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ORIGINAL RESEARCH

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Analysis of clinicopathological outcomes of atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesions (ASC-H) in cervical cancer screening for women

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Abstract

The cytological diagnosis of atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesions (ASC-H) is subjective and entails great variation in the risk of HSIL$^+$. Therefore, we retrospectively analyzed the clinicopathological outcomes of patients with ASC-H cytology from January 2018 to June 2021 to determine associated predictors for diagnosing HSIL$^+$ and explore their appropriate clinical management. Overall, 279 patients with ASC-H cytology were enrolled, 64.9% (181/279) of whom were histopathologically confirmed as HSIL$^+$. Further analysis showed that only human papillomavirus (HPV) positivity was an independent risk factor for HSIL$^+$ in ASC-H patients. Additionally, no significant difference was observed in the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the three HPV testing methods (hybrid capture (HC) II, HPV E6E7 mRNA and HPV genotyping testing) for detecting HSIL$^+$ ($p > 0.05$). The perfect agreement between colposcopy and final histology was 40.5%, with a κ value of 0.145. The sensitivity, specificity, PPV and NPV of colposcopy for detecting HSIL$^+$ were 32.6%, 91.8%, 87.9% and 42.3%, respectively. After cervical conization, none of the patients diagnosed with normal/benign histopathology by cervical biopsy was reclassified to HSIL$^+$, while 39.5% (17/43) of the low-grade squamous intraepithelial lesion (LSIL) patients were reclassified as HSIL. During follow-up, ASC-H patients diagnosed with LSIL had a high rate of normalization (70%) and a low rates of persistence (20%) and progression (10%). In four ASC-H patients younger than 30 years old with HSIL (cervical intraepithelial neoplasia (CIN) 2), two normalized and two persisted during follow-up. In conclusion, ASC-H patients should be directly referred for colposcopy and undergo biopsy irrespective of their age, menopausal status and HPV status. Relatively conservative management might be more suitable for ASC-H patients with LSIL$^-$ or ASC-H patients younger than 30 years with HSIL (CIN2).

Keywords

ASC-H; HSIL$^+$ HPV; Colposcopy-directed cervical biopsy; Cervical conization

1. Introduction

As a developing country, China has shown an increasing incidence of cervical cancer, with approximately 106,430 new cases and 47,739 deaths reported in China in 2020 [1]. However, the morbidity and mortality associated with cervical cancer and its precursor lesion (high-grade squamous intraepithelial lesion, HSIL) can be substantially reduced if the lesions are diagnosed early and treated promptly. Thus, cervical cancer screening plays an important role in identifying potentially high-risk cases via cytology, which is still the most common screening method in China.

Atypical squamous cells (ASCs), the most common category of cervical epithelial abnormalities in the results of cervical cytology, can be subdivided into two subcategories according to the 2001 Bethesda System for Reporting Cervical Cytology: atypical squamous cells of undetermined significance (ASC-US) and atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesions (ASC-H). Although the latter is characterized by abnormal cytological features that suggest suspected HSIL, they are not conclusive [2]. Additionally, despite that the cytomorphological criteria have been described for this subcategory, the diagnosis of ASC-H remains a subjective procedure with poor interobserver and intraobserver reproducibility [3]. Therefore, it is hardly surprising that the reported risk of HSIL varies between 24%

to 94% in the cytological report of patients with ASC-H [4], ultimately leading to debates about the optimal management of these cases.

