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ORIGINAL ARTICLE

무증상 성인에서 헬리코박터 파일로리 감염과 다양한 전신 염증 표지자의 연관성 결여

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Lack of Association between *Helicobacter pylori* Infection and Various Markers of Systemic Inflammation in Asymptomatic Adults

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Background/Aims: *Helicobacter pylori* (*H. pylori*) infection has been known to cause various extra-gastric diseases, which may be mediated by an increase in systemic inflammation. Thus, we examined the association between *H. pylori* infection and various markers of systemic inflammation in a large sample of asymptomatic adults.
Methods: Cross-sectional data were obtained from 17,028 adults who completed routine health check-ups. *H. pylori* infection status was determined using a serum immunoglobulin G test, and systemic inflammation was assessed using the C-reactive protein (CRP) levels, neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR).
Results: Multiple linear regression model-adjusted for potential confounders-revealed that *H. pylori* infection was not associated with CRP levels (coefficient: -0.012, 95% confidence interval [CI]: -0.037, 0.012, p=0.319), NLR (coefficient: 0.055, 95% CI: -0.027, 0.138, p=0.192), or PLR (coefficient: 1.798, 95% CI: -1.979, 5.574, p=0.351). In a multivariable logistic regression model, *H. pylori* infection was not associated with the risk of CRP levels being elevated to ≥0.1 mg/dL (odds ratio: 0.96, 95% CI: 0.81, 1.08) or ≥0.3 mg/dL (odds ratio: 1.02, 95% CI: 0.84, 1.19). In the multivariable model, CRP levels elevated to ≥0.1 mg/dL were significantly associated with body mass index, current smoking status, hypertension, and diabetes mellitus. Regular exercise and high-density lipoprotein cholesterol were factors that minimized the elevation of CRP levels.
Conclusions: Chronic infection with *H. pylori* was not associated with various inflammatory markers. Further investigation is needed to clarify the interaction between *H. pylori* infection, systemic inflammation, and extra-gastric disease. **(Korean J Gastroenterol 2018;72:21-27)**

Key Words: *Helicobacter pylori*; Inflammation; C-reactive protein

INTRODUCTION

Helicobacter pylori colonizes the stomach of approximately one-half of the world's population, and higher prevalence is generally associated with low socioeconomic status.[1-3] Infection is usually acquired early in life and persists through-

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out the host's life if left untreated.[4] The clinical manifestations of this infection are generally upper gastrointestinal diseases, such as chronic gastritis, peptic ulcer disease, gastric cancer, and gastric mucosa-associated lymphoid tissue.[5] However, epidemiological studies have also revealed that *H. pylori* infection is linked to extra-gastric diseases,[6-8] which may involve biological processes far from the primary site of infection. For example, numerous studies in the past several years have described the extra-gastric manifestations of *H. pylori* infection, including idiopathic thrombocytopenic purpura and iron deficiency anemia. Furthermore, recent reports have described the associations between *H. pylori* infection and neurological disorders, cardiovascular disease, non-alcoholic fatty liver disease, and colorectal cancer.[6,9-13]

The pathogenetic mechanism(s) linking *H. pylori* infection to extra-gastric diseases remain unclear, and there are limited data to support the various potential mechanisms. These mechanisms include the induction of a low-grade inflammatory state, induction of molecular mimicry mechanisms through the expression of proteins that mimic host peptides, and inference of the absorption of different nutrients and drugs.[6,8,14] Among the proposed mechanisms, low-grade systemic inflammation has been the most evaluated mechanism and is considered as the major mechanism linking *H. pylori* infection to cardiovascular disease.[15-17] However, the association between *H. pylori* infection and systemic inflammation remains controversial,[16-18] and the inconsistent findings are likely caused by the methodological differences between the study populations, limited sample size, or inadequate consideration of potential confounding factors. Therefore, we investigated the associations between *H. pylori* infection and various systemic inflammatory markers in a large-scale study of asymptomatic participants and carefully controlled for potential confounding factors.

