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THE ACCURACY OF DIAGNOSING CERVICAL INTRAEPITHELIAL NEOPLASIA BY COLPOSCOPY AND ITS RELATED INFLUENCING FACTORS

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ABSTRACT

Background: Colposcopy-directed biopsy is a basic method for diagnosing cervical intraepithelial neoplasia. This study aimed to evaluate the accuracy of colposcopy in the diagnosis of cervical intraepithelial neoplasia (CIN)and cervical cancer. **Methods:** A retrospective analysis was performed on 700 patients who underwent colposcopy examination and biopsy under direct vision in our hospital in January 2018 and November 2019. The pathological results of colposcopy diagnosis and biopsy were compared, and the influence of high-risk HPV results and cervical cytology results on the accuracy of colposcopy diagnosis of cervical diseases was. **Results:** From a total number of 700 patients, there were 100 patients (14.3%) had pathological diagnosis of low-grade cervical intraepithelial neoplasia, and 96 (13.7%) had pathological diagnosis of high-grade cervical intraepithelial neoplasia or cervical cancer, 429 (61.3%) cases diagnosed by colposcope met the accuracy diagnosis by pathological biopsy. The overdiagnosis rate by colposcopy was noticed in 25.7% (180/700) cases, and the lack of diagnosis rate was observed in 13.0% (91/700) cases. high-risk HPV-negative patients who underwent colposcopy diagnosis accuracy rate (68.2%), the high-risk HPV-positive patients was (60.3%), however the difference was not significant. **Conclusion:** The specificity and positive predictive value of colposcopy in the diagnosis of high-grade lesions are high, and biopsy guided by colposcopy should be performed to avoid missed diagnosis of high-grade intraepithelial neoplasia and cervical cancer. When HPV was positive in high risk, the specificity of normal colposcopic diagnosis and positive predictive value were high, and if cytology was low change, especially at ASCUS, biopsy could be considered to be avoided. When high risk HPV is positive, the accuracy of colposcopy in diagnosing normal or low-grade lesions is associated with cytological results to some extent, but cytological results are not enough to bypass biopsy.

KEYWORDS: Cervical intraepithelial neoplasia; Cervical cancer, Colposcopy; HPV.

BACKGROUND

Cervical cancer (cervical cancer) is the third-largest malignant tumor that causes the death of women worldwide. According to the latest cancer According to symptomatic statistics, there are about 500,000 new cases worldwide each year, and about 80% of them appear in the developing process at the same time, the incidence of cervical cancer tends to be toward younger aged patients.[1,2] In the past 50 years, due to cervical cytology screening that was widely used, the incidence of cervical cancer in the United States has been reduced by more than 50%. In 1975, the incidence of cervical cancer was 14.8/10 Million. By the end of 2008, it had been dropped to 6.6/100,000. Cervical cancer mortality rates have declined similarly; since 1975 the incidence rate was 5.55/10 million which then have been decreased to 2.38/10 at 2008.[3] The latest US cancer statistics estimates for the United States in 2015 estimated that there are 12,900 new cervical cancer patients (4.0/100,000) and 4,100 patients died of cervical cancer (1.28/100000).[1] Most occurrences and deaths of official Cervical cancer are women who have never been screened or have insufficient screening.[4,5] Some studies estimate that about 50% of cervical cancer patients have never undergone cervical cytology, and another 10% of Patients were not screened for cervical cancer within five years before being diagnosed with cervical cancer.[6,7] Therefore, targeting the general population Large-scale, standardized screening is one of the most effective ways to reduce cervical cancer occurrence and death.

Cervical biopsy under colposcopy is the most commonly used method for clinical diagnosis of cervical intraepithelial neoplasia (CIN), which was considered the gold standard for diagnosis. However, there are reports in the literature that the accuracy of the diagnosis of CIN under cervical biopsy under colposcopy is not very satisfactory, which brings specific difficulties to clinical decision-making.[8-10] In this study, we retrospectively collected the diagnostic results and other relevant clinical data of colposcopy patients in our colposcopy room. The pathological diagnosis of biopsy specimens was used as the gold standard to evaluate the diagnosis of cervical intraepithelial neoplasia and colposcopy results. The accuracy of cervical cancer and analysis of the HPV impact test results and cytology test results on the accuracy of colposcopy diagnosis was performed to guide the clinical practice of colposcopy.