In China, the guidelines for managing ASC-H patients are mainly based on some European and American guidelines published before 2016. To provide some light on this debatable topic, we comprehensively analyzed the clinical characteristics, colposcopy diagnoses and histopathological findings of patients with ASC-H cytology to identify potential predictors that could help to more accurately diagnose HSIL or cervical cancer and offer decisive suggestions to improve the treatment and outcomes of these patients

2. Materials and methods

2.1 Selection of patients

This retrospective study was conducted in Chengdu Women and Children's Central Hospital, a single tertiary center with approximately 300,000 gynecology outpatients annually. The data of patients diagnosed with ASC-H from January 2018 to June 2021 with complete medical records on age, menopausal status, symptoms of postcoital bleeding, HPV status before colposcopy and colposcopic and histological diagnoses were analyzed. The study exclusion criteria were: (1) incomplete medical records; (2) patients with colposcopic diagnoses who underwent histopathological examination more than three months after the initial cytological diagnosis; (3) pregnancy; and (4) a history of uterectomy or CIN before the colposcopic evaluation. The clinicopathological features of patients with ASC-H cytology were retrieved from our archived database.

The sample size for this study was determined using the G*Power software (version 3.1.9.2, Heinrich-Heine-Universität Düsseldorf, North Rhine-Westphalia, Germany). The F-test (analysis of variance (ANOVA): Fixed effects, special, main effects and interactions) was conducted and inputted into the system. The effect size, minimal significance (α) and statistical power ($1-\beta$) were set to 0.3, 0.05 and 0.95, respectively. Based on these inputs, a minimum sample of 195 participants was required to achieve the study endpoints.

2.2 Observation of variables

The diagnosis of ASC-H was made according to the Bethesda System by nine certified cytopathologists with different working experiences [2]. If the reports were interpreted by inexperienced cytopathologists, they were counterchecked by experienced cytopathologists. HPV DNA testing was performed using the polymerase chain reaction reverse dot blot (PCR-RDB) HPV genotyping (Yaneng Bioscience Co., Ltd, Shenzhen, China), which can identify 18 high risk HPV (HR-HPV) types (16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82 and 83) and 5 low risk HPV (LR-HPV) types (6, 11, 42, 43 and 81), and the hybrid capture (HC) II HPV test (Digene, Gaithersburg, MD). HPV RNA testing was performed with the HPV E6/E7 mRNA testing kits (20163401261, Kodia Bioscience Co., Ltd, Zhengzhou, China), which use the branched DNA (bDNA) signal amplification method to identify 14 HR-HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68). The assessment of colposcopy images was conducted by eight colposcopists following the 2011 nomenclature of the International Federation for Cervical Pathology and Colposcopy (IFCPC) [5]. The final diagnosis of colposcopy was classified as normal or benign, LSIL, HSIL or carcinoma. Cervical biopsy was performed under colposcopy direction for any lesion or acetowhite area. If no lesions or acetowhite areas were visible, a random biopsy was performed at the squamocolumnar junction. Endocervical curettage (ECC) was performed in patients whose colposcopic impression indicated type 3 transformation zone (TZ) or whose lesion boundaries of the lesions were deeply located in the cervical canal. A subsequent loop electrosurgical excision procedure (LEEP) or cold knife conization (CKC) was performed when the cervical biopsy or ECC showed CIN2, CIN3 or invasive cancer. All specimens were fixed in 10% formalin and routinely embedded, sliced and stained with hematoxylin and eosin (H-E). Two experienced pathologists made the histopathological diagnosis of the specimens. The diagnostic criteria for the patients were based on the WHO Classification of Female Genital Tumors • 5th edition, which included normal/benign, LSIL (condyloma or CIN1), HSIL (CIN2 or CIN3) and carcinoma.

2.3 Follow-up

During the follow-up period, cytology and HPV tests were performed. When indicated, a colposcopy with biopsy was recommended. Clinical outcomes during follow-up were classified into three types according to a previous study [6]: normalization, persistence, and progression. The definition of normalization was negative cytology, colposcopy or biopsy results. Persistence referred to the same or lower histological grade of CIN confirmed by biopsy, while progression was defined as a higher grade of CIN or carcinoma. The follow-up results were obtained by reviewing hospital records, and the follow-up deadline was June 2022.

