Research Article

Risk Factors of High-Grade CIN in Women with ASC-H: Indications for Direct Conization

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Abstract

Objective: To identify risk factors of high-grade CIN and cervical cancer in women with ASC-H

Methods: A retrospective chart review of 155 patients who had ASC-H and underwent conization between 2013 and 2022. Clinical factors (age, parity, body weight, height, medical history, prior history of abdominal surgery, and complete blood counts within 1week of conization), and pathologic results (type of HPV infection, punch biopsy results, and pathologic reports of conization) are recruited.

Results: A total of 122 women were diagnosed with high-grade CIN (≥CIN2) by punch biopsy or conization. Women with high-grade CIN were significantly correlated with younger age (<45 years old), non-multiparity, non-menopause, no prior abdominal surgery, high-risk HPV infection, and higher neutrophil to lymphocyte (NLR) ratio (≥ 2.0) than those without HSIL (<CIN2). Multiple logistic regression revealed that high-risk HPV infection (Hazard ratio 4.709; 95% Confidence interval 1.541~14.391; P= 0.007) and no regular check-up of pap smear (Hazard ratio 4.047; 95% CI (1.409~11.628; P= 0.009) were high-risk factors for high-grade CIN in women with ASC-H.

Conclusion: Direct conization might be preferred when women with ASC-H also have high-risk HPV infection and no routine check-up of pap smear.

Keywords: ASC-H; CIN; HPV; Cervix Cancer; LEEP; Conization;

Introduction

Cervical intraepithelial neoplasia (CIN) is a preinvasive disease of the cervix, which can be diagnosed with screening tests, such as pap smear, colposcopy, and punch biopsy. According to the ASCCP guidelines, women diagnosed as CIN2-3 and older than 30 years old should perform conization because of the high risk for the progression to cervical cancer.

ASC-H(atypical squamous cells, cannot exclude squamous intraepithelial lesion) is a subcategory of ASC(atypical squamous cells) by the most recent Bethesda System classification [1]. Several studies have reported that ASC-H is associated with a 30~40% incidence of high-grade CIN lesions, which is twice as high as in ASCUS [2-4]. Therefore, some authors suggested that direct conization might be a better option for women with ASC-H, which allows see-and-treatment [2, 3]. In contrast, another study suggested that women with ASC-H and other risk factors of high-grade CIN (e.g., high-risk HPV infection) should selectively perform colposcopy [4]. However, ASCCP guidelines still recommend that all women with ASC-H should perform colposcopy for the detection of high-grade CIN lesions, irrespective of other risk factors [5].

Therefore, in this study, we aimed to identify risk factors of high-grade CIN and cervical cancer in women with ASC-H.

Materials and Methods

We retrospectively reviewed all the medical charts of women with ASC-H who underwent conization between 2013

and 2022 in Hallym University Dongtan Sacred Heart Hospital. Total 155 patients were included in this study. Clinical factors (age, parity, body weight, height, medical history, regular check-up of pap smear (pap smear within 3 years), and complete blood counts within 1 week of conization), and pathologic results (type of HPV infection, and pathologic reports of punch biopsy and/or conization) are recruited. High-grade CIN was defined as CIN2-3 by pathologic reports of either punch biopsy or conization. When the pathologic reports of punch biopsy is different from those of conization, more higher CIN is adopted as the final pathology.

All the statistical analyses were performed using SPSS 26.0 (SPSS, Inc., Chicago, IL) and Medcalc software (version 15.2.2, Portland, USA). Data are described as means ± SD after confirming Gaussian distribution for qualitative variables, and n (%) for categorical ones.

Pearson's chi-squared test or Fisher's exact test was used to compare the results for categorical variables. Student's t-test was used to compare the results of qualitative variables. A P-value less than 0.05 was used to indicate a statistically significant difference.

Multivariate analysis was performed using binary logistic regression. The hazard ratio (HR) and 95% confidence intervals (CI) were calculated. The cut-off value of the neutrophil-to-lymphocyte ratio (NLR) in the discrimination of high-grade CIN from others was determined using the receiver operating characteristics (ROC) curve analysis.

This study was approved by the institutional review board (**IRB no.2023-02-017-001**) of Hallym University Dongtan Sacred Heart Hospital.

Results

During the study period, total of 122 women were diagnosed with high-grade CIN (≥CIN2) by punch biopsy or conization. Patients' characteristics are presented in Table 1. The mean age was 42.9 years old, and 29.0 % were menopaused women. 91.3% were positive for high-risk HPV. In Table 2, the clinical factors of women with high-grade CIN were compared to those of women without high-grade CIN. Women with high-grade CIN were significantly correlated with younger age (<45 years old), non-multiparity, non-menopause, non-regular check-up of pap smear, high-risk HPV infection, and higher neutrophil to lymphocyte (NLR) ratio (≥ 2.0) than those without high-grade CIN (<CIN2). Multiple logistic regression revealed that high-risk HPV infection (Hazard ratio 4.709; 95% Confidence interval 1.541~14.391; P= 0.007) and non-regular check-ups of pap smear (Hazard ratio 4.047; 95% CI (1.409~11.628; P= 0.009) were high risk factors for high-grade CIN in women with ASC-H (Table 3).

