



Cold coagulation revisited: a strategy for high-grade cervical intraepithelial neoplasia in reproductive-age women

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Objective

Cold coagulation, although less commonly used today, offers a less invasive alternative to excisional procedures for high-grade cervical intraepithelial neoplasia (CIN). This study evaluated post-treatment cytologic and virologic negativity rates among reproductive-age women with high-grade CIN.

Methods

This retrospective study analyzed the medical records of 151 reproductive-age women diagnosed with CIN2 or 3 who were treated with cold coagulation at a single tertiary referral hospital between January 2010 and April 2022. Efficacy was assessed using follow-up liquid-based cytology and human papillomavirus (HPV) tests performed 3 months to 3 years after treatment. Statistical analyses included odds ratios and a univariate Cox proportional hazards model to evaluate treatment outcomes and failure rates.

Results

At 6 months, cytologic negativity was achieved in 66.7% of patients and virologic negativity in 50.0%; these rates increased to 81.3% and 70.0%, respectively, by 3 years. Treatment failure occurred in 26.5% of patients. However, no significant differences in negative test rates were observed between CIN2 and CIN3 or between HPV16/18 and other high-risk HPV types. Persistent disease occurred in 25.8% of patients, whereas recurrence was observed in 2.6%. Minimal complications were reported and no cases of progression to cervical cancer were identified.

Conclusion

Cold coagulation demonstrated moderate post-treatment cytologic and virologic negativity rates with minimal immediate complications in this retrospective cohort. However, given the substantial rate of persistent disease and the non-standard role of ablative treatment in settings where excision is available, these findings should be interpreted with caution.

Keywords: Cryosurgery; Cervical intraepithelial neoplasia; Human papillomavirus; Treatment outcome; Women of childbearing age

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Introduction

Cervical cancer ranks as the fourth most common cancer and the fourth leading cause of cancer-related mortality among women worldwide [1]. Nearly all cases of cervical cancer and its precursor lesions are attributable to persistent infection with carcinogenic, or high-risk, human papillomavirus (HPV) genotypes [2]. Consequently, primary strategies for preventing cervical cancer include screening methods such as cytology and HPV testing, followed by colposcopy and biopsy of suspicious lesions. Additionally, treatment of cervical lesions involves excision or ablation of the cervical transformation zone when a biopsy confirms cervical intraepithelial neoplasia (CIN) grades 2 or 3 [3]. Treatment of high-grade CIN, including CIN2 and 3, often involves the loop electrosurgical excision procedure (LEEP), which is widely performed as both a diagnostic and therapeutic method because it allows definitive histologic evaluation of the excised specimen [4]. However, a substantial proportion of patients requiring treatment for CIN are women of reproductive age. Several studies have reported that LEEP is associated with an increased risk of preterm delivery and low birth weight in subsequent pregnancies [5-7]. Therefore, less invasive approaches such as cold coagulation have been considered for selected reproductive-age women with high-grade CIN, although potential reproductive benefits were not directly evaluated in the present study. Cold coagulation has demonstrated favorable treatment outcomes and may offer practical advantages, particularly in resource-limited settings [8,9]. Previous studies of cold coagulation primarily relied on conventional Papanicolaou smear results. In contemporary clinical practice, however, post-treatment surveillance of high-grade CIN increasingly relies on HPV-based testing, with or without cytology [10]. Accordingly, this study analyzed post-treatment cytologic and virologic negativity rates among reproductive-age women undergoing cold coagulation for high-grade CIN.

Materials and methods

This retrospective study included 151 reproductive-age women aged 19-45 years with punch biopsy-confirmed CIN2 or CIN3 who underwent cold coagulation at a single tertiary referral hospital between January 2010 and April 2022. Patients with CIN1, those outside the eligible age range, and

those without post-treatment follow-up were excluded. Of the 2,418 patients initially reviewed, 151 met the inclusion criteria (Fig. 1). Collected variables included age, body mass index (BMI), gravidity, parity, smoking status, immunosuppression or autoimmune disease, pre-treatment biopsy results, endocervical involvement when endocervical curettage was performed, cytology, HPV status, follow-up test results, additional treatment, recurrence, and progression to cervical cancer. Patients were stratified according to initial CIN grade (CIN2 vs. CIN3) and HPV type (HPV16/18 vs. other high-risk HPV types).