SUBJECTS AND METHODS

1. Study population

This retrospective cross-sectional study examined the data from healthy men and women (≥30 years old) who underwent routine health check-ups at the Center for Health Promotion, Samsung Medical Center, Seoul, South Korea. To evaluate the associations between *H. pylori* infection and systemic inflammation, we selected 18,946 participants who underwent a screening for *H. pylori* infection and serum inflammatory markers, including the C-reactive protein (CRP) levels, neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR). However, we subsequently excluded 1,918 participants with missing data on important covariates (smoking, alcohol, exercise, education level and body mass index [BMI]) or with a history of malignancy. Thus, a final total of 17,028 asymptomatic participants were included. The study protocol was approved by the institutional review board of Samsung Medical Center and was implemented in accordance with the Declaration of Helsinki and the current legal regulations in Korea. Specific informed consent was not required because the study only examined de-identified health screening data, although all participants had consented to the examination during the health check-ups.

2. Data collection

Under the comprehensive health-screening program, data regarding the demographic characteristics, anthropometric measurements, serum biochemical measurements, and epidemiological characteristics, including smoking habits, alcohol consumption, physical activity, education level (as a surrogate for socioeconomic status), and personal medical history, were collected using a questionnaire.[11] Smoking status was categorized as never, former, or current smoker. Alcohol consumption status was categorized as either mild (≤10 g/day) or modest (>10 g/day). Regular exercise was defined as exercising ≥3 times/week at moderate intensity. Education level was categorized as low (elementary school or below), medium (middle or high school), or high (college or higher). Participants' weights and heights were measured to the nearest 0.1 kg and 0.1 cm, respectively, while wearing light clothing and in bare feet, and BMI was calculated as weight divided by height squared (kg/m^2). After a ≥12-h fast, blood samples were collected in the morning and analyzed in the hospital's clinical laboratory. Serum immunoglobulin G (IgG) antibodies to *H. pylori* were detected using an enzyme-linked immunosorbent assay (GAP test IgG kit; Bio-Rad Laboratories Inc., Hercules, CA, USA), and *H. pylori* infection was considered present in cases with a positive assay result.

3. Statistical analysis

Continuous variables were reported as the mean±standard deviation, and categorical variables were reported as

number and percentage. Continuous variables were compared using Student's t-test, and categorical variables were compared using chi-square test. The associations of *H. pylori* seropositivity with systemic inflammation were evaluated using odds ratios and 95% confidence intervals in univariable and multivariable logistic regression analyses. The CRP cut-off values were defined as 0.1 mg/dL and 0.3 mg/dL because patients have a low risk of cardiovascular disease if their CRP is ≤0.1 mg/dL, a moderate risk if their CRP is 0.1-0.3 mg/dL, and a high risk if their CRP is >0.3 mg/dL.[19] Multivariable analysis included the following variables: age, sex, BMI, smoking status, alcohol consumption, exercise level, education level, hypertension, fasting glucose level, diabetes mellitus, low-density lipoprotein cholesterol level, high-density lipoprotein cholesterol level, dyslipidemia, cardiovascular disease, and aspirin use. The relationships between *H. pylori* seropositivity and each inflammatory marker (as continuous variables) were investigated using multiple linear regression analysis after adjusting for potential confounders (age, sex, smoking status, alcohol consumption, exercise level, education level, hypertension, fasting glucose level, diabetes mellitus, low-density lipoprotein cholesterol level, high-density lipoprotein cholesterol level, dyslipidemia, cardiovascular disease, and aspirin use). Moreover, we evaluated the correlation between *H. pylori* antibody titers and the inflammatory markers (CRP, NLR and PLR) using Pearson's correlation coefficient. A p-value of <0.05 was considered statistically significant, and all analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA).

RESULTS

1. Baseline characteristics of the study participants

Among the 17,028 participants (mean age: 49.3±9.3 years), the prevalence of *H. pylori* infection was 58.2% (n=9,918). The baseline characteristics of the participants according to *H. pylori* infection status are shown in Table 1. The participants with *H. pylori* infection were significantly older, more likely to be male, more likely to be current smokers, and less educated, relative to the participants without *H. pylori* infection. Moreover, the group with *H. pylori* infection had sig-

