

# The prevalence of abnormal pap smear in women with pelvic inflammatory disease and determine the risk factors of cervical intra-epithelial neoplasia 2/3

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**Objective:** To investigate the prevalence of abnormal Pap (ASCUS or worse) and HPV infection in women with pelvic inflammatory disease (PID) and assess the risk factors for CIN2/3. **Methods:** Retrospective chart review of 249 women who were admitted to the hospital for the treatment of PID between 2013 and 2019 was performed. Patients' characteristics including age, parity, sexually transmitted disease (STD) infection, Pap results, human papilloma virus (HPV) infection, Nugent score, C-reactive protein (CRP), and neutrophil to lymphocyte ratio (NLR) were retrieved. Clinical characteristics were compared between group 1 (women with normal pap; N = 159) and group 2 (women with abnormal Pap; N = 90). **Results:** Of 249 women, abnormal Pap rate was 36.1% and HPV positivity was 41.0%. Of those with HPV infection, 78.4% had high-risk HPV subtypes. Group 2 was significantly associated with high-risk HPV infection ( $P < 0.0001$ ) and low NLR ( $P = 0.047$ ). 74 women underwent colposcopy-directed punch biopsy, and 14 showed CIN2/3. Multivariate analysis showed that high-risk HPV infection ( $P = 0.040$ ; 95% CI 1.081-32.389) and low Nugent score ( $\leq 3$ ) ( $P = 0.003$ ; 95% CI 2.130-39.807) were independent risk factors of CIN2/3 in women with abnormal Pap and PID. **Conclusions:** Women with PID showed high prevalence of abnormal Pap. Nonetheless, high-risk HPV infection and low Nugent score are the most reliable factors in determining colposcopy for the diagnosis of CIN2/3.

## Keywords

Abnormal Pap; Cervical intraepithelial neoplasia (CIN); Human papilloma virus (HPV); Pelvic inflammatory disease (PID)

## 1. Introduction

Cervical cancer is the 4th most common gynecologic malignancy worldwide [1]. Although human papilloma virus (HPV) vaccination was expected to decrease incidence of cervical intra-epithelial neoplasia (CIN) which is a pre-invasive disease of cervix cancer, global incidence of cervical cancer in 2018 was 570,000 and the annual death was 311,000 [2]. In South Korea, 3348 women newly diagnosed as cervical cancer, and the annual death was 1029 in 2018 [3]. A major risk factor of CIN and cervical cancer is HPV infection, which can be transmitted through sexual intercourse [4, 5]. Therefore, women with pelvic inflammatory disease (PID), a typical sexually transmitted disease, have been considered risk for CIN

and cervical cancer [6, 7].

Clinically, many physicians can experience high ASCUS prevalence in patients with PID. Basically, Pap smear should be refrained if there is a sign of severe cervicitis or PID, which may disturb definite interpretation of Pap smear. However, general physicians cannot rule out which case can be done or not. Moreover, most women are unwilling to visit gynecologic outpatient clinic frequently because of the repulsion to pelvic exam with lithotomy position. Therefore, most of gynecologists prefer to perform Pap smear even if there is a sign of cervicitis or PID.

Nonetheless, there have been no worldwide reports evaluating prevalence of abnormal Pap (ASCUS or worse) and risk factors of CIN2/3 in women with PID.

In this study, thus, we evaluated the incidence of abnormal Pap (ASCUS or worse) in women with PID, and furthermore, clarified significant risk factors of CIN2/3 in women with PID.

## 2. Methods and materials

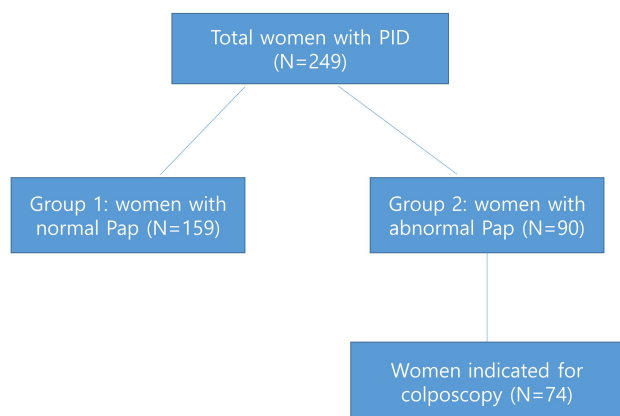
We retrospectively reviewed medical records of all women who diagnosed as pelvic inflammatory disease (PID) in Hallym University Dongtan Sacred Heart Hospital, between 2013 and 2018. Inclusion criteria is as follows; 1. Women who diagnosed as PID by symptom evaluation, imaging study (transvaginal ultrasonography, abdominal-pelvic computed tomography, or magnetic resonance imaging) or sexually-transmitted disease (STD) test; 2. Women admitted to our hospital for PID; 3. Women who did STD test, Pap smear, and HPV test during the admission period. Women with pathologically-confirmed cervical cancer were excluded in this study. According to the inclusion and exclusion criteria, a total of 249 women were included in this study.