Cold coagulation was performed using a WiSAP Coagulator (WiSAP, Munich, Germany) with a pointed thermo-probe (Model 6008) set at 100°C. Each application lasted approximately 20-30 seconds and overlapping applications were applied as needed to cover the entire transformation zone or visible lesion. The procedures were performed by clinicians

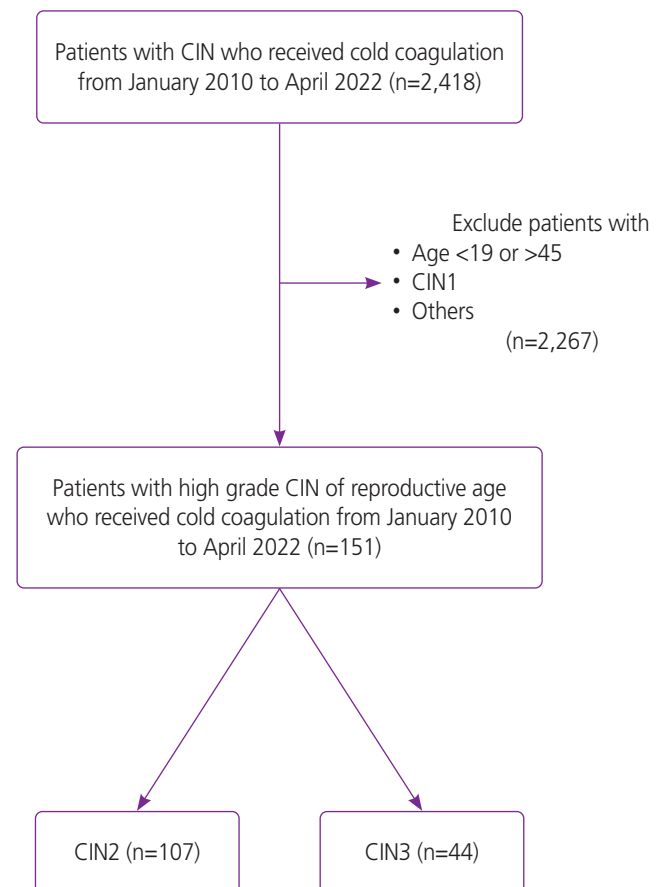


Fig. 1. Flowchart illustrating the patient selection process for reproductive-age women with high-grade cervical intraepithelial neoplasia (CIN).

in the colposcopy clinic using the same institutional device settings and a generally standardized procedural approach throughout the study period.

HPV testing was performed using the cobas® 4800 HPV Test (Roche Molecular Systems, Pleasanton, CA, USA), which reports HPV16 and HPV18 individually and 12 other high-risk HPV types as a pooled result.

Cold coagulation was considered only for patients deemed suitable for ablative treatment after clinicopathologic evaluation. Eligibility generally required satisfactory colposcopy with complete visualization of the squamocolumnar junction and lesion margins, no suspicion of invasive carcinoma or glandular disease on cytology or colposcopy, and no indication for immediate diagnostic excision. Patients with suspected invasive disease, unsatisfactory colposcopy, or lesions extending into the endocervical canal were not considered suitable candidates. In patients with CIN3 on punch biopsy, cold coagulation was reserved for carefully selected cases in which the lesion was fully visible and invasive disease was considered unlikely based on pre-treatment evaluation. The treatment modality was selected at the discretion of the treating clinician based on the biopsy result, colposcopic impression, lesion extent, and endocervical assessment.

Patients were scheduled for follow-up at 3, 6, and 12 months after treatment. Follow-up included clinical examination, liquid-based cytology, and colposcopy, with HPV testing performed at the clinician's discretion. Patients with abnormal cytology and/or positive HPV results underwent further evaluation and additional treatment, if indicated.

Post-treatment cytologic negativity was defined as normal cytology at follow-up and virologic negativity was defined as the absence of detectable high-risk HPV at each follow-up time point. Because serial HPV testing at uniform intervals was not available for all patients, sustained HPV-negative conversion could not be used as a primary endpoint. Persistent disease was defined as abnormal cytology or positive HPV at 6 months and recurrence was defined as biopsy-confirmed CIN2 or higher after an initially normal post-treatment cytology result. Treatment failure was defined as abnormal cytology or positive HPV within 6 months after treatment; atypical squamous cells of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesions (LSIL) with a negative HPV test were not considered treatment failure.