MATERIALS AND METHODS

A retrospective collection of women who underwent colposcopy investigation at the colposcopy room of our hospital from January 2018 to November 2019 and was evaluated as "satisfactory".

The inclusion criteria are: women post pathological diagnosis of colposcopy biopsy with a complete cervix; no history of physical therapy for the official cervix; none of the previous history of cervical lesions and cervical cancer; cytological examination and HPV-DNA test result before the examination; Exclusion criteria: women with non-cervical squamous epithelial lesions.

A total of 700 women were included in this study. Median Age 36 ramged between (19 and 64) years old.

HPV-DNA testing for exfoliated cervical cell

There are two methods for detecting HPV-DNA of the exfoliated cervical cell; one is HC. 2 (US NDigene), detection of 13 high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68). The other is Cervista (Hologic America), which detects 14 high-risk types (formerly 13+66). A gynecologist performed the material collection. The method is to put the special brush for material collection into the external cervical 1-1. Of the 700 women collected, 88 high-risk HPV were negative and 612 were positive (87.4%).

Cervical cancer screening tests

Cervical cytology adopts the Thinprep Liquid-based Cytology test (TCT) and reports the results according to the vaginal cell TBS (the Bethesda system) naming system revised by the International Cancer Society in 2001. Cervical cytology examination materials are completed by a gynecologist, using the brush method. Cytyc/z, produced by Shiji (automatically provided by FhinPrep processor and read by a pathologist). Among 700 patients, no squamous intraepithelial neoplasia (NSIL) 418 (59.7%), atypical squamous cell of undetermined significance (ASCUS) 110 (15.7%), low-grade squamous intraepithelial lesions (1ow-grade squamous intraepithelial lesion, LSIL) 108 (15.4%), atypical squamous cell couldnot-exclude HISL (ASC-H) 26 (3.7%), high-grade squamous cells (HSIL) 38 (5.4%) cases.

Method of colposcopy and biopsy of the cervix under direct vision

The video colposcopy detection system is a product of American welchAllyn company, and the inspection is carried out by a full-time doctor in our hospital. The indications for colposcopy are: Those with cytology results> LSIL; Those whose cytological examination is ASCUS and/or positive high-risk HPV patients; Those who have suspicious cervical lesions during colposcopy. No sexual intercourse or vaginal medications 24 hours before colposcopy. Abnormalities of colposcopy mainly include thin, thick vinegar white epithelium, leukoplakia, thick and thin punctate blood vessels, thick and thin mosaics, ulcers, atypical blood vessels, iodine-free areas, etc. Biopsies of the diseased area. All tissues were fixed with 10% formaldehyde and sent for pathological examination.

Pathological examination and diagnosis

All specimens were serially sectioned for histological examination. All pathological paraffin sections were prepared by a pathologist in our hospital, and the pathological diagnosis was reviewed by a senior doctor in the pathology department. The diagnostic criteria for CIN and cervical invasive cancer pathology refer to the eighth edition of the Obstetrics and Gynecology standard.[11]

Data analysis and statistical methods

According to the clinical treatment of CIN Ⅱ and CIN Ⅲ in the CIN treatment guidelines recommended by the American Colposcopy Cervical Pathology Association (ASCCP) in 2003 which is precisely the same[12], we divided the diagnosis results by non-CIN, CIN 1, ≥CIN2 and invasive carcinoma The biopsy and the final pathological results under the colposcopy under the same category were deemed to conform, otherwise, they were not in compliance. The statistical significance of the difference between the two groups was calculated using the $\chi 2$ test and the exact probability of the four-grid table, with a test level of $\alpha = 0.05$ (two-sided). Data statistical analysed by SPSS software (Chicago, USA) version 22.0.

