

Original Research

# Factors Associated with Concordance between Colposcopy-Directed Cervical Biopsy and Loop Electrosurgical Excision Procedure: A Retrospective Cohort Study

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## Abstract

**Background:** Colposcopy-directed cervical biopsy (CDB) is the most commonly used diagnostic method for the detection of cervical precancerous lesions, while the loop electrosurgical excision procedure (LEEP) is the most common surgical technique for treatment. However, discrepancies between CDB and LEEP results have been reported in the literature. Therefore, identifying the factors that influence concordance between these two procedures is crucial for accurately diagnosing precancerous lesions and preventing over- and under-treatment. **Methods:** A retrospective analysis was conducted on women who underwent conization between January 2015 and December 2023 due to a preoperative CDB revealing lesions classified as  $\geq$  cervical intraepithelial neoplasia 2 (CIN2+), including CIN 2, CIN3, and invasive cancer. Demographic data, along with colposcopy and conization results, were obtained from patient records and the electronic gynecologic oncology clinic database. **Results:** A total of 358 patients were included in the analysis. The overall concordance between CDB and LEEP pathology was 68.7% (n = 246/358). In the univariate analysis, age, menopausal status, and endocervical curettage (ECC) result were identified as factors associated with concordance between CDB and LEEP result ( $p = 0.006, 0.008, \text{ and } 0.005$ , respectively). In the multivariate analysis, human papillomavirus (HPV) 16 positivity, premenopausal status, and absence of preoperative positive ECC result were identified as independent predictors of high concordance between CDB and LEEP results [odds ratio (OR): 1.72, 95% confidence interval (CI): 1.05–2.83,  $p = 0.031$ ; OR: 2.47, 95% CI: 1.46–4.17,  $p = 0.001$ ; and OR: 0.345, 95% CI: 0.193–0.616,  $p < 0.001$ , respectively]. **Conclusion:** The detection rate of  $\geq$  CIN2 lesions in LEEP is predicted to be higher in patients with HPV type 16 positivity, premenopausal status, and the presence of a  $\geq$  CIN2 lesion in the preoperative ECC.

**Keywords:** cervical cancer; cervical precancerous lesions; concordance; colposcopy; loop electrosurgical excision procedure

## 1. Introduction

Cervical cancer is the fourth most common form of cancer among women worldwide. In 2022, approximately 660,000 new cases and 350,000 deaths were reported, highlighting a significant threat to women's health [1]. Given the well-established role of persistent high-risk human papillomavirus (HPV) infection, cervical cancer is the only malignant tumour with a clear defined etiology [2]. The identification of cervical cancer's etiology has facilitated the development and implementation of a comprehensive prevention and control system.

The diagnosis and management of precancerous cervical lesions are crucial aspect for the prevention of cervical cancer. Colposcopy is an essential diagnostic tool for identifying precancerous cervical lesions and obtaining histological data through biopsy of suspicious lesions during examination. Once a histological diagnosis of a precancerous cervical lesion is made through colposcopy-directed cervical biopsy (CDB), the lesion is typically treated by excisional procedures, with the loop electrosurgical excision procedure (LEEP) being the most commonly used method

[3]. Nevertheless, a long-standing debate persists in the literature regarding the diagnostic value of cervical biopsy and colposcopy. Available evidence indicates discrepancies between CDB and LEEP results, with overall concordance ranging from 43% to 86%. However, it is worth noting that discrepancies between studies may be influenced by variations in study population characteristics, study design, and statistical methods used [4–7].

An underestimation of the precancerous lesion identified by CDB may result in inadequate treatment, increasing the risk of persistent lesions or progression to invasive cancer. Conversely, overestimation may lead to overtreatment, potentially resulting in adverse effects on fertility and various obstetric complications [8–12].

The limited accuracy of CDB in determining the severity of precancerous cervical lesions poses a significant clinical challenge [13,14]. While LEEP offers numerous advantages, including simplicity, safety, and cost-effectiveness, it is crucial to identify the factors influencing concordance between CDB and LEEP in order to prevent unnecessary invasive procedures and ensure accurate pa-



tient management. Therefore, the present study, we aimed to identify factors associated with the concordance between CDB and LEEP.

