의학석사 학위논문

Association between *Helicobacter pylori seropositivity* and mild to moderate chronic obstructive pulmonary disease

만성폐쇄성폐질환과 *Helicobacter pylori* 혈청양성과의 관련성 연구

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이 논문을 의학석사 학위논문으로 제출함
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이하연의 의학석사 학위논문을 인준함
2018 년 8 월

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초 록

Helicobacter pylori(H.pylori) 와 여러 질환과의 관련성이 있다는 여러 보고가 있어, 본 연구에서는 만성폐쇄성폐질환(COPD) 와 *H.pylori* 혈청양성율과의 연관성이 있는지 알아보았다. 또한 *H.pylori* 혈청양성과 COPD 환자의 폐기능 감소속도와 관련성이 있는지 분석하였다.

보라매병원 검진센터에서 *H.pylori* 특이 IgG 검사를 시행하고, 3회 이상 1년 간격으로 폐기능 검사를 시행한 환자를 대상으로 하였다. 총 603명(COPD 환자 201명, 대조군 402명)이 포함되었다. COPD 환자의 45.8% 가 *H.pylori* IgG 양성이었으며, 대조군은 52.5% 로 양 군의 차이가 없었다(p=0.134). 정량적으로, *H.pylori* IgG 수준 역시 COPD군과 대조군 차이가 없었다(114.8 and 109.6 units/ml, respectively; p=0.549). 1초간호기속도 및 호기용적을 이용하여 연간 폐기능 감소 속도를 분석하였으나, *H.pylori* 양성과 음성군을 비교시 통계적으로 유의한 차이가 없었다. 결론적으로, *H.pylori* 감염율이 높은 국내 환자를 대상으로 한 본 연구의 경우, COPD와 *H.pylori* 감염과의 관련성을 보이지 않았다.

주요어 : 헬리코박터, 만성폐쇄성폐질환, 폐기능감소
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목 차

표 목차

그림 목차

제 1 장 Introduction

Helicobacter pylori can be resistant in the acidic conditions of the stomach and colonize the gastric epithelium by producing urease[1]. This microorganism also causes gastric inflammation via various virulence factors such as vacuolating cytotoxin A, cytotoxin-associated gene product A, and neutrophil-activating protein A [1,2]. *Helicobacter pylori* infection is a major cause of gastric diseases such as chronic active gastritis, peptic ulcer disease, and mucosa-associated lymphoid tissue lymphoma [3-5]. Infection with *H. pylori* can be detected by gastric mucosal biopsy, a rapid urease test, and simple serologic tests. Despite the limitations of serologic testing for *H. pylori* infection, this technique has been widely used because it is simple and non-invasive.

Interestingly, *H. pylori* infection may not be restricted to the stomach. Since the first report that coronary heart disease might be associated with *H. pylori* seropositivity in 1994 [6], several studies on the implications of *H. pylori* infection in various diseases outside the gastrointestinal system have been published. Such systems include the cardiovascular, neurological, dermatological, immunological, hematological, hepatobiliary, ophthalmological, endocrinologic, and gynecological systems [7-9].

Until now, the extra-gastrointestinal implications of *H. pylori* infection have been hypothesized to be associated with systemic inflammation, which might in turn be associated with *H. pylori*-induced gastric inflammation. The chronic gastric inflammatory response induces systemic inflammation and immune responses by altering the polarized T-helper 1 and 2 responses. However, whether *H. pylori*-

induced inflammation plays a role in the pathogenesis of extra-gastric diseases remains unclear [10].