RESULT

Accuracy of colposcopy in diagnosis of cervical intraepithelial neoplasia and cervical cancer

From a total number of 700 patients, 100 patients (14.3%) had pathological diagnosis of low-grade cervical intraepithelial neoplasia, and 96 (13.7%) had pathological diagnosis of high-grade cervical intraepithelial neoplasia or cervical cancer. The colposcopy diagnosis and the final cervical biopsy pathological diagnosis were completely in accordance with 429 (61.3%), and 271 cases (38.7%) were not in compliance, as shown in Table 1 and Figure 1.

Table 1: The accuracy of colposcopy in diagnosing cervical intraepithelial neoplasia and cervical cancer.

	Biopsy pathological diagnosis			
Colposcopy diagnosis	**Normal**	**CIN1**	**≥CIN2**	**Total**
Normal	332	41	15	388
Low-grade lesions	158	51	35	244
High-grade lesions or cancer	14	8	46	68
Total	504	100	96	700

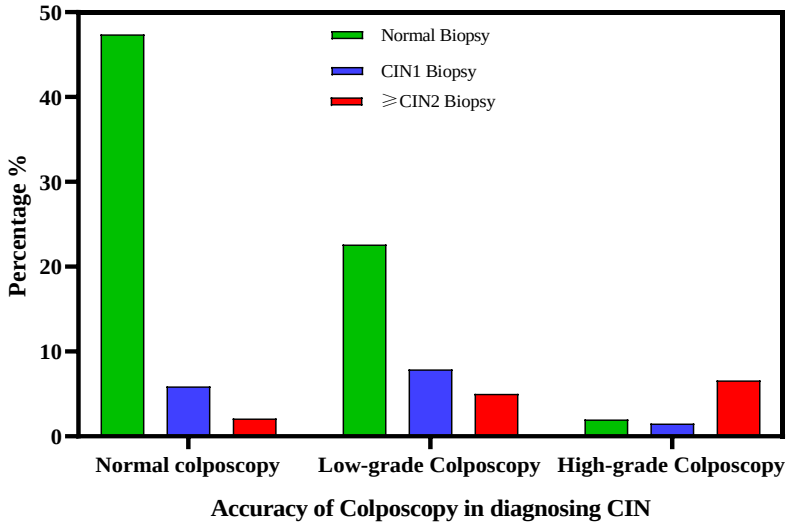

Figure 1: Graph showing the diagnostic accuracy rate in the three groups; CIN: cervical intraepithelial neoplasia; G: group; L: lesion.

Further analysis of the accuracy of colposcopy diagnosis found that (65.87%), when colposcopy was diagnosed as a high-grade lesion, when colposcopy was diagnosed as normal, the sensitivity was high and specificity was high (96.36%) See Table 2.

Table 2: Evaluation of the accuracy of colposcopy in the diagnosis of cervical intraepithelial neoplasia and official cervical cancer (%).

	Sensitivity	**Specificity**	**Accuracy**	**Positive prediction rate**	**Negative predictive rate**
Normal	65.87	71.43	67.43	85.57	44.87
≥High-grade lesions or cancer	47.92	96.36	89.71	67.65	92.09

Further analysis of the accuracy of colposcopy diagnosis revealed that the overdiagnosis rate was 25.7% (180/700) and the lack of diagnosis rate was 13.0% (91/700). The lack of diagnosis rate was significantly lower than the overdiagnosis rate ($P<0.01$), in contrast, when the colposcopy is diagnosed with low-grade lesions, the over-diagnosis rate is significantly higher than the the lack of diagnosis rate ($P<0.01$), see Table 3 and Figure2.

Table 3: Colposcopic diagnosis of cervical intraepithelial neoplasia and cervical cancer over and under conditions.