## 2. Material and Method

### 2.1 Study Population

Between January 2015 and December 2023, women who underwent conization due to a preoperative CDB (cervical biopsy and/or endocervical curettage (ECC)) revealing lesions classified as  $\geq$  cervical intraepithelial neoplasia 2 (CIN2+), including CIN 2, CIN3, and invasive cancer, were retrospectively analyzed.

A colposcopic examination is indicated in cases with abnormal cytological results, including low-grade intraepithelial lesion (LSIL), atypical squamous cells—cannot exclude high-grade squamous intraepithelial lesion (ASC-H), high-grade squamous intraepithelial lesion (HSIL), atypical glandular cell (AGC), recurrent atypical squamous cells of undetermined significance (ASC-US), high-risk HPV positivity (including patients with HPV types other than 16 and 18 with normal cytology), and cases suspicious for carcinoma. The HPV test employed was Hybrid Capture 2 (Qiagen, Hilden, Germany), the reference test routinely employed in numerous laboratories. In cases where the Hybrid Capture 2 (Qiagen, Hilden, Germany) test indicated the presence of HPV, genotyping was conducted using the CLART kit (Array ID: 50516, Genomica, Madrid, Spain). The inclusion criteria for this study were patients with an indication for conization, as determined by CIN2+ lesions in either a cervical biopsy or ECC.

### 2.2 Exclusion Criteria

The analysis excluded patients who had undergone a hysterectomy or were diagnosed with gynecological cancers. Additionally, patients with indications for conization other than those mentioned above (e.g., HPV type 16 positivity with HSIL cytology) were also excluded.

### 2.3 Data Collection

Data for patients who underwent colposcopies at our institution were collated from patient files and the electronic database system. Demographic data, including age, menopausal status, and pathological results of CDB, ECC, and LEEP, were obtained. The colposcopic examination database was thoroughly evaluated to ascertain whether the colposcopy had been performed adequately.

### 2.4 Surgical Procedure

During the specified period, all colposcopies were conducted by gynecological oncologists. Cervical biopsies were obtained in cases where lesions suspicious for HSIL were identified during colposcopic examination. Additionally, random biopsies were performed at the discretion of the colposcopist in cases where no abnormal findings were detected during colposcopy. The ECC was performed when

the colposcopy was inadequate, i.e., when the cervix was obscured by bleeding, inflammation, or scar tissue; when the squamocolumnar junction was not visible or only partially visible; when the transformation zone (TZ) was type 3; when the visualized lesion extended into the endocervical canal; or when HSIL and ASC-H cytological results were present. The ECC was also performed according to the clinical judgment of the colposcopist, even in the absence of the aforementioned factors. The ECC was performed with a Novak curette, which involved the scraping of the entire endocervical canal and subsequently processing the sample for histopathological analysis. The term CIN2 or CIN2+ refers to lesions including CIN2, CIN3, and invasive cancer.

### 2.5 Statistical Analysis

CDB was accepted as concordant with the conization result when the conization pathology revealed the presence of at least a CIN2 lesion or higher (CIN 3, microinvasive cancer, invasive cancer) in the conization specimen. The factors that could affect concordance were analyzed.

SPSS version 22.0 (SPSS Inc, Chicago, IL, USA) was used for data analysis. Descriptive statistics were used, with binary variables reported as counts and percentages. Descriptive analyses were presented using both medians and ranges. Kolmogorov-Smirnov test was used to determine whether or not variables were normally distributed. Since age was not normally distributed, the median ages in the groups were compared using the Mann-Whitney U test. The Chi-square test or Fisher's exact test, as appropriate, was used to compare the proportions across different groups. The potential factors affecting concordance were further analyzed using logistic regression. A  $p$ -value of less than 0.05 was considered statistically significant.