Table 1. Characteristics of the Study Participants

	All (n=17,028)	*H. pylori* (-) (n=7,110)	*H. pylori* (+) (n=9,918)	p-value
Age (years)	49.3±9.3	48.3±9.9	50.0±8.7	<0.001
Male (%)	51.6	49.5	53.1	<0.001
BMI (kg/m^2)	23.0±2.6	22.9±2.6	23.1±2.5	<0.001
Current smoker (%)	16.4	17.2	15.8	0.003
Modest alcohol intake (%)	13.3	12.7	13.7	0.08
Regular exercise (%)	36.7	36.4	36.9	0.69
Education level (%)				<0.001
Low	8.2	7.9	8.5	
Medium	28.1	26.0	29.6	
High	63.7	66.1	61.9	
Fasting glucose (mg/dL)	93.6±17.2	93.5±16.7	93.6±17.5	0.649
LDL-C (mg/dL)	124.3±29.8	122.8±29.7	125.3±29.9	<0.001
HDL-C (mg/dL)	54.9±13.9	55.7±14.2	54.3±13.8	<0.001
Hypertension (%)	21.3	20.7	21.6	0.219
Diabetes mellitus (%)	6.8	6.3	7.1	0.069
Dyslipidemia (%)	16.7	16.1	17.1	0.138
Cardiovascular disease (%)	2.7	2.7	2.8	0.772
Aspirin use (%)	13.5	13.6	13.5	0.798
Neutrophil count (/μL)	3,070±1,240	3,000±1,250	3,120±1,230	<0.001
Platelet count (×10^3/μL)	237.6±52.6	238.28±53.0	236.6±51.9	0.064
Lymphocyte count (/μL)	1,930±530	1,900±510	1,960±530	<0.001
NLR	1.63±0.79	1.61±0.77	1.64±0.80	0.28
PLR	124.6±39.7	126.3±39.9	123.4±39.6	0.015
CRP (mg/dL)	0.06 (0.03-0.11)	0.05 (0.03-0.11)	0.06 (0.03-0.11)	0.889

Values are expressed as mean±standard deviation, percentage, or median (interquartile range).
H. pylori, Helicobacter pylori; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; CRP, C-reactive protein.

Table 2. Association between *H. pylori* Infection and Systemic Inflammation Using Two Cutoffs for C-reactive Protein in Multivariable Analyses

	CRP>0.1 (mg/dL)			CRP>0.3 (mg/dL)		
	OR	95% CI	p-value	OR	95% CI	p-value
Age	1.01	1.00-1.02	0.061	1.00	0.99-1.02	0.602
Sex (male)	1.04	0.88-1.34	0.639	1.16	0.86-1.56	0.34
BMI	1.14	1.12-1.17	<0.001	1.10	1.07-1.14	<0.001
Current smoker	1.50	1.26-1.79	<0.001	1.04	0.76-1.41	0.811
Alcohol intake	1.01	0.86-1.18	0.906	0.96	0.74-1.26	0.787
Regular exercise	0.85	0.75-0.95	0.005	0.95	0.77-1.16	0.587
High education level	0.94	0.76-1.16	0.567	0.68	0.49-0.96	0.03
Fasting glucose	1.01	1.00-1.01	<0.001	1.01	1.00-1.01	0.071
LDL-C	1.00	0.99-1.00	0.169	1.00	0.99-1.00	0.103
HDL-C	0.98	0.98-0.99	<0.001	0.99	0.98-0.99	<0.001
Hypertension	1.78	1.03-1.35	0.02	0.85	0.67-1.09	0.201
Diabetes mellitus	1.23	1.05-1.43	0.009	0.68	0.45-1.03	0.071
Dyslipidemia	1.03	0.89-1.19	0.711	1.18	0.91-1.51	0.209
Cardiovascular disease	0.94	0.67-1.31	0.696	1.19	0.71-1.98	0.519
Aspirin use	0.88	0.74-1.05	0.148	1.11	0.83-1.48	0.476
H. pylori positive	0.96	0.81-1.08	0.415	0.92	0.77-1.10	0.369

Odds ratios with 95% confidence intervals were calculated using multivariate logistic regression analysis.
H. pylori, *Helicobacter pylori*; CRP, c-reactive protein; OR, odds ratio; CI, confidence interval; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

Table 3. Relationship between *H. pylori* Infection and Inflammatory Markers as a Continuous Variable