An association between *H. pylori* infection and respiratory disease has recently been reported [11]. Bronchiectasis, tuberculosis, and lung cancer are reportedly associated with higher *H. pylori* seroprevalence [12]. However, several epidemiological studies have shown an inverse relationship between *H. pylori* infection and the incidence of allergic airway diseases including asthma [10,13,14]. A few studies, including some with small study samples, have identified a potential association between *H. pylori* infection and chronic obstructive lung disease (COPD). The prevalence of *H. pylori* seropositivity was found to be higher in patients with than without COPD [15,16]. Additionally, a significant relationship between *H. pylori* seropositivity and the forced expiratory volume in 1 s (FEV_1) was recently demonstrated[17]. However, considering that the prevalence of *H. pylori* infection exhibits regional variability [18], we suspected that the clinical impact of *H. pylori* infection on the prevalence of COPD and lung function may differ according to the regional prevalence of *H. pylori*. Nevertheless, until now, no reports have addressed the association between *H. pylori* infection and COPD and the impact of *H. pylori* infection on lung function in Asian countries with a high burden of *H. pylori* infection.

In this study, we aimed to elucidate the association between *H. pylori* infection and the presence of mild to moderate COPD in an Asian country with high prevalence of *H. pylori* infection. We also aimed to identify the impact of *H. pylori* infection on declining lung function in patients with COPD.

제 2 장 Methods

제 1 절 Study population

For this case-control study, we recruited participants aged ≥ 40 years who underwent a medical check-up and serologic test for *H. pylori* at Seoul Metropolitan Government–Seoul National University Boramae Medical Center from January 2013 to February 2015. Routine check-ups during the study period also included esophagogastroduodenoscopy (EGD), spirometry, and a basic demographic questionnaire.

The patients' information was obtained from the clinical records and anonymized prior to analysis. The Institutional Review Board of Seoul Metropolitan Government–Seoul National University Boramae Medical Center approved the study protocol (IRB No. 16-2015-40/041).

제 2 절 Selection of cases and controls

Among the participants who underwent a medical check-up and serology test for *H. pylori*, patients with mild to moderate COPD were selected as cases and participants without airflow limitation on spirometry were regarded as controls.

Mild to moderate COPD was defined as a prebronchodilator FEV_1/forced vital capacity (FVC) ratio of <0.7 and FEV_1 (% predicted) of ≥50%; these patients were assigned to the case group. Participants with an FEV_1/FVC ratio of ≥0.7 were assigned to the control group. Age- and sex-matched controls were randomly selected at a control:case ratio of 2:1.

We excluded participants with allergic diseases such as asthma or allergic rhinitis as well as those with lung diseases that may contribute to airflow limitations such as lung cancer, pulmonary tuberculosis, and bronchiectasis involving more than one lobe.

The following clinical information was collected: age, sex, body mass index, comorbidities, smoking status, spirometric and laboratory data, radiographic findings, and EGD findings.

Among 236 patients with a defined airflow limitation, the following 35 patients were excluded: 14 patients with asthma, 8 patients with bronchiectasis involving more than one lobe, 2 patients with lungs destroyed by tuberculosis, 1 patient with empyema, 4 patients without available EGD data, 5 patients with severe COPD characterized by an FEV_1 of <50%, and 1 patient without a matched control. Finally, 201 patients with mild to moderate COPD and their 402 matched controls were included in this analysis.

제 3 절 Measurements

Seropositivity and rapid urease test for H. pylori infection

Helicobacter pylori-specific immunoglobulin G (IgG) concentrations were measured with a commercially available enzyme-linked immunosorbent assay (DIESSE Diagnostica Senese, Siena, Italy) according to the manufacturer's protocol. The lower limit of a positive *H. pylori* IgG titer was 20 units/mL. To determine the *H. pylori* infection status, a rapid urease test (CLO test; Ballard, Australia) was performed at the time of endoscopy with a gastric mucosa specimen obtained by endoscopic biopsy. The CLO test was positive when the gel pellet

turned a dark pink to magenta color for up to 24 hours.

Spirometry and annual rate of lung function decline

Spirometry was performed according to the criteria of the American Thoracic Society [19]. The method described by Morris [20] was used for the predicted FEV_1 and FVC. Pre-bronchodilator spirometry data were used for analysis because screening post-bronchodilator testing is not performed in Korea. To assess the annual decline in lung function, we collected the participants' spirometry data if they had undergone spirometry more than three times per year since January 2010.