In reference, we investigated the prevalence of abnormal Pap (ASCUS, AGC, ASC-H, LSIL, and HSIL) in women who visited healthcare center for routine pelvic exam during the same period of our study.

Patients' characteristics including age, parity, STD results (test for infection of Chlamydia trachomatis, Neisseria gonorrhoea, Mycoplasma genitalium, Ureaplasma urealyticum, and Candida species), PAP results, HPV infection (high-risk HPV subtypes are included 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 69, 73 and 82).

Nugent score, CRP, and NLR (neutrophil to lymphocyte ratio) were retrieved from the medical records. Nugent Score is a Gram stain scoring system for vaginal swabs to diagnose bacterial vaginosis, which is calculated by assessing for the presence of large Gram-positive rods (Lactobacillus morphotypes; decreased in Lactobacillus scored as 0-4), small Gram-variable rods (Gardnerella vaginalis morphotypes; scored as 0-4), and curved Gram-variable rods (Mobiluncus species morphotypes; scored as 0-2). A score of 7 to 10 is consistent with bacterial vaginosis without culture [8].

Clinical characteristics were compared between group 1 (women with normal Pap; N = 159) and group 2 (women with abnormal Pap; N = 90) (Fig. 1). Statistical analyses were performed using SPSS for Windows (version 26.0, SPSS Inc.). Komogorov-Smirnov test revealed that all variables showed normal distribution. Dichotomous variables were compared using the Fisher exact test or chi-square test. Continuous variables were compared using the independent-samples *t*-test. Multivariate analysis was performed using binary logistic regression. Hazard ratio (HR) and 95% confidence interval (CI) were calculated. ROC curve analysis and cut-off value of Nugent score, CRP, and NLR were determined by Medcalc software (version 15.2.2). For all statistical tests, a *P*-value less than 0.05 were considered significant.



**Fig. 1.** Among 249 women with PID, 159 women had normal pap and 90 women had abnormal pap. Of those 90 women with abnormal pap, 74 women indicated for colposcopy.

### 3. Results

Total 249 women underwent inpatient treatment of PID. Mean age of all patients was  $36.1 \pm 9.68$  years old. The prevalence of abnormal Pap was 36.1% and HPV infection was 41.0%. In reference, 3.13% of women who visited our health-

**Table 1. Comparison of clinical characteristics between patients with normal and abnormal pap ( $\geq$  ASCUS).**

	Normal pap (N = 159)	Abnormal pap (N = 90)	<i>P</i> value
Age	36.2 ± 9.44	35.8 ± 10.15	0.760
Parity	1.1 ± 1.04	1.1 ± 1.10	0.952
STD			0.426
negative	85 (53.5)	50 (55.6)	
positive	74 (46.5)	40 (44.4)	
HPV			< 0.0001*
negative	112 (70.4)	35 (38.9)	
positive	47 (29.6)	55 (61.1)	
HR-HPV			< 0.0001*
negative	127 (79.9)	42 (46.7)	
positive	32 (20.1)	48 (53.3)	
Nugent score	3.2 ± 2.52	2.9 ± 2.75	0.382
CRP	29.6 ± 55.88	20.6 ± 39.17	0.245
NLR (neutrophil to lymphocyte ratio)	5.3 ± 6.73	3.8 ± 3.31	0.047*

Data are presented as mean ± SD or absolute numbers (%). \**P*-value < 0.05.

care center for routine pelvic exam were reported to have abnormal Pap, during the same study period (472/15059).

Among 102 women with HPV infection, 78.4% had high-risk HPV (HR-HPV) subtypes.

Clinical characteristics were compared between group 1 (women with normal Pap; N = 159) and group 2 (women with abnormal pap; N = 90). Group 2 were associated with HPV infection ( $P < 0.0001$ ), high-risk HPV infection ( $P < 0.0001$ ), and low NLR ( $P = 0.047$ ) (Table 1).