## 3. Results

During the specified time period, 358 patients underwent conization. The median age of the patients was 43 years (range, 27–68 years). 259 patients (72%) were premenopausal. Among the patients with known smoking status, 29 (31.5%) were current smokers. The most prevalent HPV type was HPV 16 (46.4%), as shown in Table 1. The results of the preoperative colposcopic biopsies are presented in Table 2. The concordance between CDB and conization pathology was 68.7% ( $n = 246/358$ ) for the entire cohort. Table 3 presents the details of the comparison between the colposcopic biopsy results and the conization pathology. The median age of patients with concordant conization results was 42 (range, 27–68), while that of patients with discordant results was 45 (range, 29–65) ( $p = 0.004$ ). When the median age of 43 years for the study population was used as the cutoff, it was observed that 75% of patients under the age of 43 exhibited concordance, while the proportion among patients aged  $\geq 43$  years was 61.4% ( $p = 0.006$ ). The factors affecting concordance between

CDB and conization result are presented in Table 4. In the univariate analysis, age, menopausal status, and ECC result were identified as factors associated with concordance between CDB and conization result ( $p = 0.006, 0.008,$  and  $0.005,$  respectively), while HPV result and smoking status were not ( $p = 0.06$  and  $0.24,$  respectively).

**Table 1. HPV status of the patients undergoing conization.**

HPV type	n	(%)
Unknown	29	8.1
Negative	3	0.84
HPV16	166	46.4
HPV18	30	8.4
HPV16 + 18	16	4.5
HPV other	114	31.8
Total	358	100

HPV, human papillomavirus.

**Table 2. Preoperative CDB results.**

	CDB n (%)	ECC n (%)
Not performed	51 (14.3%)	55 (15.4%)
Normal	37 (10.3%)	196 (54.7%)
HSIL	264 (73.7%)	105 (29.3%)
Invasive cancer	6 (1.7%)	2 (0.6%)
Total	358 (100%)	358 (100%)

CDB, colposcopy-directed cervical biopsy; ECC, endocervical curettage; HSIL, high-grade squamous intraepithelial lesion.

A multivariate analysis was conducted, with the inclusion of the HPV result, menopausal status, and ECC result (Table 5). Age and menopausal status showed correlation. Consequently, only menopausal status was included in the multivariate analysis. Smoking status was known for less than 20% of the patients. It was therefore excluded from the multivariate analysis. In the multivariate analysis, the presence of HPV 16 positivity, being premenopausal, and the absence of a preoperative positive ECC result were identified as independent factors predicting high concordance between CDB and conization result [odds ratio (OR): 1.72, 95% confidence interval (CI): 1.05–2.83,  $p = 0.031$ ; OR: 2.47, 95% CI: 1.46–4.17,  $p = 0.001$ ; and OR: 0.345, 95% CI: 0.193–0.616,  $p < 0.001,$  respectively].

#### 4. Discussion

In the present study, factors affecting concordance between CDB and LEEP were investigated. Multivariate analysis revealed that HPV 16 positivity, being premenopausal, and having a positive preoperative ECC result were independent factors associated with concordance between CDB and LEEP.

Although numerous studies have examined the concordance between cervical biopsy and LEEP, there is a lack of studies that have employed rigorous methodology and statistical analyses to investigate the factors affecting this concordance. A substantial number of studies have analyzed the concordance and discrepancy between cervical biopsy and LEEP results, expressed as percentages, in relation to the presence or absence of cervical dysplasia and its degree [4–7].

The goal of cervical cancer screening programs is to diagnose precancerous lesions and ensure that patients receive treatment before invasive cancer develops. This can be achieved by detecting and appropriately treating  $\geq$  CIN2 lesions. In this context, the current study used the detection of CIN2 lesions via conization in patients diagnosed with  $\geq$  CIN2 by biopsy as a reference to determine the concordance between CDB and LEEP. The factors affecting concordance were statistically analyzed within this context. We believe that designing the study in this way will contribute significantly to the literature. As such, the present study revealed a concordance rate of 68.7% between CDB and LEEP, while previous studies have reported rates ranging from 43.8% and 85.8% [6,15–19]. These findings are consistent with those of earlier studies [6,15–19].