2.4 Statistical analysis

All data analyses were conducted using the statistical software SPSS (version 26, SPSS Inc., Chicago, IL, USA). The chi-square test or Fisher's exact test was used for univariate analysis. Binary logistic regression was used for multivariate analysis. The agreement between colposcopy and the final histology was estimated by a perfect agreement and weighted κ statistics. The strength of agreement was judged based on the following criteria: poor ($\kappa < 0.20$), fair (κ, 0.21–0.40), moderate (κ, 0.41–0.60), substantial (κ, 0.61–0.80), and almost perfect (κ, 0.81–1.0) [7]. PPV, NPV, false positive rate and false negative rate were used to evaluate the validity and predictability of HPV and colposcopy. The confidence interval (95% CI) was calculated where appropriate. Statistically significant was set at $p < 0.05$.

3. Results

3.1 Baseline characteristics of patients diagnosed with ASC-H

Between 01 January 2018, and 09 June 2021, 634 (0.48%, 634/132202) of the 132,202 cervical cytology samples were

diagnosed as ASC-H. After applying the inclusion criteria to the group of women with ASC-H cytology, 279 subjects were found eligible for this study. The subjects' ages ranged from 19–75 years, with a mean age of 40.21 ± 11.36 years. A total of 59.5% (166/279) of the patients with ASC-H cytology were under 40 years, and 44.1% (123/279) of the women were between 30 and 39 years old. Based on the median age, the most prevalent age range and the age threshold provided in previous studies [8–13], 40 years was chosen as the cutoff value for age in this study.

The baseline characteristics of the subjects are summarized in Table 1. The percentage of ASC-H patients who were younger than 40 years (59.5%, 166/279), premenopausal (74.2%, 207/279), HPV positive (92.8%, 259/279) and without postcoital bleeding (79.2%, 221/279) was higher than that those who were older than 40 years (40.5%, 113/279), postmenopausal (25.8%, 72/279), HPV negative (7.2%, 20/279) and had postcoital bleeding (20.8%, 58/279).

TABLE 1. Baseline characteristics of 279 women with ASC-H.

Characteristics	Number (%)
Age (years)	
≥40	113 (40.5)
<40	166 (59.5)
Menopausal status	
Premenopause	207 (74.2)
Postmenopause	72 (25.8)
Postcoital bleeding	
Yes	58 (20.8)
No	221 (79.2)
HPV status	
Negative	20 (7.2)
Positive	259 (92.8)

HPV: human papillomavirus; ASC-H: atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesions.

3.2 Risk of HSIL$^+$ in 279 women with ASC-H stratified by baseline characteristics

Given that the clinical implication of ASC-H cytology mainly lies in predicting the risk of HSIL$^+$, we further stratified ASC-H patients with histopathological HSIL$^+$ based on their baseline characteristics (Table 2). Univariate analysis showed that the ASC-H patients who were younger than 40 years, premenopausal and HPV positive had a higher risk of HSIL$^+$ (HSIL or higher) than those who were older than 40 years, postmenopausal and HPV negative (70.5% (117/166) *vs.* 56.6% (64/113), relative risk (RR): 1.244, 95% CI: 1.030–1.503; 68.6% (142/207) *vs.* 54.2% (39/72), RR: 1.266, 95% CI: 1.005–1.597; 67.2% (174/259) *vs.* 35.0% (7/20), RR: 1.919, 95% CI: 1.050–3.509, respectively; all $p < 0.05$). However, the risk of HSIL$^+$ in ASC-H patients with or without irregular vaginal bleeding was not significantly different (64.3% *vs.* 67.2%, RR: 0.956, 95% CI: 0.779–1.173, $p > 0.05$). Logistic regression analysis revealed that only HPV positivity was an independent risk factor for HSIL$^+$ in ASC-H patients ($p = 0.017$, odds ratio (OR): 3.293, 95% CI: 1.237–8.767).