제 4 절 Statistical analysis

The chi-square test was used to compare categorical variables, a t-test was used to compare normally distributed continuous data, and the Wilcoxon rank-sum test was used to compare non-normally distributed continuous variables. The associations between the *H. pylori* IgG level and various pulmonary function parameters were investigated using Pearson's correlation coefficient. Multivariable association analysis was performed with logistic regression analyses adjusting for sex, age, smoking status, gastric diseases known to be related to *H. pylori* infection, and severity of airflow limitation as defined by the FEV_1. Concordance between the CLO test result and IgG seropositivity for *H. pylori* infection was analyzed with the kappa index. Declines in the FEV_1 or FVC over time were analyzed with random-slope, random-intercept mixed linear regression adjusted for age, sex, body mass index, smoking status, and baseline FEV_1 or FVC. All statistical analyses were performed using SPSS for Windows (ver. 22.0; IBM Corp., Armonk, NY, USA) and Stata software (ver. 12.1; StataCorp, College Station, TX, USA).

제 3 장 Results

제 1 절 Baseline characteristics of study population

In total, 603 participants (201 patients with COPD and 402 controls) were analyzed in this study. The baseline characteristics of the study population are listed in Table 1. The participants' mean age was 60 years, and most were men (87.1%). The mean FEV_1 of patients with COPD was 88.60% ± 14.9% of predicted, and nonsmokers comprised 15.4% of all patients with COPD. Hypertension and diabetes were the most common comorbidities and were suggested to be associated with *H. pylori* infection. The prevalence rates of these suggested comorbidities were not significantly different between the cases and controls.

Table 1. Baseline clinical characteristics of COPD patients and control groups

	COPD (n = 201)	Control (n = 402)	*p*-value
Age, yr	*60.68* ± 8.24	60.68 ± 8.23	
Male (%)	*175 (87.1%)*	350 (87.1%)	
Body mass index, kg/m^2	*24.07* ± 3.02	24.16 ± 2.73	0.685[†]
Height	*1.68* ± 0.069	1.67 ± 0.069	0.095[†]
Smoking status			<0.001
Current smoker	*73 (36.3%)*	86 (21.4%)	
Ex-smoker	*95 (47.3%)*	166 (41.3%)	
Non-smoker	*31 (15.4%)*	144 (35.8%)	
Median pack-years (IQR)	*25 (15.0, 40.0)*	20.0 (12.5, 35.0)	0.312
Spirometry			
FEV_1	*2.58* ± 0.59	3.04 ± 0.53	<0.001
FEV_1 (%)	*88.6* ± 14.94	106.0 ± 13.02	<0.001
FVC	*3.91* ± 0.812	3.83 ± 0.66	0.241[†]
FVC (%)	*96.8* ±13.52	96.6 ± 11.27	0.833[†]
FEV_1/FVC	*65.91* ±6.18	79.45 ± 5.13	< 0.001
Hypertension	*59 (29.4%)*	121 (30.1%)	0.850[‖]
Diabetes mellitus	*27 (13.5%)*	67 (16.7%)	0.313[‖]
Chronic kidney disease	*1 (0.5%)*	10 (2.5%)	0.111[‖]
Iron Deficiency anemia	*0 (0%)*	2 (0.5%)	0.555[‖]
Cardiovascular disease			0.711[‖]
Coronary artery disease	*3 (1.5%)*	8 (2.0%)	
Cerebrovascular disease	*2 (1.0%)*	2 (0.5%)	

Continuous data are shown as mean±SD.

IQR, interquartile range

[†] *P* value from chi-squared test

[‖] *P* value from Mann-Whitney test

제 2 절 *Helicobacter pylori* seropositivity and COPD

As shown in Table 2, IgG seropositivity for *H. pylori* was present in about half the participants in each group without a significant difference (cases, 45.8%; controls, 52.2%; p=0.13). Additionally, in a quantitative comparison of the association between the IgG level of *H. pylori* and the presence of COPD, no significant difference was found between the two groups (cases, 114.8 units/mL; controls, 109.6 units/mL; p=0.55) (Table 2, Figure 1).