Statistical analyses were conducted using SPSS Statistics for Windows, Version 26.0 (IBM SPSS Inc., Chicago, IL, USA).

Continuous variables that followed a normal distribution were analyzed using Student's *t*-test. Categorical variables were evaluated using Pearson's chi-square test or Fisher's exact test, as appropriate. To assess the impact of variables on treatment failure, univariate Cox proportional hazards regression analysis was performed. A *P*-value <0.05 was considered statistically significant.

Table 1. Demographic and clinicopathologic characteristics of patients (n=151)

Characteristic	Value
Age (yr)	28.8±4.9
BMI (kg/m ²)	20.8±2.9
Gravidity	0
Parity	0
Current smoking	25 (16.6)
Immunodeficiency disorders or autoimmune disease	4 (2.6)
Initial colposcopic findings	
Normal	5 (3.3)
Grade 1	131 (86.8)
Grade 2	15 (9.9)
Initial liquid cytology	
Negative	2 (1.3)
ASCUS	78 (51.7)
LSIL	34 (22.5)
HSIL	37 (24.5)
Initial HPV test	
Negative	6 (4.0)
Positive	145 (96.0)
Low risk HPV	
High-risk HPV	145 (96.0)
HPV 16 and 18	49 (32.4)
HPV, other high-risk types	96 (63.6)
CDB	
CIN2	107 (70.9)
CIN3	44 (29.1)
Endocervical involvement	2 (1.3)

Values are presented as mean±standard deviation or median or number (%).

BMI, body mass index; ASCUS, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; HPV, human papillomavirus; CDB, colposcopy-directed biopsy; CIN, cervical intraepithelial neoplasia.

Results

1. Overall study population

In this cohort of 151 patients, the mean age was 28.8 ± 4.9 years, and the mean BMI was 20.8 ± 2.9 kg/m² (Table 1). The median gravidity and parity were both 0. Current smoking was reported in 16.6% (n=25) of patients and 2.6% (n=4) had immunodeficiency disorders or autoimmune diseases. Initial colposcopic findings showed that most patients had grade 1 lesions (86.8%). Liquid-based cytology results indicated that 1.3% (n=2) of patients had negative results, 51.7% (n=78) had ASCUS, 22.5% (n=34) had LSIL, and 24.5% (n=37) had high-grade squamous intraepithelial lesions (HSIL). Initial HPV testing showed that 4.0% (n=6) of patients were HPV-negative, whereas 96.0% (n=145) tested positive for high-risk HPV types; 32.4% (n=49) had HPV16/18, and 63.6% (n=96) had other high-risk HPV types. Initial colposcopy-directed biopsy (CDB) results showed that 70.9% (n=107) had CIN2 and 29.1% (n=44) had CIN3. Endocervical involvement was present in 1.3% (n=2) of patients.

2. Cytologic and virologic negativity during the follow-up period

Cytologic and virologic negativity rates during the follow-up period were documented for the cohort of 151 patients (Table 2). The proportion of patients achieving cytologic negativity, defined as negative liquid-based cytology results, gradually

increased from 58.5% (n=79) at 3 months to 66.7% (n=62) at 6 months, 76.1% (n=83) at 12 months, 81.8% (n=54) at 2 years, and 81.3% (n=26) at 3 years. Similarly, virologic negativity, defined as the absence of detectable HPV, increased from 49.6% (n=67) at 3 months to 70.0% (n=21) at 3 years.

3. Negative test rates stratified by initial CIN grade and HPV status

To assess variables influencing negative test rates, we analyzed the cohort of 151 patients at the 3- and 6-month follow-up time points. A negative test result was defined as normal cytology with a negative HPV test, including cases of ASCUS or LSIL with a negative HPV result.

At 3 months, 66.7% (90/135) of patients achieved a negative test result, with patients with CIN2 showing a 66.3% (61/92) negative test rate and those with CIN3 showing a 67.4% (29/43) rate (Table 3). At 6 months, the negative test rate increased slightly to 69.9% (65/93), with CIN2 patients demonstrating a 72.5% (50/69) negative test rate compared with 62.5% (15/24) among CIN3 patients. Adjusted odds ratios that accounted for potential confounders, including age, gravidity, parity, smoking status, and immunodeficiency or autoimmune disease, showed no significant differences in negative test rates between patients with CIN2 and CIN3.