Then, we further analyzed the predictability of the different HPV testing methods for distinguishing HSIL$^+$ histopathology in patients with ASC-H cytology encompassing HC-2, HPV E6E7 mRNA and HPV genotyping testing. As shown in Table 3, the sensitivity and PPV of these three HPV testing methods for detecting HSIL$^+$ in patients with ASC-H cytology were not statistically significant ($p > 0.05$). Moreover, the differences in the specificity and NPV of HC-2 and HPV genotyping testing methods for detecting HSIL$^+$ in patients with ASC-H cytology were not statistically significant ($p > 0.05$). Of the patients with HPV negativity, none used the HPV E6E7 mRNA testing method. Therefore, the specificity and NPV of HPV E6E7 mRNA testing for detecting HSIL$^+$ could not be calculated.

3.3 Accuracy of colposcopy in predicting HSIL$^+$ in patients with ASC-H cytology

As shown in Table 4, the colposcopic diagnosis was normal/benign in 41 patients (14.7%, 41/279), LSIL in 172 patients (61.6%, 172/279), HSIL in 55 patients (19.7%, 55/279) and carcinoma in 11 patients (3.9%, 11/279). Regarding final histological diagnosis, the findings were normal/benign in 15 patients (5.4%, 15/279), LSIL in 83 patients (29.7%, 83/279), HSIL in 154 patients (55.2%, 154/279) and carcinoma in 27 patients (9.7%, 27/279). The agreement between colposcopic diagnosis and final histology was perfectly matched for 113 patients (40.5%, 113/279), and the weighted κ strength of agreement was 0.145 ($p < 0.05$). The concordance to HSIL$^+$ was 22.1% (40/181). In addition, 5.7% (16/279) of the ASC-H patients were overestimated, and 53.7% (150/279) were underestimated by colposcopy.

The sensitivity, specificity, PPV and NPV of colposcopy for the detection of HSIL$^+$ were 32.6% (95% CI: 25.4%–39.4%), 91.8% (95% CI: 84.1%–96.2%), 87.9% (95% CI: 77.0%–94.3%) and 42.3% (95% CI: 35.6%–49.2%), respectively. In addition, the false positive rate was 12.1% (5.7%–23.0%), and the false negative rate was 57.7% (50.8%–64.4%).

3.4 Analysis of histopathology results for patients with ASC-H cytology

Overall, 256 patients with ASC-H cytology underwent colposcopy-directed biopsy, and the histopathological results were normal/benign in 3 patients (1.2%, 3/256), LSIL in 105 patients (41.0%, 105/256), HSIL in 126 patients (49.2%, 126/256), and carcinoma in 22 patients (8.6%, 22/256). Of these 256 patients, 130 underwent cervical conization after cervical biopsy. The distribution of the patients' histological results is shown in Table 5. After cervical conization, no patient with normal/benign histopathology by cervical biopsy was reclassified as HSIL$^+$. Moreover, 39.5% (17/43) of the LSIL histology cases in cervical biopsy were upgraded to HSIL, although 64.7% (11/17) were HSIL (CIN2), and no case was upgraded to carcinoma.

TABLE 2. The associated predictors for diagnosing HSIL$^+$ in 279 Women with ASC-H cytology.

Characteristics	Proportion of women with HSIL^{+a}	Univariate		Multivariate analysis	
		p	OR*b* (95% CI)	*p*	OR (95% CI)
Age (years)					
≥40 (n = 113)	64 (56.6%)				
<40 (n = 166)	117 (70.5%)	0.017	1.244 (1.030–1.503)	0.212	1.562 (0.776–3.142)
Menopause status					
Postmenopause (n = 72)	39 (54.2%)				
Premenopause (n = 207)	142 (68.6%)	0.027	1.266 (1.005–1.597)	0.748	1.137 (0.520–2.483)
Postcoital bleeding					
Yes (58)	39 (67.2%)				
No (221)	142 (64.3%)	0.671	0.956 (0.779–1.173)	NS^c	
HPV status					
Negative (n = 20)	7 (35.0%)				
Positive (n = 259)	174 (67.2%)	0.004	1.919 (1.050–3.509)	0.017	3.293 (1.237–8.767)

[a]Including HSIL (high grade squamous intraepithelial lesion) and carcinoma; [b]OR, odds ratio; [c]NS, no significance. CI: confidence interval. HPV: human papillomavirus.