In a comparison of the concordance between *H. pylori* seropositivity and the CLO test results, 71 of 89 (79.8%) with a CLO-positive test result showed *H. pylori* seropositivity and 99 of 147 (67.3%) patients with a CLO-negative test result showed *H. pylori* seronegativity (kappa index, 0.442; p<0.001) (Table 3). The discordant fractions between the two tests were not different in either group (kappa index for cases, 0.407; kappa index for controls, 0.464; p<0.001 for both) (Table 3).

Table 2. The prevalence of positive H. pylori serology by COPD stage

	COPD (n = 201)	Control (n = 402)	*p*-value
Hp IgG seropositivity, (%)	*92 (45.8%)*	210 (52.2%)	0.134
Hp IgG level, units/ml (median, IQR)	*114.8 (33.6, 191.0)*	109.6 (34.3, 166.4)	0.549

Figure 1. *H.pylori* serum IgG levels in COPD patients and control subjects. Median, IQR.

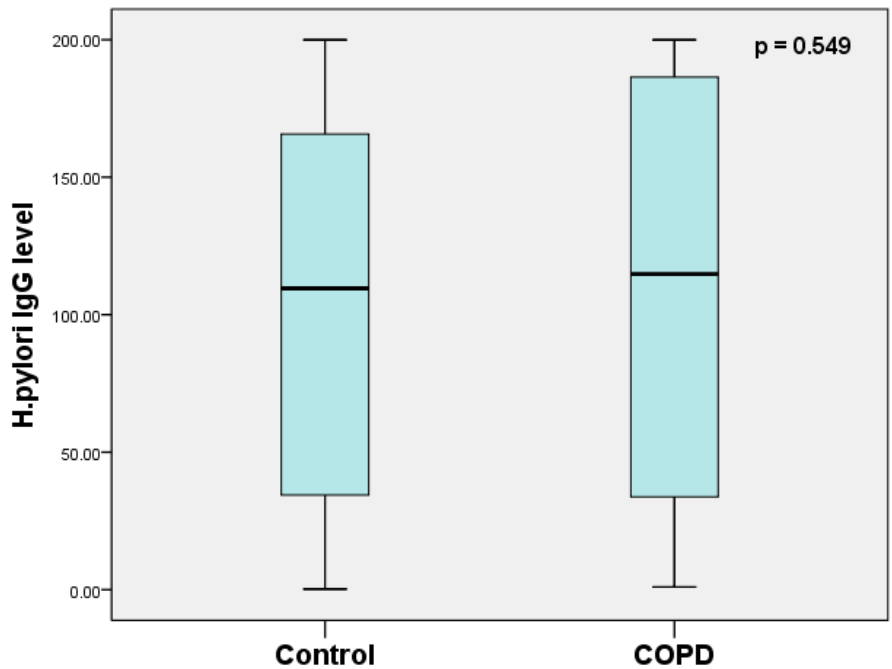


Table 3. The association of seropositivity of *H.pylori* and CLO tests

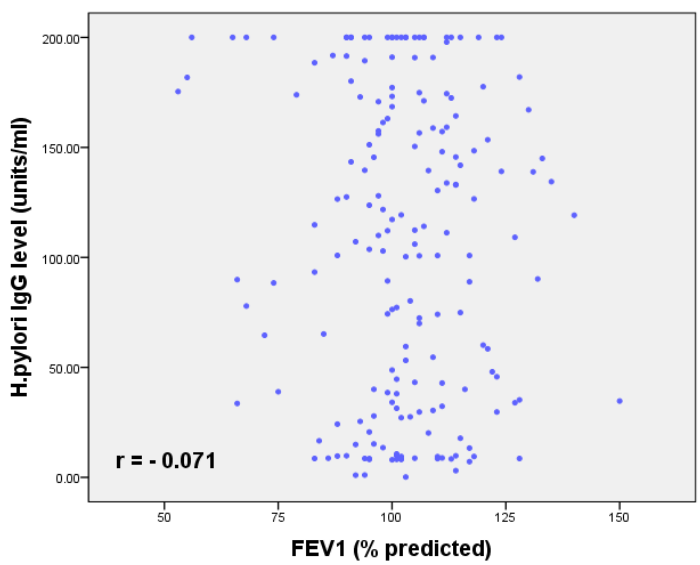
	Hp Seropositive (119)	Hp Seronegative (117)
CLO positive (89)	*71 (79.8%)*	18 (20.2%)
CLO negative (147)	*48 (32.7%)*	99 (67.3%)