Stratification by HPV status showed that HPV-negative patients had an 80.0% (4/5) negative test rate at 3 months (Table 4), which was higher than the 71.1% (32/45) rate among patients with HPV 16/18 and the 63.5% (54/85) rate among

Table 2. Post-treatment cytologic and virologic negativity rates

	Initial	3 months f/u	6 months f/u	12 months f/u	2 years f/u	3 years f/u
Cytologic negativity results						
Negative	2 (1.3)	79 (58.5)	62 (66.7)	83 (76.1)	54 (81.8)	26 (81.3)
ASCUS	78 (51.7)	28 (20.7)	16 (17.2)	14 (12.8)	8 (12.1)	3 (9.4)
LSIL	34 (22.5)	23 (17.0)	11 (11.8)	11 (10.1)	4 (6.1)	1 (3.1)
HSIL	37 (24.5)	5 (3.7)	4 (4.3)	1 (0.9)		2 (6.2)
Total	151	135	93	109	66	32
Virologic negativity results						
Negative	6 (4.0)	67 (49.6)	41 (50.0)	67 (62.6)	41 (64.1)	21 (70.0)
Positive	145 (96.0)	68 (50.4)	41 (50.0)	40 (37.4)	23 (35.9)	9 (30.0)
Total	151	135	82	107	64	30

Values are presented as number (%). Percentages may not total 100 because of rounding.

f/u, follow-up; ASCUS, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion.

Table 3. Post-treatment negativity rates at 3 and 6 months following cold coagulation, stratified by initial CDB result (n=151)

Intervals	Negative test rate			Adjusted OR ^a (95% CI)
	All patients	CIN2	CIN3	
3 months	90/135 (66.7)	61/92 (66.3)	29/43 (67.4)	1.15 (0.51-2.61)
6 months	65/93 (69.9)	50/69 (72.5)	15/24 (62.5)	1.63 (0.56-4.75)

Values are presented as number (%) unless otherwise indicated.

CDB, colposcopy-directed biopsy; CIN, cervical intraepithelial neoplasia; OR, odds ratio; CI, confidence interval; HPV, human papillomavirus.

^aThe reported odds ratios compare the likelihood of achieving a negative test result between patients with CIN2 and those with CIN3. The odds ratios were adjusted for potential confounders, including age, gravidity, parity, smoking status, immunodeficiency or autoimmune disease, and HPV status.

Table 4. Post-treatment negativity rates at 3 and 6 months following cold coagulation, stratified by HPV status (n=151)

Intervals	Negative test				Adjusted OR ^a (95% CI)
	All patients	HPV negative	HPV positive (HPV 16, 18)	HPV positive (other high-risk HPV)	
3 months	90/135 (66.7)	4/5 (80.0)	32/45 (71.1)	54/85 (63.5)	1.35 (0.59-3.06)
6 months	65/93 (69.9)	2/2 (100.0)	18/25 (72.0)	45/66 (68.2)	1.60 (0.55-4.68)

Values are presented as number (%) unless otherwise indicated.

HPV, human papillomavirus; OR, odds ratio; CI, confidence interval.

^aThe reported odds ratios compare the likelihood of achieving a negative test result between patients with HPV 16/18 and those with other high-risk HPV types. The odds ratios were adjusted for potential confounders, including age, gravidity, parity, smoking status, immunodeficiency or autoimmune disease, and initial colposcopy-directed biopsy results.

those with other high-risk HPV types. At 6 months, HPV-negative patients had a 100.0% (2/2) negative test rate. In comparison, patients with HPV 16/18 had a negative test rate of 72.0% (18/25), and those with other high-risk HPV types had a rate of 68.2% (45/66). Adjusted odds ratios showed no significant differences among the HPV groups ($P=0.478$ at 3 months and $P=0.706$ at 6 months) after adjustment for potential confounders, including initial CDB results.