	Diagnosis (number of cases)					**χ^2 Value**	***P-Value***
Colposcopy diagnosis	**Lack diagnosis**	**accurate**	**overdiagnosis**	**total**	**Accuracy (%)**		
Normal	56	332	0	388	85.57	66.979	< 0.001
Low-grade lesions	35	51	158	244	20.90	129.673	< 0.001
High-grade lesions or cancer	0	46	22	68	67.65	26.246	< 0.001
Total	91	429	180	700	61.29	36.245	< 0.001

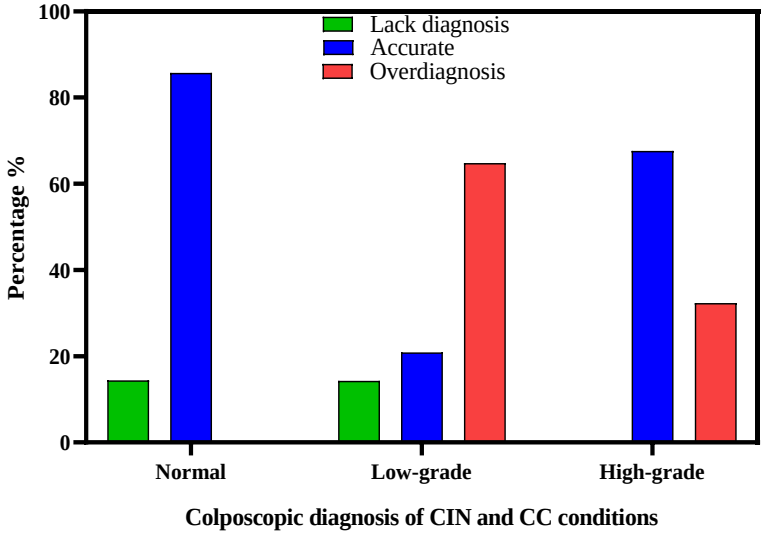

Figure 2: Graph demonstrating the different conditions of diagnosing CIN and CC; CIN: cervical intraepithelial neoplasia, CC: cervical cancer.

Accuracy analysis of colposcopy diagnosis under different HPV and cytology status

The colposcopy diagnosis was accurate 429 patients age ranged between 19-62 years old, with a median age of 37 years. The age distribution of the inaccurate colposcopy diagnosis 271 patients ranged between 20-62 years old, with median age of 35 years old. There was no significant difference between the two (p=0.660). Age has no significant effect on the accuracy of diagnosis. A comparative analysis of the relationship between high-risk HPV results and the accuracy off colposcopy diagnosis demonstrated that among 700 patients, high-risk HPV-negative patients who underwent colposcopy diagnosis accuracy rate (68.2%), the high-risk HPV-positive patients was (60.3%), however the difference is not significant, P=0.155. See Table 4.

Table 4: Accuracy analysis of high-risk HPV in the diagnosis of cervical intraepithelial neoplasia and cervical cancer by colposcopy.

High-risk HPV		Colposcopy diagnosis and biopsy case diagnosis		P-Value
	No	meets the diagnosis n(%)	Non-meeting with diagnosis n(%)	
Positive	612	369(60.3)	243(39.7)	0.155
Negative	88	60(68.2)	28(31.8)	
Total	700	429(61.3)	271(38.7)	

Accuracy analysis of high-risk HPV positive colposcopy in the diagnosis of cervical intraepithelial neoplasia and cervical cancer

The high-risk HPV positive colposcopy diagnosis of cervical intraepithelial neoplasia and cervical cancer is shown in Table 5 and Figure3.

Table 5: Accuracy analysis of high-risk HPV-positive colposcopy in the diagnosis of cervical intraepithelial neoplasia and cervical cancer.

	Biopsy pathological diagnosis			
Colposcopy diagnosis	Normal	CIN1	≥CIN2	Total
Normal	278	34	14	326
Low-grade lesions	142	46	33	221
High-grade lesions or cancer	12	8	45	65
Total	432	88	92	612