Kappa Index : 0.442, P <0.001

제 3 절 *Helicobacter pylori* seropositivity and severity of air flow limitation

When the airflow limitation (FEV_1) in patients with COPD was graded using the Global Initiative for Chronic Obstructive Lung Disease criteria, there was no significant difference in *H. pylori* seropositivity between patients with stage 1 and stage 2 COPD (46.1% and 44.9%, respectively; p=0.89 for all comparisons). In addition, no relationship between the serum level of IgG for *H. pylori* and FEV_1 was found in the cases or controls, or among the entire study population (n = 187, r = −0.07, p>0.05) (Figure 2). Using an absolute value of FEV_1 there was no relationship between the serum level of IgG for *H. pylori* and FEV_1(n = 187, r = −0.026, p=0.729).

Figure 2. Correlation between *H.pylori* IgG titer and FEV_1 (The distribution of Hp IgG titer according to the airflow limitation)



Linear regression of the *H.pylori* IgG versus FEV_1 (%). No significant correlation was found between two variables (n=187, r= -0.071, p=0.333).

제 4 절 Multivariate analysis of association between *H.pylori* infection and COPD

The presence of *H. pylori* infection was evaluated by seropositivity and the CLO test. Therefore, the association between *H. pylori* infection and COPD was tested with respect to seropositivity and the CLO test results.

The univariate analysis of associations with seropositivity revealed that smoking status, presence of cardiovascular disease, gastric diseases including gastritis and peptic ulcer disease, and COPD were not associated with *H. pylori* seropositivity, while gastroesophageal reflux disease (GERD) showed a significant negative association with *H. pylori* seropositivity (Table 4). After adjustment for smoking status, presence of cardiovascular disease, presence of endoscopic gastritis and peptic ulcers, and GERD, we found that COPD was not associated with *H. pylori* seropositivity in this analysis. Only GERD was negatively associated with *H. pylori* seropositivity.

A total of 232 (38.5%) study participants underwent the CLO test because it was performed at the discretion of the endoscopist. Of these 232 patients, 89 (38.4%) showed CLO positivity. The CLO test was not associated with COPD, smoking status, the presence of cardiovascular disease, or the presence of gastric disease. However, GERD tended to be associated with a lower rate of CLO positivity.

Table 4. Univariate and multivariate analysis of *H.pylori* seropositivity

	Seropositivity				**CLO positivity**			
Variables	Unadjusted OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*	Unadjusted OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Smoking	0.857 (0.602-1.220)	0.391	0.909 (0.630-1.313)	0.612	1.304 (0.668-2.544)	0.464	1.296 (0.647-2.596)	0.464
CVD	1.510 (0.531-4.297)	0.440	1.340 (0.467-3.845)	0.586	0.991 (0.231-4.250)	0.990	0.900 (0.208-3.899)	0.888
Gastritis/ peptic ulcer	1.343 (0.761-2.371)	0.309	1.132(0.629-2.037)	0.679	4.4 (0.532-36.372)	0.169	3.961 (0.468-33.519)	0.207
GERD	0.482 (0.322-0.721)	<.001	0.485 (0.321-0.733)	0.001	0.494(0.241-1.013)	0.054	0.527 (0.254-1.091)	0.084
COPD	0.772 (0.550-1.084)	0.135	0.778 (0.546-1.108)	0.164	1.023 (0.597-1.755)	0.933	1.014(0.577-1.781)	0.963