4. Treatment failure

Treatment failure was defined as persistent abnormal cytology or a positive HPV test at 6 months after treatment. However, cases of ASCUS and LSIL with a negative HPV test were not classified as treatment failures. Overall, 40 patients were classified as treatment failures at 6 months after treatment. The demographic and clinicopathologic characteristics of these patients are presented in Supplemental Table 1. A univariate Cox proportional hazards regression model was used to assess potential predictors of treatment failure and yielded no statistically significant associations (Supplemental Table 2). Gravidity (hazard ratio [HR], 0.713; $P=0.612$), parity (HR, 1.575; $P=0.604$), current smoking status (HR, 1.147; $P=0.837$), and the presence of immunosuppression or auto-

immune disease (HR, 1.306; $P=0.799$) were not associated with treatment failure. Initial colposcopic findings (normal, grade 1, or grade 2) were not significant predictors of treatment failure ($P>0.122$). HPV status, regardless of genotype, was also not associated with treatment failure ($P>0.834$). Additionally, initial CIN grade (CIN2 vs. CIN3) and endocervical involvement were not statistically significant predictors ($P>0.268$).

5. Disease outcomes and additional treatment

The median follow-up duration was 24.3 months (range, 2.6-90.7 months). During the treatment period, the only complication related to cold coagulation was vaginal spotting in one patient, which resolved after 1 day of vaginal roll-gauze packing.

Persistent disease was defined as persistent abnormal cytology or a positive HPV test at 6 months after initial treatment. In addition, cases in which patients had normal cytology after cold coagulation but were subsequently diagnosed with CIN2 or higher on punch biopsy were classified as disease recurrence.

Persistent disease was identified in 25.8% of patients (n=39), of whom 20 underwent additional treatment-13

received cold coagulation, eight underwent LEEP, and one received laser ablation (Table 5). One patient underwent both cold coagulation and LEEP and another received sequential cold coagulation followed by laser ablation. Among patients with persistent disease, 14 did not undergo further treatment for various reasons, including referral to another institution, loss to follow-up, pregnancy, or conservative management of minor cytologic abnormalities that were confirmed as chronic nonspecific inflammation or CIN1 on CDB.

Disease recurrence occurred in 2.6% of patients (n=4), with a mean time to recurrence of 13.7 months. Three of these patients received additional treatment (two with cold coagulation and one with LEEP). One patient diagnosed with CIN2 at 30.9 months after treatment had negative cytology but persistent HPV positivity and nonspecific inflammation on repeated colposcopy-directed biopsies, prompting continued surveillance.

Of the 151 patients, 128 (84.8%) did not receive additional treatment. The remaining 23 patients (15.2%) received additional treatment, including cold coagulation in 15 patients (9.9%), LEEP in nine patients (6.0%), and laser ablation in one patient (0.7%). The mean time to additional treatment was 7.1 months (range, 3.3-23.3 months). No cases of progression to cervical cancer were observed during the study period.

Table 5. Disease persistence, recurrence, and additional treatment details (n=151)

Disease outcome	
Persistent disease	39 (25.8)
Recurrence	4 (2.6)
Mean duration until recurrence (months)	13.7 (3.3-30.9)
Progression to cervical cancer	
Additional treatment details	
No additional treatment	128 (84.8)
Additional treatment ^a	23 (15.2)
Cold coagulation	15 (9.9)
LEEP	9 (6.0)
Laser ablation	1 (0.7)
Mean duration until additional treatment (months)	7.1 (3.3-23.3)

Values are presented as number (%) or mean (range).

LEEP, loop electrosurgical excision procedure.

^aOne patient underwent both cold coagulation and LEEP and another underwent sequential cold coagulation followed by laser ablation.

Discussion

In this cohort, cytologic and virologic negativity rates improved over time after cold coagulation but remained lower than those reported in several previous studies. No significant predictors of treatment failure were identified in the univariate analysis.

Persistent disease occurred in 25.8% of patients and 15.2% ultimately required additional treatment. Although most patients did not require retreatment, these findings indicate that disease persistence and recurrence remain clinically relevant after cold coagulation.

Previous studies evaluating the effectiveness of cold coagulation have reported cytologic negativity rates of 97% among patients with CIN3 at the first follow-up visit and an overall negative test rate of 95.7% among patients with CIN 1-3 after 1 year [11,12]. Studies assessing virologic outcomes have shown that, among patients with high-grade CIN, HPV was undetectable in 81.8% at 6 months and 83.3% at 18 months of follow-up [13]. Additionally, a meta-analysis evaluating the efficacy of cold coagulation reported a negative test rate of 95% (95% confidence interval, 92-98%) for high-grade CIN; procedure-related adverse events were rare, and fertility was not impaired [9]. However, these studies, including the present study, acknowledge that estimates of negative test rates may be biased because of frequent loss to follow-up, which may result in underestimation or overestimation of the true negative test rates. In a comparative analysis, a retrospective cohort study evaluated negative test rates in patients with high-grade CIN treated with cold coagulation versus large loop excision of the transformation zone (LLETZ) [14]. At 6 months after treatment, the negative test rates were 91.6% for cold coagulation and 97.1% for LLETZ ($P=0.02$). By 12 months, the negative test rates converged to 96.5% for cold coagulation and 97.3% for LLETZ ($P=0.76$).