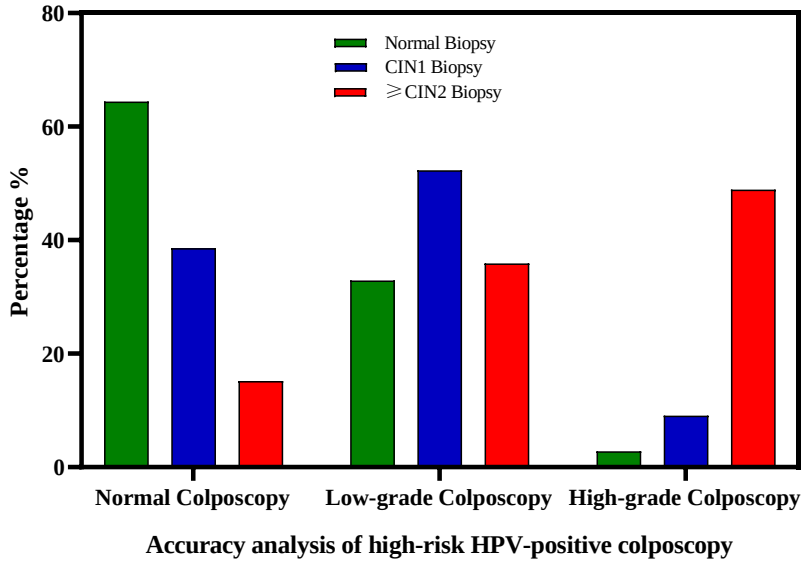

Figure 3: Graph representing the different conditions of diagnosing CIN under high-risk HPV condition; CIN: cervical intraepithelial neoplasia.

From table5 which showed when colposcopy is diagnosed as normal and low-grade lesions, there is a higher proportion of ≥CIN2, further stratified by cytology, and it is found that the cases of missed diagnosis when the colposcopy is normal are mainly distributed in the NSIL group. The misdiagnosed cases by colposcopy was diagnosed as low-grade lesions were mainly distributed in LSIL group. See Table 6.

Table 6: Accuracy of colposcopic diagnosis of cervical intraepithelial neoplasia and cervical cancer in high-risk HPV positive cytological stratification.

		Biopsy pathological diagnosis			
Diagnosis under colposcopy	**Cervical cytology**	**Normal**	**CIN1**	**≥CIN2**	**Total**
Normal	NSIL	236	20	9	265
	ASCUS	25	10	1	36
	LSIL	12	3	4	19
	ASC-H	3	1	0	4
	HSIL	2	0	0	2
Low-grade lesions	NSIL	84	17	6	107
	ASCUS	26	3	5	34
	LSIL	30	23	10	63
	ASC-H	1	1	9	11
	HSIL	1	2	3	6
High-grade lesions or cancer	NSIL	6	2	6	14
	ASCUS	2	2	5	9
	LSIL	2	2	1	5
	ASC-H	0	0	9	9
	HSIL	2	2	24	28
	Total	432	88	92	612

DISCUSSION

Colposcopy acting as an important role in the assessment of abnormal cervical cancer showing results. We support the recommendation As suggested by European Guidelines[13], "objective colposcopic criteria and training of the colposcopists are keys for improving the accuracy of colposcopy."; however, we also trust the fact the sensitivity of the colposcopy examination can be speedily enhanced for all caregivers, regardless of their admittance to, or benefit from, superiority training plans, only by recommending a standard protocol of directed and random biopsies.[14]

Inappropriately, not all of the CIN and cervical cancer leads to a visible lesion, which could be distinguished by colposcopy.[13,15] We and others have shown that the sensitivity of colposcopy for CIN II and III increased by the performance of a random biopsy in cervical quadrants, which do not cover colposcopic abnormal lesions.[13,15,16] As it was previously shown in 2001 using