제 5 절 Impact of *H. pylori* seropositivity on lung function decline

A total of 195 participants (51 cases, 144 controls) underwent spirometry 3 or more times per year. Among them, 93 (47.7%) exhibited *H. pylori* seropositivity. Because the final trends were not different between cases and controls, we assessed the association between *H. pylori* seropositivity and the decline in lung function in the total study population. Even in the whole study population, there was no difference in the annual rate of decline in the FEV_1 between the *H. pylori*-seropositive and -seronegative groups (7.8±6.8 and 6.8±6.6 mL/yr, respectively; p=0.92) (Table 5, Figure 3). Similarly, the annual rate of decline in the FVC was not different between the *H. pylori*-seropositive and -seronegative groups (28.9±8.7 and 27.4±8.5 mL/yr, respectively; p=0.90).

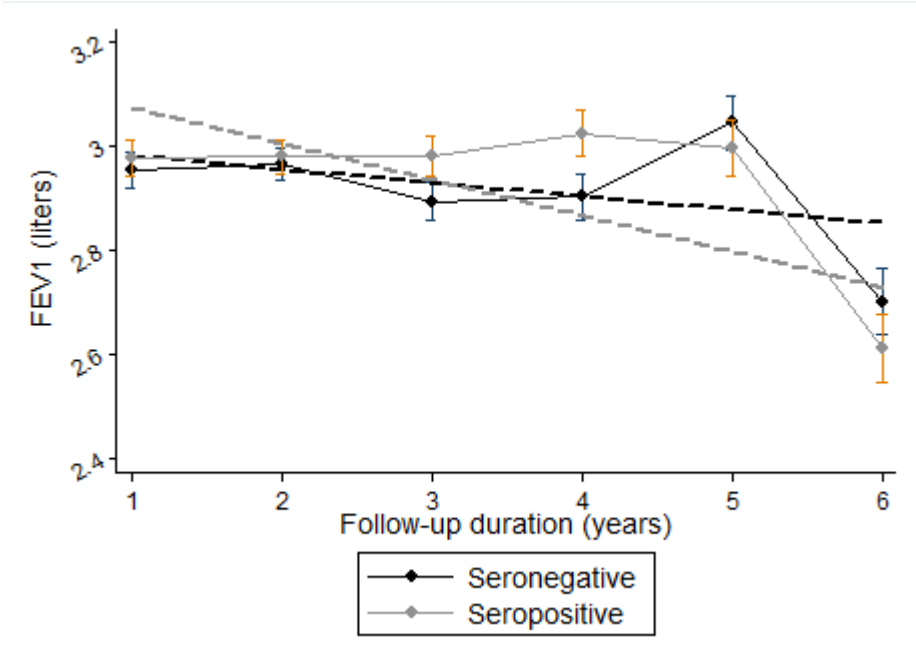
Table 5. Impact of *H. pylori* test on the lung function decline

Total (195)	Hp Seropositive (93)	Hp Seronegative (102)	*p*-value
FEV_1 (SE)	*7.8 ml/yr (6.8)*	*6.8 ml/yr (6.6)*	0.92
FVC (SE)	*28.9 ml/yr (8.7)*	*27.4 ml/yr (8.5)*	0.90