In this study, the observed cytologic and virologic negativity rates were 76.1% and 62.6%, respectively, at 1 year, increasing to 81.8% and 64.1% at 2 years and reaching 81.3% and 70.0% at 3 years. These rates were lower than those previously reported. Several factors may explain the lower negativity rates observed in our cohort, including substantial loss to follow-up, restriction of the study population to reproductive-age patients with high-grade CIN, and the use of more sensitive contemporary HPV assays.

With respect to risk factors for treatment failure, previous

studies have identified endocervical crypt involvement and multiparity as being associated with an increased risk of failure. However, our analysis did not demonstrate significant associations between treatment failure and variables such as gravidity, parity, current smoking status, immunosuppression or autoimmune disease, initial colposcopic findings, HPV status, or initial CIN grade [15,16]. Only two patients had endocervical involvement and neither experienced treatment failure, suggesting that the small sample size may have limited the ability to detect statistically significant associations.

In the present cohort, post-treatment cytologic and virologic negativity rates were lower than those reported in several previous studies, and persistent disease was observed in 25.8% of patients. These findings suggest that cold coagulation should be interpreted with caution and should not be considered interchangeable with excisional treatment in routine practice. This consideration is particularly important for patients with CIN3, for whom excisional treatment is generally preferred because it provides a histologic specimen and allows margin assessment. Therefore, our findings should not be interpreted as supporting cold coagulation as a standard first-line treatment for all patients with high-grade CIN, but rather as observational outcomes from selected cases in which invasive disease was considered unlikely based on pre-treatment evaluation. Although cold coagulation has been less commonly used in recent years, previous studies have suggested that it may offer certain advantages as a less invasive alternative to excisional procedures such as LEEP, particularly with respect to subsequent obstetric outcomes and procedure-related burden. Excisional procedures such as LEEP have been associated with higher rates of spontaneous preterm birth and first-trimester miscarriage in subsequent pregnancies compared with cold coagulation [17]. The relatively limited disruption of deep cervical stromal tissue by cold coagulation may contribute to these findings [18]. However, these potential benefits should be interpreted with caution in the context of our study, given the moderate cytologic and virologic negativity rates observed in our cohort, the absence of histologic margin assessment, and the lack of directly evaluated reproductive or obstetric outcomes. In addition, although cold coagulation has been reported to have a low failure rate in the treatment of subclinical HPV infection [19], the fertility-preserving implications of this procedure in our study remain indirect and should not be considered definitively demonstrated.

Despite the demonstrated effectiveness of cold coagulation, the occurrence of persistent disease and recurrence after treatment presents ongoing challenges in the management of CIN. The absence of identifiable risk factors for these outcomes underscores the need for further research to identify biomarkers that may enable more targeted treatment strategies. These findings highlight the importance of careful follow-up and the potential need for additional interventions to achieve optimal outcomes. Moreover, recent proposals to use cold coagulation in conjunction with LEEP for hemostatic purposes or to treat residual dysplastic cells suggest potential innovative applications of this treatment modality [20,21]. Further investigation into the role of cold coagulation within treatment protocols is warranted and may contribute to advances in patient care and management.

This study has several important limitations, including its retrospective design, single-center setting, and relatively small sample size. A major limitation is the substantial loss to follow-up over time. Based on the available data, follow-up completeness declined markedly during the study period, raising concerns about attrition bias and limiting the representativeness of the analyzed cohort. Because loss to follow-up in retrospective observational studies is unlikely to be random, the reported post-treatment cytologic and virologic negativity rates may have been either overestimated or underestimated. Furthermore, the denominators differed between cytology and HPV testing at each follow-up time point, which further complicates direct longitudinal interpretation. We also acknowledge that a single negative HPV test does not necessarily indicate durable virologic clearance; therefore, our outcome definitions should be interpreted as time point-specific post-treatment negativity rather than as evidence of definitive cure. Finally, because ablative treatment is inherently operator dependent, inter-operator or temporal variability in technique may have influenced treatment outcomes over the extended study period. Another important limitation is the potential for selection bias. Because this study included only patients who underwent cold coagulation, the cohort likely represents a selected subgroup considered suitable for ablative treatment in clinical practice. Patients with smaller lesions, more favorable colposcopic findings, lower suspicion of occult invasion, or better anticipated follow-up adherence may have been preferentially selected for cold coagulation, which may have influenced both the observed outcome rates and the generalizability of the

findings.