It has been established that HPV type 16 is the most prevalent HPV genotype in precancerous cervical lesions and invasive cancers [20]. Similarly, in the present study, 46.4% of patients who underwent LEEP conization were found to be positive for HPV type 16. In the present study, the concordance between CDB and LEEP in the presence of HPV 16 positivity was 74.7%, while in HPV 18 and other high-risk HPV positivity, it was 62%. A review of the existing literature revealed a limited number of studies that have examined association between HPV genotype and the concordance between CDB and LEEP. In contrast with the findings of the present study, the study by Jung *et al.* [6] did not identify an association between HPV genotype and the concordance between CDB and LEEP in multivariate analyses. However, the findings of this study indicated that HPV types 39, 45, 51, 53, 59, 66, 68, and 73 were associated with an increased likelihood of biopsy underestimation [6]. In a study by Stoler *et al.* [21] utilizing data from the Gardasil clinical trial, it was demonstrated that the presence of HPV 16 and/or HPV 18 enhanced the accuracy of colposcopy in relation to the HPV 16 and/or HPV 18 status of the lesion, improving overall concordance and reducing overall underestimation of CIN 2–3/cervical adenocarcinoma in situ (AIS), thereby supporting the findings of the present study. In the study conducted by Ureyen *et al.* [22], the risk of CIN2+ was found to be 22% in the group with normal cytology and HPV type 16 positivity, 8% in the group with normal cytology and HPV type 18 positivity, and 2.5% in the group with normal cytology and positivity for other high-risk HPV types. Based on the aforementioned data, it can be proposed that the elevated

**Table 3. Comparison of the CDB results and conization pathology concordance.**

		LEEP pathology			Total
		Normal	HSIL	Invasive disease	
CDB and/or ECC pathology	HSIL	111 (31.5%)	223 (63.4%)	18 (5.1%)	352 (100%)
	Microinvasive disease or suspicion of invasion	1 (16.7%)	0 (0%)	5 (83.3%)	6 (100%)
Total		112 (31.3%)	223 (62.3%)	23 (6.4%)	358 (100%)

LEEP, loop electrosurgical excision procedures; CDB, colposcopy-directed cervical biopsy; ECC, endocervical curettage; HSIL, high-grade squamous intraepithelial lesion.

**Table 4. Factors affecting concordance between CDB and conization results.**

Clinico-pathological characteristics	Concordance <sup>a</sup> (246/358)	Discordance (112/358)	<i>p</i> -value	$\chi^2$ value
Age (years)			0.006	7.608
<43	144 (75%)	48 (25%)		
≥43	102 (61.4%)	64 (38.6%)		
HPV			0.060	5.640
HPV negative or unknown	22 (68.8%)	10 (31.2%)		
HPV 16	124 (74.7%)	42 (25.3%)		
HPV 18 + other	100 (62.5%)	60 (37.5%)		
Menopausal status			0.008	9.543
Unknown	2 (66.7%)	1 (33.3%)		
Premenopausal	190 (73.4%)	69 (26.6%)		
Postmenopausal	54 (56.3%)	42 (43.7%)		
Smoking status			0.098	2.738
Smoker	23 (79.3%)	6 (20.7%)		
Non-smoker	39 (61.9%)	24 (38.1%)		
ECC status			0.005	7.952
Not taken or negative	159 (64.1%)	89 (35.9%)		
≥ CIN2	87 (79.1%)	23 (20.9%)		

HPV, human papillomavirus; ECC, endocervical curettage.

<sup>a</sup> the percent of patients whose conization revealed ≥ cervical intraepithelial neoplasia 2 (CIN2) lesions in each subgroup of clinico-pathological characteristics. The statistical analysis performed was a univariate analysis.

**Table 5. Factors affecting concordance between colposcopic biopsy and conization results.**

	OR (95% CI)	<i>p</i> -value	$\beta$ /SE/Wald values
HPV (HPV 16 vs. HPV 18 + other and HPV unknown/negative)	1.72 (1.05–2.83)	0.031	0.545/0.252/4.651
Menopausal status (Premenopausal vs. Postmenopausal and Unknown group)	2.47 (1.46–4.17)	0.001	0.904/0.267/11.446
ECC status (negative vs. positive)	0.345 (0.193–0.616)	<0.001	–1.065/0.296/12.934

HPV, human papillomavirus; ECC, endocervical curettage; OR, odds ratio; CI, confidence interval. The statistical analysis performed was a multivariate analysis.

prevalence of HPV type 16 in precancerous and invasive cervical lesions has resulted in more comprehensive colposcopic examination and an increased number of punch biopsies performed by the colposcopist. This has enhanced sensitivity and accuracy of colposcopy and contributed to improved concordance.