Characteristics	Mean ± SD or N (%)
Age (years old)	42.9 ± 12.12
BMI (kg/m^2)	23.36 ± 4.05
Parity	1.6 ± 1.04
Menopause	45 (29.0)
Hormone replacement therapy	3 (1.93)
HPV infection	114 (73.5)
High risk HPV infection	105 (91.3)
Smoker	4 (2.6)
Prior history of PID	70 (45.2)
Punch biopsy	
Yes	102 (65.8)
No	53 (34.2)
Final pathology	
Negative or chronic cervicitis	18 (11.6)
CIN1	15 (9.7)
CIN2	20 (12.9)
CIN3	38 (24.6)
CIS	39 (25.1)
Invasive cervical cancer	25 (16.1)
*P value less than 0.05	

Table 1: Patients' Characteristics

Characteristics	Non-high-grade CIN (N=33)	High-grade CIN (N=122)	*P* value
Age (years old)			0.005*
<45	12 (36.4)	78 (63.9)	
≥45	21 (63.6)	44 (36.1)	
BMI (kg/m^2)	23.5 ± 3.17	23.3 ± 4.26	0.757
Multiparity	23 (74.2)	67 (55.4)	0.043*
Menopause	16 (48.5)	29 (23.8)	0.009*
Hormone replacement	1 (3.0)	2 (1.7)	0.518
Smoker (present or prior)	0 (0.00)	4 (3.3)	0.390
Regular check-up of pap smear			0.016*
No	21 (63.6)	49 (40.2)	
Yes	12 (26.4)	73 (59.8)	
History of PID	1 (3.1)	6 (4.9)	1.000
High risk HPV infection	14 (46.7)	91(81.3)	< 0.0001*
HPV 16 or 18 infection	3 (10.7)	39 (34.5)	0.019*
NLR ratio			0.013*
< 2.0	27 (84.4)	72 (62.1)	
2.0 ≥	5 (15.6)	44 (37.9)	
Data are Presented as Mean ± SD or N (%). *P value less than 0.05			

Table 2: Clinical factors comparing women with final diagnosis of high-grade CIN (CIN2 ≥) and those with non-high-grade CIN

Risk Factors	HR (95% CI)	*P* value
Age (≥45 years old)	0.941(0.206-4.301)	0.938
Multiparity	0.954 (0.285-3.188)	0.939
Menopause	0.251 (0.048-1.323)	0.103
Non-regular check-up of pap smear	4.047 (1.409-11.628)	0.009*
High risk HPV infection	4.709 (1.541-14.391)	0.007*
HPV 16 or 18 infection	1.745 (0.406-7.504)	0.454
NLR ratio (> 2.0)	2.312 (0.698-7.654)	0.170
*P value less than 0.05		

Table 3: High risk factors of high-grade CIN in women with ASC-H

Discussion

There are some debates about the management of women with ASC-H. Generally, the risk of high-grade CIN in women with ASC-H is known to be up to 33% and the risk of cancer is up to 3% [6, 7]. Although ASCCP guidelines recommended that colposcopy for women with ASC-H, regardless of their age, some clinicians suggest that direct LEEP (loop electrosurgical excision procedure) might be a better option for the diagnosis and treatment of high-grade CIN all at once [8]. The diagnosis of ASC-H is notorious for its poor reproducibility. One study showed that interobserver agreement among 3 cytopathologists was only 14% for ASC-H and 18%

for ASC-US [1]. Another single-tertiary center study suggested that biopsy revealed low-grade dysplasia in 18.8% of the cases, high-grade dysplasia in 27.8%, and infiltrating carcinoma in 2.3% [3]. A diagnosis of ASC-H/squamous intraepithelial lesion in the repeated cytology had a sensitivity of 74.2%, specificity of 39.6%, positive predictive value of 44.8%, and negative predictive value of 70% for the diagnosis of dysplasia [3]. The authors suggested that all the patients with this diagnosis should be examined with colposcopy and biopsy if suspicious lesions are found [3].

In contrast, a retrospective study in Korea reported that 47.4% of the women with ASC-H who were HPV positive had high-grade CIN [9]. There were no cases of invasive cervical cancer among women with ASC-H who were HPV-negative [9]. Logistic regression revealed that HPV infection was significantly correlated with high-grade CIN (OR 14.42, 95%CI 7.50~27.75, P value <0.001) [9]. They suggested that Reflex HPV testing should be an option for the management of women with cytology showing ASC-H to decrease unnecessary colposcopy [9].