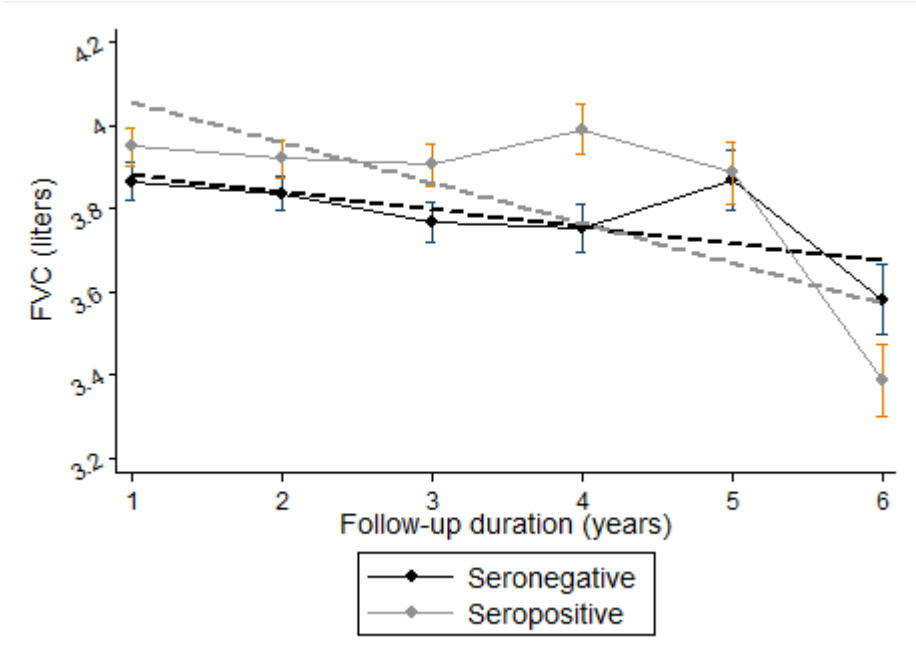
Adjusted by age, sex, bmi, initial FEV_1 or FVC, smoking status

Figure 3. Impact of *H. pylori* seropositivity on lung function decline

A. FEV_1 decline



B. FVC decline



제 4 장 Discussion

The seroprevalence of *H. pylori* among patients with COPD was not different from that of healthy controls in this study. Additionally, *H. pylori* seropositivity did not accelerate the annual rate of lung function decline during the 3-year follow-up period. This indicates that the seroprevalence of *H. pylori* might not be associated with the incidence and progression of COPD in countries with a high burden of *H. pylori* infection. Our results regarding lung function decline are consistent with a recent large cohort study that demonstrated no difference in the annual rate of lung function decline between seropositive and seronegative individuals[17].

Although a few studies have suggested a cross-sectional relationship between *H. pylori* seroprevalence and COPD, there is no definitive evidence of a causal pathophysiologic association between *H. pylori* and COPD. Moreover, compared to the two previous studies, our study included relatively healthy patients because we used data from participants in an annual health screening program. GERD and cigarette smoking have been suggested as important confounding factors that explain this inconsistent seroprevalence in patients with COPD. As in the present study, many epidemiological studies have demonstrated a negative association between *H. pylori* infection and GERD [21,22]. However, according to epidemiologic reports of COPD, GERD is one of the most common comorbidities in patients with COPD, especially advanced-stage COPD [23,24]. This inverse relationship among COPD, GERD, and *H. pylori* infection is related to the inconsistent seroprevalence of *H. pylori* in patients with COPD. Nevertheless, because only patients with mild to moderate COPD were recruited in this study, the impact of COPD severity on

the prevalence of GERD and *H. pylori* infection may be minimal.

Cigarette smoking might also have an ambivalent influence on the association between COPD and *H. pylori* infection. Smoking is a major risk factor for the development of COPD, but whether *H. pylori* infection is associated with smoking remains unclear. Both higher and lower seropositivity of *H. pylori* have been reported in smokers compared with nonsmokers [25-28].

Seropositivity in the present study was relatively high (up to half of patients with COPD), similar to the general population of Korea [29,30]. Therefore, *H. pylori* infection is so common that it may have only a modest effect on the incidence and disease progression of COPD in countries with a high burden of *H. pylori* infection, even if it is a real contributor.

Another point should be considered when interpreting the results of studies on the seroprevalence of *H. pylori* and its extra-gastric manifestations; namely, the limitations of seropositivity testing for *H. pylori* infection. As shown in this study, there is a discrepancy between the serum *H. pylori* IgG level and CLO test results. Although serum *H. pylori* IgG measurement is a clinically useful noninvasive diagnostic test for *H. pylori* infection, some studies have shown that it has lower accuracy than the 13C urea breath test and exhibits disagreement with histopathological findings (kappa statistic, 0.72; accuracy, 86%) [31-33].