Total 74 women indicated for colposcopy-directed punch biopsy according to the American Society of Colposcopy and Cervical Pathology (ASCCP) guidelines, and 14 showed CIN2/3. Univariate analysis revealed that high-risk HPV infection ( $P = 0.031$ ), low Nugent score ( $P = 0.025$ ), low CRP ( $P = 0.007$ ), and low NLR ( $P = 0.026$ ) were significantly associated with CIN2, 3 (Table 2).

Multivariate analysis showed that high-risk HPV infection ( $P = 0.040$ ; 95% CI 1.081-32.389) and low Nugent score ( $\leq 3$ ) ( $P = 0.003$ ; 95% CI 2.130-39.807) were independent risk factors of CIN2/3 in women with PID who showed abnormal Pap (Table 3).

### 4. Discussion

In this study, we examined the prevalence of abnormal Pap in women visited our inpatient clinic for PID treatment, compared to women without gynecologic problems who visited healthcare center for routine pelvic exam. In our data, abnormal Pap was reported in 3.13% of women with no gynecologic problems. In contrast, women with PID who had been treated at the inpatient clinic was reported to have 36.1% of abnormal Pap, which is approximately 12 times larger than normal women. According to our data, HR-HPV infection rate was 78.4% among women with HPV in-

**Table 2. Univariate analysis for risk factors of CIN2, 3.**

Risk factors	CIN1 ≤ (N = 60)	CIN2, 3 (N = 14)	P value
Age	37.3 ± 10.24	35.4 ± 8.41	0.488
Parity	1.21 ± 1.14	0.6 ± 0.93	0.090
STD			0.463
negative	35 (58.3)	9 (64.3)	
positive	25 (41.7)	5 (35.7)	
PAP			0.405
negative	9 (15.0)	3 (21.4)	
Positive (more than ASCUS)	51 (85.0)	11 (78.6)	
HR-HPV			0.031*
negative	27 (45.0)	2 (14.3)	
positive	33 (55.0)	12 (85.7)	
Nugent score	3.3 ± 2.71	1.5 ± 1.94	0.025*
CRP	23.6 ± 42.46	1.6 ± 1.30	0.007*
NLR	3.4 ± 2.94	2.0 ± 0.77	0.026*

Data are presented as mean ± SD or absolute numbers (%). \*P-value < 0.05.

**Table 3. Multivariate analysis for risk factors of CIN2, 3.**

Risk factors	Hazard ratio	(95% CI)	P value
HR-HPV	5.916	(1.081-32.389)	0.040*
Nugent score 3 or less	9.208	(2.130-39.807)	0.003*
CRP 3.7 or less	1.368	(0.228-8.219)	0.732
NLR 3.7 or less	1.054	(0.184-6.038)	0.953

\*P-value < 0.05.

fection, which is higher than overall prevalence of HR-HPV in Korean women. A study evaluating HPV prevalence from liquid-based cytology in Korean women reported that overall HPV positivity rate was 34.2%. Among the HPV positive women aged 30-39 years, HR-HPV positive women were 20.08% (3395/16907) [9]. The higher prevalence of HR-HPV in our data confirmed that sexually active young women with PID is at high risk of HR-HPV infection than normal women with no gynecologic problems.

In our data, 36.1% of women with PID showed abnormal Pap, which is more than 10-fold compared to women visiting our healthcare center without gynecologic problems. In addition, women with abnormal Pap were significantly correlated with any HPV or HR-HPV infection, and lower NLR. It is well-known that cervical intraepithelial neoplasia and cervical cancer is mainly caused by persistent HPV infection from high-risk HPV types [10]. Thus, theoretically it is rational that any HPV or HR-HPV infection was significantly correlated with abnormal Pap results.

Peripheral neutrophil-lymphocyte ratio (NLR) has been regarded as a simple and effective marker of inflammation [11-13]. The causal association between chronic inflammation and cancer development has been well established [14-17]. Several studies reported that inflammatory markers, including leukocytosis, hypoalbuminemia, elevated C-reactive protein, high cytokine levels, and high NLR can pre-