There have been several studies to identify risk stratification in women with ASC-H. Recently, a cross-sectional study in a single-center suggested a new scoring system of colposcopy (Reid modified index and Swede score) for the detection of HSIL+ [10]. They included 66 women with ASC-H and reported that the sensitivity (86.11%), specificity (83.33%), positive (86.11%) and negative predictive value (83.33%), and positive likelihood ratio (5.17; 95% CI 2.3~11.6) of modified Reid colposcopic index at a cutoff of ≥4 for the detection of HSIL+ lesions [10]. Also, the Swede score showed comparable results to the modified Reid index with the increased sensitivity (94.44%) with a cutoff value ≥5 [10]. Interestingly, they suggested that Swede score > 8 might be an indication for 'see and treatment' in the management of ASC-H [10].

Another meta-analysis for the detection of diagnostic markers for high-grade CIN in women with ASC-H reported that the pooled absolute sensitivity and specificity of the Hybrid Capture 2 (HC2) assay for high-grade CIN were 93% and 45%, respectively [11]. p16INK4a staining (only 3 studies) had similar sensitivity (93%) but superior specificity (specificity ratio, 1.69) to HC2 for the detection of high-grade CIN [11]. The average pretest risk was 34% for CIN2+ and 20% for CIN3+. When the HC2 is negative, the average pretest risk of CIN2+ and CIN3+ is 8% and 5%, respectively, whereas a positive result upgraded the risk to 47% and 28%, respectively [11]. They suggested that direct colposcopy should be a standard option for women with ASC-H, otherwise, repeated pap smear may be allowed for women with ASC-H and negative for high-risk HPV DNA or p16INK4a test [11].

There have been few studies comparing the efficacy of direct conization to that of a three-step approach (colposcopy) in women with ASC-H. A retrospective study comparing the pathologic results of direct conization to those of the three-step approach in women with ASC-H reported that there the incidence of high-grade CIN was not different between the two groups (100% vs. 81.8%; P=1.000) [8]. They suggested that direct conization might be advantageous in ASC-H management [8]. Another study comparing the 2-step method (biopsy followed by treatment) with a see-and-treat (conization) approach in women with abnormal pap reported that in women with high-grade cytology results, which includes ASC-H, see-and-treat was inversely associated with overtreatment (11.3% [529 of 4677] versus 14.3% [1015 of 7100], respectively; odds ratio, 0.68; 95% confidence interval, 0.58-0.81). The authors suggested that a see-and-treat approach is justified only in women with high-grade cytology results who have completed their childbearing [12].

Another issue of colposcopy in women with ASC-H is a discrepancy of pathologic results between colposcopy and conization. According to a retrospective study, 23% of ASC-H required more than 1 biopsy to diagnose CIN 2-3, which suggests that high-grade CIN in women with ASC-H may be focal and more likely to be missed with colposcopy [13]. Similarly, our data showed that discrepancy rate of punch biopsy and LEEP were 63.7% (65/102). In our data, 62.6% of women with ASC-H were finally diagnosed with high-grade CIN and 16.1% were cervix cancer. In addition, there were no women who were diagnosed with cervical cancer, in case of negative HPV infection. Interestingly, women who had not had regular check-ups of pap smear showed higher risk for high-grade CIN. There have been many studies focusing on the importance of regular cervical cancer screening. Prior studies focusing on socio-demographic disparities in cervical cancer found that older, socioeconomically disadvantaged, and minority women were less likely to be screened compared to their white counterparts, leading to late-stage diagnosis of cervical cancer [14-16]. Regular screening allows the early detection of cervical cancer. Regular screening has reduced cervical cancer-related mortality by 70-80% in all countries and by approximately 90% in developing countries [17] Nonetheless, there are a lot of barriers to cervical cancer screening, including sociodemographic factors, cultural factors, previous experiences, access, cost, safety, insurance, and health system-related factors [18]. In South Korea, we are conducting cervical cancer screening as a national project. However, according to data based on the National Cancer Screening Program (NCSP) in South Korea, the screening participation rate in 2020 was only 52.2%. We consider the low participation rate to be caused by multiple factors, including reduced access to the hospital with COVID-19, lower birth rate and marital rates, and repulsion to pelvic exams in Korean women [19].

In conclusion, women with ASC-H, high-risk HPV infection, and no regular screening of cervical cancer should be considered for the indication of a see-and-treat approach, which can avoid

treatment delay and noncompliance.

Our study has several limitations, such as a retrospective study with small subjects, and probable selection biases caused by subjects for women with ASC-H who underwent conization. Based on our results, a large-scaled prospective study might be required.

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