TABLE 3. Predictability of HPV testing methods in distinguishing HSIL$^+$ histopathology of ASC-H patients.

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
HC-2	100.0% (86.3%–100.0%)	5.3% (0.3%–28.1%)	63.3% (48.3%–76.2%)	100.0% (5.4%–100.0%)
HPV E6E7 mRNA	100.0% (65.5%–100.0%)	/ *	76.9% (46.0%–93.8%)	/ *
HPV genotyping	95.0% (89.6%–97.8%)	15.8% (8.8%–26.4%)	67.5% (60.4%–73.9%)	63.2% (38.6%–82.8%)
p	0.568	0.646	0.646	0.452

**: Of patients with HPV negativity, there was no patient performed HPV E6E7 mRNA testing method. Thus, the specificity and NPV of HPV E6E7 mRNA testing method can't be calculated. PPV: positive predictive value; NPV: negative predictive value; CI: confidence interval; HC: hybrid capture. HPV: human papillomavirus.*

TABLE 4. The agreement of colposcopic diagnosis and final histopathology diagnosis in patients with ASC-H (n = 279).

Colposcopic diagnosis	Final Histopathology diagnosis				Total
	Normal/Benign	LSIL	HSIL	Carcinoma	
Normal/Benign	4*	19	15	3	41
LSIL	8	60*	99	5	172
HSIL	3	4	39*	9	55
Carcinoma	0	0	1	10*	11
Total	15	83	154	27	279

**Perfect agreement; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion.*

TABLE 5. Comparison of histopathology diagnosis from preoperative colposcopic biopsy and conization specimens in patients with ASC-H (n = 130).

Histopathology diagnosis after colposcopic-directing cervical biopsy	Histopathological results after cervical conization				Total
	Normal/Benign	LSIL	HSIL	Carcinoma	
Normal/Benign	2	1	0	0	3
LSIL	5	21	17	0	43
HSIL	5	22	53	3	83
Carcinoma (Microinvasive)	0	0	0	1	1
Total	13	43	70	5	130

LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion.

Furthermore, 23 patients underwent cervical conization immediately without any previous histological result due to type 16 or 18 HPV infection, but their colposcopy impressions were unsatisfactory, or the boundaries of the lesions were deeply located in the cervical canal. The postoperative histopathology results were as follows: LSIL, 52.2% (12/23); HSIL, 34.8% (8/23); and microinvasive carcinoma, 13.0% (3/23).

3.5 Follow-up results of ASC-H patients diagnosed with LSIL$^-$ or HSIL (CIN2) by cervical biopsy who did not undergo cervical conization

In our hospital, there is no consensus regarding the management of women with ASC-H cytology and LSIL$^-$ or HSIL (CIN2) biopsy. Therefore, we collected the follow-up results of these patients who did not undergo cervical conization. For ASC-H patients diagnosed with LSIL$^-$ by cervical biopsy but did not undergo cervical conization, only 20 cases had complete medical follow-up records. Normalization was documented in 14 patients (70%, 14/20), persistence (LSIL) in 4 patients (20%, 4/20) and progression (HSIL (CIN2)) in 2 patients (10%, 2/20). In addition, only 4 ASC-H patients with an HSIL (CIN2) diagnosis by cervical biopsy selected for follow-up had complete follow-up records. All of these patients were younger than 30 years and wanted to retain fertility, of whom two cases (50%, 2/4) were normalized, while the other two cases (50%, 2/4) had persisting HSIL (CIN2) during follow-up.