dict cancer development or recurrence [17-20]. Recently, a retrospective study reported that NLR can be an independent predictor of recurrent CIN [21]. The authors reported that NLR > 2.1 was significantly correlated with lesser recurrence-free survival ( $P = 0.001$ , HR 7.66; 95% CI 2.34-25.10). Another meta-analysis, including 9 studies, consisting of 2804 patients with cervical cancer, also revealed that elevated pre-treatment NLR can serve as a predictive factor for poor prognosis [22]. High pre-treatment NLR level was significantly associated with poorer overall survival (HR 1.88, 95% CI 1.30-2.73) and shorter progression free survival (HR 1.65, 95% CI 1.18-2.29). On the contrary, our data showed that mean NLR was higher in women with normal Pap than abnormal Pap. Univariate analysis in patients who underwent punch biopsy or loop electrosurgical excision procedure (LEEP) revealed that inflammatory markers, including mean Nugent score, CRP, and NLR were all significantly lower in women who diagnosed as CIN2/3 than women diagnosed as CIN1 or less. However, multivariate analysis showed that independent risk factors for CIN2/3 were HR-HPV infection and Nugent score, not CRP or NLR. According to our data, low inflammatory markers can discriminate high risk and low risk group for CIN2/3 in PID women with abnormal Pap.

In our data, HR-HPV infection was another strong predictor to determine which patient needs colposcopy or not, in case of PID women with abnormal Pap. There have been several reports investigating the correlation of PID, abnormal Pap, and HPV infection. A study from India, which included 11,427 women over a period of 2000-2012, reported that 7.9% of women with reproductive tract infection had ASCUS. In addition, *Trichomonas vaginalis* infection was significantly associated with abnormal Pap, such as ASCUS and LSIL ( $P < 0.001$ ) [23].

A cross-sectional laboratory-based study investigating the association between *Trichomonas vaginalis* and HPV infection in cervical samples at Flanders (North Belgium) reported that the prevalence of *Trichomonas vaginalis* infection was higher in women with HPV infections compared to women without HPV (0.61 vs. 0.33%,  $P < 0.0001$ ) [24].

Nonetheless, HPV infection was the strongest factor in cervical oncogenesis. A study investigating the association between *Candida* spp. and *Trichomonas vaginalis* coinfection with HPV in cervical oncogenesis suggested that coinfection with *Trichomonas vaginalis* did not alter the risk of low grade or high grade lesions among HPV positive women [25].

HPV is the main cause of cervical intraepithelial neoplasia and cervical cancer. Specifically, HPV 16 and 18 account for approximately 80% of causes of cervical cancer [26].

HR-HPV includes high-risk HPV subtypes are included high-risk HPV subtypes are included 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 69, 73 and 82 [27].

Although the introduction of HPV vaccination was expected to decrease the incidence of CIN and cervical cancer, routine screening is also recommended regardless of vacci-

nation [28, 29] Moreover, American Cancer Society recommends primary HPV test in women aged 25 to 65 every 5 years. If primary HPV testing is not available, screening may be done with either a co-test that combines an HPV test with a Pap test every 5 years or a Pap test alone every 3 years, which is because HR-HPV infection can accelerate CIN or cervical cancer even if Pap smear is normal [29, 30]. In addition, American Society of Colposcopy and Cervical Pathology (ASCCP) guidelines recommend triage for ASCUS/LSIL [31]. In women with ASCUS/LSIL, 1. direct colposcopy, 2. HPV test, 3. HPV & colposcopy could be done to discriminate actual CIN or cervix cancer from normal cervix [31]. In women with ASCUS, about 20-25% are reported to have CIN or cervical cancer. In other words, about 75-80% of ASCUS are caused by the inflammation of cervix or other reasons. Therefore, ASCUS can be frequently observed in women with PID. In these patients, discrimination of the actual risk group of CIN2/3 is important. Theoretically, women with PID are at high risk for CIN and cervical cancer. However, doing direct colposcopy in all PID women with abnormal Pap could lead to over-diagnosis and over treatment. Even in PID women with abnormal Pap, HR-HPV infection status and level of inflammatory markers should be considered as predictive factors for CIN2/3 or cervical cancer. Our finding supports that HR-HPV infection status is the most important factor deciding colposcopy in patients with PID and abnormal Pap. We think that our findings warrant confirmation by a larger prospective study.

## 5. Conclusions

In conclusion, women with PID showed high prevalence of abnormal Pap. Nonetheless, high-risk HPV infection and low Nugent score are the most reliable factors in determining colposcopy for the diagnosis of CIN2/3. Our data supports that HR-HPV infection status is the strongest risk factor for CIN or cervical cancer, even in patients with other risk factors.

## Author contributions

HY and MS designed the research study, and provided the data. HY, SB, and IY analyzed the data. HY wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

This study was approved by the local institutional review board of Hallym University Hospital (IRB No. 2020-07-010-001).

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## Conflict of interest

The authors declare no competing interests.

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