This study has some strength in terms of investigating the role of *H. pylori* in patients with COPD. First, to the best of our knowledge, this is the first report on the association between *H. pylori* seroprevalence and the prevalence of COPD, and between *H. pylori* seroprevalence and annual lung function decline in a country with a high burden of *H. pylori* infection. Additionally, because the study population was recruited from among individuals who participated in an annual

health screening program and were thought to be relatively healthy, the participants' characteristics are considered to be very similar to those of the Korean general population with respect to the prevalence of diseases such as diabetes mellitus and hypertension, despite the fact that the study population was small [34,35]. Furthermore, the *H. pylori* seropositivity rate was similar to that in previous reports on Korean populations[29,30,36]. This indicates that our study population was minimally affected by selection bias.

Second, this study focused on patients with mild to moderate COPD. In patients with advanced COPD, GERD is a common comorbidity and may be associated with lung hyperinflation, increased abdominal pressure, and a high rate of medical treatment for COPD [37]. Therefore, in patients with advanced COPD, the actual association between *H. pylori* infection and COPD may be affected by GERD. This suggests that the present study may provide more reliable data regarding the association between *H. pylori* seroprevalence and COPD.

Third, we tested participants for *H. pylori* infection using both the CLO test and serologic tests. Our results were consistent using both methods, indicating that the data of this study are reliable.

Despite these merits and interesting results, this study had some limitations. First, the study design prevented evaluation of additional contributing factors related to the causal role of *H. pylori* in the pathogenesis of COPD. Second, the small sample size may be an obstacle to generalizing the results to the general population. Third, the follow-up period may have been too short to fully elucidate the rate of decline in lung function, and we could not evaluate the change in the annual decline in lung function after *H. pylori* eradication. Although 3 years may be a rather short period, we thought it was possible to identify a rapid or slower decline even with a 3-year

follow-up period. Moreover, there is uncertainty regarding *H. pylori* infection at the first FEV1 measurement, even though we used spirometry data within a couple of years from the time the serology test was performed. Finally, the effects of respiratory medications on the decline in lung function were not considered because we could not verify the use of respiratory medications.

In conclusion, this study demonstrated no association between *H. pylori* infection and mild to moderate COPD in a country with a high burden of *H. pylori* infection. Furthermore, *H. pylori* infection did not affect the rate of decline in lung function in this study population.

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Abstract

Association between *Helicobacter pylori* seropositivity and mild to moderate chronic obstructive pulmonary disease

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In this study, we investigated the seroprevalence of *H. pylori* in patients with mild to moderate chronic obstructive pulmonary disease (COPD) in an Asian country with a high prevalence of *H. pylori* infection. Additionally, we aimed to elucidate the association between the seroprevalence of *H. pylori* and the decline of lung function in patients with COPD.

Participants who underwent a medical check-up for *H. pylori* at a referral hospital in Korea were recruited for this study. All participants were tested for *H. pylori* infection using an immunoassay of the *H. pylori*-specific IgG concentration and a rapid urease test at the time of endoscopy with a gastric mucosa specimen. We assessed the decline in lung function using spirometric data of those who underwent spirometry more than three times.

In total, 603 participants (201 patients with COPD and 402

controls) were analyzed. The seroprevalence of *H. pylori* IgG in the patients and controls was 45.8% and 52.2%, respectively (p=0.134). The *H. pylori* IgG level in patients with COPD was not significantly different from that of the controls (114.8 and 109.6 units/ml, respectively; p=0.549). In addition, there were no significant differences in the annual forced expiratory volume in 1 s or forced vital capacity between participants with *H. pylori* seropositivity and seronegativity. This study showed no relationship between H. pylori infection and COPD in a country with a high burden of *H. pylori* infection. Furthermore, *H. pylori* infection did not affect the rate of lung function decline in this study population.

Keywords : *Helicobacter pylori*, COPD, lung function decline
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