data from SPOCCS I[17] when compared with CIN II detected by colposcopy-directed biopsy, CIN II detected by random biopsy intricate fewer quadrants of the cervix (it was smaller), and it was related with cervical cytology of Negative, ASC-US, LSIL, or AGC (Negative/Lo) rather than cytology of HSIL.[18] Cytology of Negative/Lo was linked to the small CIN II, and once measured for lesion size, it no longer predicted diagnosis by random biopsy. We also have discovered that CIN III diagnosed by random biopsy is more probable in women aged nearby 51 years or older. We speculate that CIN III is more expected randomly diagnosed by biopsy in elder women because the CIN in elder women is thinner, and thinner CIN is less likely to consequence in colposcopic noticeable lesions.[19] In the review by Gage et al.,[20] recently detected HPV infections in females aged 60 to 64 years had a lesser 5-year risk of CIN III (3.5%) than afresh detected HPV infections in females aged 30 to 34 years (5.1%, p = .014), signifying that the natural history of HPV in elder females is less infectious than that in younger females. As the diagnosis of CIN III by random biopsy is linked with older females and elder females have a lesser risk of development from HPV infection to CIN III, once more, it is likely that random biopsy for diagnosing CIN is less virulent than that diagnosed by colposcopy-directed biopsy.

Postmenopausal women as a result of the reduction of estrogen levels in the body, the cervical scale column conversion area retreated into the cervical canal has difficulty in concluding a clear observation, therefore colposcopy is easy to miss the diagnosis. In this study, by analyzing the relationship between the age of patients and the diagnostic accuracy of colposcopy, we found that there was no significant difference between the age of the group with accurate colposcope diagnosis and the age of the group with inaccurate colposcope diagnosis. The reason may be that the colposcope did not classify the patients according to premenopausal and postmenopausal classification in this study.

As a retrospective analysis, this study has the defects of missing data. HPV detection is an important concept of cervical cancer screening. By analyzing the relationship between the results of high-risk HPV and the diagnostic accuracy of colposcopy, we found that the accuracy of colposcopy for high-risk HPV negative patients was significantly higher than that for high-risk HPV positive patients. This study further analyzed and found that in the case of 26 high-risk HPV negative and cell ASCUS, there was no one case CIN II or higher. Nineteen cases of high-risk HPV negative, LSIL cytology only 1 case of CINII and more. The above results suggested that if the HIGH-RISK HPV was negative and the cytology was a low change, especially when ASCUS contained no abnormalities, so as not to perform the biopsy and suggested follow-up should be feasible. It also avoids client trauma, reduces the workload of pathologists and saves health care resources. These finding also inconsistent with the 2013 American Vaginoscopy and Cervical Pathology Association new Guidelines for Cervical Cancer Screening:[21] which suggested that combined cervical cancer screening measures should be adopted three years later for the cytological results which were negative for high-risk HPV, also was consistent with the recommendation of HPV and cytology review. From a psychological point of view, a study on patients with ASCUS, patients are more willing to choose to repeat cytology (58.4%), rather than repeat lines of high-risk HPV examination (7.3%) or the colposcope examination (cervical, 20.6%) even biopsy under colposcopy (13.8%).[22] HPV positive doesn't mean it's similar to that in the cervix lesions, but usually contains a higher proportion of cervix lesions.

HPV positive does not equate to cervical lesions, but usually includes a higher proportion of cervical lesions. In this study, high-risk HPV positive was analyzed, and the overall accuracy of colposcopy diagnosis was high, especially in 332 cases diagnosed as normal by colposcopy, 15 cases (3.9%) were CIN2 and above. But further analysis found that with the increase of level of cytology in the diagnosis of lesions, the accuracy of colposcopy in the diagnosis of normal, specific degree, positive predictive value, diagnosis rate is on the decline, suggest when high risk HPV positive lesions, cytology, a low level, if seen colposcope without exception, is still likely to avoid some unnecessary biopsies. However, due to the limited sample size of this study, the differences were not significant, which still needed to be further verified by larger samples.

CONCLUSION

The specificity and positive predictive value of colposcopy in diagnosing high-grade lesions are high, and biopsy guided by colposcopy should be performed to avoid the missed diagnosis of high-grade intraepithelial neoplasia and cervical cancer. When HPVN was high, the specificity of normal colposcope diagnosis and positive predictive value were high, and when cytology was low lesions, especially at ASCUS, a biopsy could be considered to be avoided. When high-risk HPV is positive, the accuracy of colposcopy in diagnosing normal or low-grade lesions is associated with cytological results to some extent. Still, cytological findings are not enough to bypass biopsy.

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