Nonetheless, this study is distinguished by its specific focus on women of reproductive age, a population that frequently encounters HPV infection and is at considerable risk for high-grade CIN. This focus provides important insights into treatment outcomes within this subgroup. In contrast to previous research, which primarily relied on conventional assessment methods, this investigation incorporated liquid-based cytology and HPV genotyping for follow-up evaluation. These diagnostic approaches enhance the precision and reliability of post-treatment outcome monitoring and offer a more comprehensive and contemporary perspective on the role of cold coagulation in the management of high-grade CIN within current clinical practice.

In conclusion, cold coagulation demonstrated moderate post-treatment cytologic and virologic negativity rates with minimal immediate complications in this retrospective cohort. However, given the relatively high rate of persistent disease, the lack of histologic margin assessment, and the nonstandard role of ablative treatment in settings where excisional treatment is available, these findings should be interpreted with caution. Cold coagulation may be considered only in carefully selected patients after thorough exclusion of invasive disease and with close follow-up, rather than as a routine first-line treatment for all reproductive-age women with high-grade CIN.

Conflict of interest

The authors have no financial or other interests relevant to this article to declare.

Ethical approval

The Institutional Review Board of Yonsei University Health System, Severance Hospital, approved this study (Protocol number: 4-2023-1386, dated December 13, 2023), and informed consent was waived.

Patient consent

The need for informed consent was waived as patient infor-

mation was anonymized, and the study does not include any data that may identify the patients.

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Supplemental Table 1. Demographic and clinicopathologic characteristics of patients with treatment failure within 6 months (n=40)

Characteristic	Value
Age (yr)	27.75±5.1
BMI (kg/m ²)	21.0±2.8
Gravidity	0
Parity	0
Current smoking	4 (10.0)
Immunodeficiency disorders or autoimmune disease	1 (2.5)
Initial colposcopic findings	
Normal	2 (5.0)
Grade 1	32 (80.0)
Grade 2	6 (15.0)
Initial liquid cytology	
Negative	
ASCUS	19 (47.5)
LSIL	8 (20.0)
HSIL	13 (32.5)
Initial HPV test	
Negative	1 (2.5)
Positive	39 (97.5)
Low risk HPV	
High risk HPV	39 (97.5)
HPV 16, 18	12 (30.0)
HPV other high-risk type	27 (67.5)
CDB	
CIN2	26 (65.0)
CIN3	14 (35.0)
Endocervical involvement	

Values are presented as mean±standard deviation or median or number (%).

BMI, body mass index; ASCUS, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; HPV, human papillomavirus; CDB, colposcopy-directed biopsy; CIN, cervical intraepithelial neoplasia.

Supplemental Table 2. Univariable Cox proportional hazards regression analysis for treatment failure

Characteristic	HR (95% CI)
Gravidity	
0	Reference
≥1	0.713 (0.19-2.63)
Parity	
0	Reference
≥1	1.575 (0.28-8.77)
Current smoking	
No	Reference
Yes	1.147 (0.31-4.23)
Immunodeficiency disorders or autoimmune disease	
No	Reference
Yes	1.306 (0.17-10.28)
Initial colposcopic findings	
Normal	Reference
Grade 1	0.304 (0.07-1.37)
Grade 2	0.493 (0.09-2.60)
Initial HPV test	
Negative	Reference
Positive, HPV 16, 18	0.863 (0.09-7.97)
Positive, HPV other high-risk type	0.793 (0.09-6.97)
CDB	
CIN2	Reference
CIN3	0.657 (0.31-1.38)
Endocervical involvement	
No	Reference
Yes	0.903 (0.10-7.94)

HR, hazard ratio; CI, confidence interval; HPV, human papillomavirus; CDB, colposcopy-directed biopsy; CIN, cervical intraepithelial neoplasia.