4. Discussion

Cervical cytology reports of ASC-H are extremely rare, ranging from 0.22% to 1.09% among all cervical cytological test results [10]. At our institution, the mean prevalence of patients with ASC-H cytology is 0.48%. Despite its low morbidity, the management of ASC-H is very important in clinical practice because it is frequently associated with high-grade lesions of the cervix, which are identified as precancerous lesions that need to be treated. However, the complicated cytological appearance of ASC-H leads to a wide variation in consistency regarding subsequent histopathology with a diagnosis of HSIL (ranging from 24%–94%) [8, 14]. The rate of HSIL$^+$ in patients with ASC-H cytology in our study was 64.9% (181/279), in which HSIL accounted for the majority (55.2%, 154/279) and carcinoma accounted for the minority (9.7%, 27/279) of the cases. The wide variability in the proportions of HSIL histopathological results among ASC-H patients often confuses gynecologists about the appropriate management and treatment of these cases. Therefore, we further analyzed the clinicopathological characteristics of patients with ASC-H to identify the associated predictors for diagnosing HSIL$^+$ in ASC-H cases and explore their appropriate clinical management.

Univariate analysis showed that the significant factors that predicted HSIL$^+$ in patients with ASC-H cytology included the patient's age, menopausal status and HPV results. In contrast, logistic regression analysis revealed that only HPV status was an independent risk factor for predicting HSIL$^+$ in ASC-H patients (Table 2). Nevertheless, although lower than that of the patients younger than 40 years and premenopausal, the proportion of histopathological HSIL$^+$ diagnoses in ASC-H patients older than 40 years and postmenopausal patients surpassed 50% (56.6% and 54.2% respectively), which is quite significant. Notably, 70.4% (19/27) of ASC-H patients diagnosed with invasive cancer were older than 40 years. These findings were consistent with that of Louro *et al.* [13] and Kietpeerakool *et al.* [12] who also reported that all invasive squamous cell carcinomas occurred in ASC-H patients who were 40 years or older.

In addition, although the risk of developing HSIL$^+$ in ASC-H patients with HPV negativity was much lower than those with HPV positivity, the rate of HSIL$^+$ in ASC-H patients with HPV negativity (35%, 7/20) was still too high, and it was worth noting that two patients (10%, 2/20) were diagnosed with invasive cervical cancer. A meta-analysis demonstrated that the risk of developing histologic CIN2$^+$ in HPV-negative ASC-H women was 8%, and the 5-year cancer risk was up to 2% [15, 16]. The revised guidelines of the ASCCP in 2019 also showed that HPV-negative ASC-H and HPV-positive ASC-H patients had very different CIN 3$^+$ rates (3.4% *vs.* 26%) but similar cancer rates (0.69% *vs.* 0.92%) [17]. In addition, testing for HR-HPV infection in our study demonstrated good sensitivity but low specificity and moderate PPV and NPV (Table 3). The sensitivity, specificity, PPV and NPV of different HPV testing methods for detecting HSIL$^+$ in patients with ASC-H cytology were not statistically significant ($p > 0.05$). Therefore, our experience supported that patients with

ASC-H cytology, irrespective of their age, menopausal status, and HPV result, should undergo aggressive work-ups rather than only observation.

Adequate colposcopic evaluation is particularly important for patients with ASC-H cytology. A recent study reported that colposcopy demonstrated good diagnostic accuracy when performed by expert clinicians and represents an excellent triaging method for ASC-H cytology, in which the colposcopic-histological concordance in ASC-H patients was up to 85.4% [18]. Nevertheless, our results showed poor diagnostic accuracy in colposcopy because the perfect agreement between colposcopic impression and histopathological diagnosis for patients with ASC-H cytology was 40.5% (113/279), while the κ value was only 0.145. The colposcopic-histological concordance of HSIL$^+$ was only 27.1% (49/181). The sensitivity and NPV (32.6% (95% CI: 25.4%–39.4%) and 42.3% (95% CI: 35.6%–49.2%), respectively) were also obviously lower than those in the studies by Marujo *et al*. [18] (100% and 100%, respectively) and Kudela *et al*. [19] (86.11% (95% CI: 70.5–95.3) and 83.33% (95% CI: 64.5–93.7), respectively). The false negative rate of colposcopy was 57.7% (95% CI: 50.8%–64.4%), and 53.7% of the ASC-H cases (150/279) were underestimated by colposcopy. Thus, our research emphasizes that although colposcopy is a very useful tool for the real-time evaluation of cervical lesions in the uterine cervix of ASC-H patients, its accuracy might be limited. Thus, patients with ASC-H cytology should be recommended to undergo cervical biopsy.

