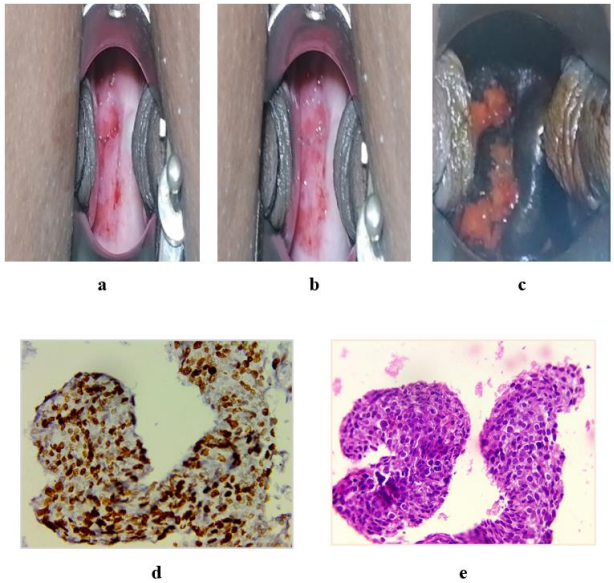

Figure 5. a-Gross picture of the cervix.b-Cervix after application of acetic acid(positive acetowhite areas).c-cervix after application of lugols iodine (positive lugols iodine).d-Ki67 expression(score-3).e- H&E histopathological results(CIN3).

4. Discussion

A p-value of 0.000 indicates that there was a statistically significant difference between the study population's CIN staging groups(histopathology) and the colposcopic findings, suggesting that a high grade of CIN is associated with more suspicious colposcopic findings.

According to Fan et al.,[7] clinicopathological analysis of 2262 patients, 1482-patients(65.5%) had a perfect match between colposcopic diagnosis and cervical biopsy pathology, with a p-value of less than 0.01. Colposcopic findings and CIN grade(histopathology) were found to be statistically significantly related(P-value 0.0001) in a prospective research by Rema et al.,[8] that included 56-patients.

This study showed a statistically highly significant difference among CIN grading groups (histopathology) and expression of immunohistochemical marker(Ki67) with a p-value of 0.000. As Ki67 expressed in 80%(48/60 patients) of CIN1 patients, 100%(14\14) of CIN2 pts, 100%(3\3)of CIN3pt This was supported by results obtained by Sripathi et al.,[9] The study found a statistically significant correlation between CIN staging(histopathology) and the expression of immunohistochemical markers; these biomarkers are upregulated in SILs and cervical cancer, and the researcher used 80-cervical punch biopsy specimens to draw this conclusion. Out of 25 instances of CIN I(LSIL), 16 tested positive for p16 and 19 tested positive for Ki67. With a higher score, all instances of invasive cervical cancer(17/17SCC and 3/3 adenocarcinoma) and HSIL(10/10 CIN II and 3/3 CIN III) tested positive for p16INK4A expression.

Also, Secosan et al.,[10] The results of a prospective study that included all patients who were eligible for a loop electrosurgical excision procedure(LEEP) lend credence to the idea that certain immunohistochemical markers, like p16 and Ki-67, have a statistically significant correlation with histological abnormality. Additionally, the degree of histological abnormality was found to be correlated with diffuse staining, or over-expression, of p16 and Ki-67.

It also agrees with results obtained by Yu et al.,[11] in which 1079 women from five hospitals in China participated in cervical cancer screenings and found that the presence of p16/Ki-67 was inversely proportional to the grade of their tumors. Among the histological types, 18.4% occurred in normal histology, 54.0% in CIN1, 81.0% in CIN2, 93.3% in CIN3, 71.4% in adenocarcinoma, and 95.2% in squamous cell carcinoma.

As regards the relation between coloscopic findings and Ki67 expression. Our study shows a statistically highly significant relation between both of them, but there are no other available studies. The current study shows that the sensitivity and specificity of colposcopy as a method of prediction of CIN are 92.2%, 30.1% respectively; its PPV(Positive predictive value) is 52.2% and its NPV(Negative predictive value) is 82.3% and the accuracy of colposcopy is 58.2%.

Hariprasad et al.,[12] According to his research, which sought to understand how colposcopy can be used to help women with abnormal cytology, the average sensitivity of colposcopy for a normal diagnosis was 96% and the specificity was 48% when compared to all other cervical abnormalities(atypia, low-grade SIL, high-grade SIL, and cancer). Sensitivity reports for the identification of cervical precancer and cancer range from 85 to 94%, demonstrating a strong correlation between colposcopy and high-grade abnormalities. However, it is not as effective for women with few cytological abnormalities(because of too low specificity and low repeatability, both of which are 50%).

Additionally, the current study demonstrates that the immunohistochemical marker Ki67 has a sensitivity of 84.4% and a specificity of 100% when it comes to predicting CIN. Its PPV is 100%, its NPV is 88.6%, and its accuracy is 92.9%.

Sripathi et al., [9] His study sought to evaluate the usefulness of p16 and ki-67 in detecting and grading cervical neoplasms; specifically, p16 had a 100% specificity and ki 65 had a 90% specificity. In contrast to their 100% sensitivity to HSIL and carcinomas, p16 and Ki-67 are only 65% and 75% sensitive to LSIL, respectively.

Our data clearly show that ki67out exceeds colposcopy in terms of specificity(100%), PPV(100%), NPV(88.6%), and accuracy(92.9%).

Solares et al.,[13] conducted research. One hundred sixty women were sent to the colposcopy unit if their cytology was abnormal(ASC-US, LSIL, or otherwise normal), but they had high-risk HPV. After rerunning the cytology and HPV tests, a new cytological specimen was stained with dual p16/Ki-67. Patients were then evaluated colposcopically and followed up prospectively for one year, after which the process was repeated. There was also the option of an intermediate colposcopic evaluation at the six-month mark. Thirteen out of one hundred and forty-three women who had a normal initial colposcopy did not receive a follow-up. During the one-year follow-up period, nine out of the remaining 130 patients developed cervical intraepithelial neoplasia or higher-grade lesions, as confirmed by histology. Initially, 6 out of 9 were positive for p16/Ki-67. Biomarker identification could help

find women who are more likely to have CIN2+, and early colposcopic evaluation could help these individuals. Eventually, a less strenuous regimen may be appropriate for women whose tests for the biomarkers come back negative.

4. Conclusion

Sensitivity and specificity of colposcopy as method of prediction of CIN were 92.2%,30.1% respectively and its PPV is 52.2% comparing to immunohistochemestry sensitivity and specificity of Ki67 as immmunohistochemical marker in prediction of CIN were 84.4%, 100% respectively and its PPV is 100% which means that Ki67 improve accuracy of prediction of CIN.

Disclosure

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Authorship

All authors have a substantial contribution to the article

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