In the present study, the concordance rate between CDB and LEEP was 73.4% in premenopausal patients and 56.3% in postmenopausal patients, as determined by univariate analysis. Furthermore, multivariate analysis revealed that premenopausal status was an independent factor associated with concordance. Menopausal status has

been identified as a factor that may potentially compromise the accuracy of CDB, as cervical atrophy during colposcopy can obscure the visualization of the TZ. Moreover, the presence of atrophic cells with an increased nucleus-to-cytoplasm ratio in postmenopausal women may result in misdiagnosis as dysplastic cells in the CDB. These factors may provide a potential explanation for the observed increase in concordance observed in premenopausal patients. Indeed, studies by Baldauf *et al.* [23], Fan *et al.* [15], and Cheng *et al.* [24] have similarly identified premenopausal status as a key factor that increases concordance between CDB and the final histological diagnosis.

In the study conducted by Müller *et al.* [25], the concordance between the initial and final histological results for ECC was 49.1%. In the study by Fan *et al.* [15], the corresponding rate was 30.8%. In the present study, preoperative positive  $\geq$  CIN2 in ECC was associated with an 81.3% concordance in univariate analysis and was identified as a statistically significant independent factor in multivariate analysis. It is important to note that, during the course of our study, LEEP was performed on patients presenting with  $\geq$  CIN2 lesions following CDB. As a result, the findings revealed a relatively high level of concordance between patients undergoing ECC and those with  $\geq$  CIN2 lesions. This may help explain the discrepancy in rates observed in other studies. A review of the existing literature indicated that the present study is the only one to identify ECC with preoperative  $\geq$  CIN2 positivity as an independent factor affecting the concordance between CDB and LEEP. As such, it makes a significant contribution to the existing body of knowledge in this field.

Endocervicopy can be utilized in a manner analogous to ECC when visualization of the squamocolumnar junction is challenging, and a potential lesion in the endocervical canal may be overlooked. It is believed that the probability of pregnancy complications can be diminished by avoiding unnecessary LEEP procedures and determining the length and volume of LEEP, particularly in women who harbour concerns regarding future pregnancy outcomes [26].

#### *Limitations and Strengths*

Previous studies have identified various parameters that may influence the accuracy of CDB and the concordance between CDB and LEEP. These factors include the type of TZ, the number of punch biopsies taken, the size of the lesion visualized during colposcopy, the number of vaginal deliveries, and the delay in treatment [4,6,15]. However, the inclusion of these parameters in the present study was hindered by its retrospective nature, which made it impossible to obtain relevant information from patient records. This constitutes an important limitation of the study.

In view of the paucity of studies examining the concordance between CDB and LEEP, and considering that the present study had an adequate sample size of 358 patients undergoing conization, with all surgical procedures performed by experienced physicians specializing in gynecological oncology, these factors represent the strengths of the present study.

## **5. Conclusions**

The multivariate analysis revealed that HPV type 16 positivity, premenopausal status, and the presence of a  $\geq$  CIN2 lesion in the preoperative ECC were independent factors associated with the concordance between CDB and LEEP. Based on the aforementioned information, our study

makes a significant contribution to the existing literature, particularly by identifying the presence of a  $\geq$  CIN2 lesion in preoperative ECC as a crucial factor influencing concordance. In this context, understanding the factors that determine the concordance between CDB and LEEP will help inform the clinician's approach to patient counseling and subsequent management.

## **Availability of Data and Materials**

Should further information be required, it will be made available upon reasonable request. The raw data were generated at the Antalya Training and Research Hospital, which is affiliated with the Health Science University. The data derived from this study that support the findings presented herein are available from the corresponding author upon request.

## **Author Contributions**

NY: Conceptualization, validation and formal analysis, data collection, writing original draft preparation, funding acquisition. AA: Data collection, data curation. MuG: Data collection, data curation. MeG: Data curation, visualization. TT: Visualization, project administration; contribution to study design and analysis of data. IU: Conceptualization, methodology, validation and formal analysis, writing–review and editing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## **Ethics Approval and Consent to Participate**

The study was conducted in accordance with the ethical standards set forth in the Declaration of Helsinki and approved by the Ethics Committee of Antalya Training and Research Hospital (approval date: 10 October 2024, approval number: 2024-318). As this was a retrospective study, the participants were not asked to provide informed consent prior to their involvement.

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## **Conflict of Interest**

The authors declare no conflict of interest.

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