However, it should be noted that we disagree with performing cervical conization immediately after colposcopy in patients with ASC-H cytology without any previous histological sample because it could lead to the overtreatment if they are ultimately diagnosed with LSIL$^-$ on final histopathology. In our study, 23 patients with ASC-H cytology underwent cervical conization immediately without cervical biopsy because of type 16 or 18 HPV infection, but the TZ of colposcopy showed the 3-type. The histopathological results showed that over 50% of patients (52.2%, 12/23) were diagnosed with LSIL after cervical conization. In a retrospective study by Nogara *et al*. [20], 26.3% (10/38) of the women with ASC-H cytology who underwent immediate cervical conization none had CIN2$^+$, while 18.4% (7/38) had CIN1.

We also disagree with conducting cervical conization for ASC-H patients with histological results of LSIL$^-$ by cervical biopsy because it might also lead to overtreatment. In our study, no ASC-H patient who was diagnosed with normal/benign histopathology by cervical biopsy was diagnosed with HSIL$^+$ after cervical conization. Although 39.5% (17/43) of the ASC-H patients diagnosed with LSIL by cervical biopsy were upstaged to HSIL after cervical conization (Table 5), 64.7% (11/17) of the patients were HSIL(CIN2), and no patient was diagnosed with invasive carcinoma. In addition, the follow-up results of ASC-H patients with LSIL histology by cervical biopsy showed a high rate of normalization (70%, 14/20) and low rates of persistence (20%, 4/20) and progression (10%, 2/20). Additionally, 4 ASC-H patients were younger than 30 years of age and were diagnosed with HSIL (CIN2) by cervical biopsy but because they wanted to preserve fertility, they were selected for follow-up. Of them, 2 patients (50%, 2/4) had normalization, while 2 (50%, 2/4) showed persistence (LSIL) during the follow-up period. Therefore, our experience supports that for ASC-H patients diagnosed with LSIL$^-$ by cervical biopsy and HSIL (CIN2) by cervical biopsy who are younger than 30 years of age (especially those with fertility demand), follow-up, rather than treatment, could be more suitable.

There were limitations worth noting in this study. First, this was a retrospective study. Second, this was a single center study, and the sample size was relatively small. Moreover, some data were unavailable, such as smoking history and BMI, which might influence the rate of HSIL$^+$ lesions. Lastly, some patients diagnosed histopathologically with LSIL or HSIL (CIN2) following cervical biopsy did not undergo cervical conization and were lost during follow-up, which might have influenced the accuracy of our conclusion to a certain extent.

5. Conclusions

In summary, ASC-H patients, irrespective of age, menopausal status, symptoms or HPV results, should be directly referred for colposcopy and should undergo biopsy. Relatively conservative management might be more suitable for ASC-H patients diagnosed with LSIL$^-$ by cervical biopsy and HSIL (CIN2, diagnosed by cervical biosy) younger than 30 years old (especially those with fertility demand).

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

JL—Study conception and design, data analysis, manuscript writing. HXW, JC, XLY, CMY and WW—Data collection. QLD—Study conception and design, writing-review and editing.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Before its initiation, this study was approved by the ethics committee of the Chengdu Women's and Children's Central Hospital (file no. 2019(9)). As this was a retrospective study and the data were analyzed and reported anonymously, our ethics committee waived the need for informed consent.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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