	C-reactive protein		Neutrophil/lymphocyte ratio		Platelet/lymphocyte ratio	
	Coefficient[a] (95% CI)	p-value	Coefficient[a] (95% CI)	p-value	Coefficient[a] (95% CI)	p-value
Age	0.002 (0.001, 0.003)	0.013	-0.002 (-0.006, 0.002)	0.339	-0.424 (-0.619, -0.228)	<0.001
Sex (male)	0.024 (-0.001, 0.049)	0.064	0.023 (0.015, 0.328)	<0.001	-3.045 (-7.402, 1.312)	0.171
BMI	0.007 (0.004, 0.01)	<0.001	0.026 (0.015, 0.037)	<0.001	-1.431 (-1.975, -0.886)	<0.001
Current smoker	0.002 (-0.026, 0.029)	0.895	-0.029 (-0.126, 0.067)	0.545	-12.33 (-17.12, -7.55)	<0.001
Alcohol intake	-0.006 (-0.03, 0.018)	0.63	-0.031 (-0.099, 0.037)	0.369	-1.189 (-5.651, 3.273)	0.602
Regular exercise	-0.012 (-0.029, 0.006)	0.182	-0.072 (-0.141, -0.004)	0.038	-0.917 (-4.308, 2.474)	0.596
High education level	-0.022 (-0.054, 0.011)	0.193	0.087 (-0.027, 0.202)	0.135	3.602 (-2.077, 9.279)	0.214
Fasting glucose	0.0002 (-0.0004, 0.001)	0.549	-0.001 (-0.003, 0.001)	0.382	-0.059 (-0.153, 0.035)	0.219
LDL-C	-0.0003 (-0.0001, 0)	0.059	-0.001 (-0.002, 0.0004)	0.293	0.042 (-0.006, 0.089)	0.088
HDL-C	-0.001 (-0.002, -0.001)	0.004	-0.001 (-0.003, 0.002)	0.619	0.249 (0.137, 0.362)	<0.001
Hypertension	-0.013 (-0.035, 0.008)	0.228	0.058 (-0.017, 0.133)	0.128	2.133 (-1.568, 5.833)	0.259
Diabetes mellitus	-0.024 (-0.061, 0.014)	0.214	0.087 (-0.04, 0.214)	0.181	-2.874 (-9.169, 3.422)	0.371
Dyslipidemia	0.112 (-0.022, 0.025)	0.883	-0.069 (-0.155, 0.018)	0.12	0.538 (-3.757, 4.832)	0.806
Cardiovascular disease	-0.023 (-0.074, 0.028)	0.574	0.019 (-0.192, 0.231)	0.858	-3.546 (-14.04, 6.95)	0.501
Aspirin use	0.008 (-0.019, 0.034)	0.574	0.036 (-0.058, 0.129)	0.455	-0.352 (-5.007, 4.303)	0.882
H. pylori positive	-0.012 (-0.037, 0.012)	0.319	0.055 (-0.027, 0.137)	0.192	1.798 (-1.979, 5.574)	0.351

H. pylori, *Helicobacter pylori*; CI, confidence interval; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.
[a]Coefficients were calculated using multivariable linear regression analysis after adjusting for all variables.

nificantly higher neutrophil counts, lymphocyte counts, and low-density lipoprotein cholesterol levels, as well as significantly lower platelet counts, PLR values, and high-density lipoprotein cholesterol levels. No significant inter-group differences were observed with respect to NLR, CRP levels, and histories of hypertension, diabetes mellitus, dyslipidemia, cardiovascular disease, or aspirin use.

2. Association between *H. pylori* infection and systemic inflammation

Multivariable logistic regression analyses were performed using high and low CRP cut-off values to identify systemic in-

Table 4. Correlation between *H. pylori* Antibody Titers and Inflammatory Markers

	H. pylori titer	CRP	NLR	PLR
H. pylori titer				
Pearson Correlation	-	0.004	0.022	0.002
p-value	-	0.634	0.128	0.886
CRP				
Pearson Correlation	0.004	-	0.214	0.066
p-value	0.634	-	<0.001	<0.001
NLR				
Pearson Correlation	0.022	0.214	-	0.423
p-value	0.128	<0.001	-	<0.001
PLR				
Pearson Correlation	0.002	0.066	0.423	
p-value	0.886	<0.001	<0.001	

Correlations were considered significant at the 0.01 level (two-tailed). *H. pylori*, *Helicobacter pylori;* CRP, C-reactive protein; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio.

flammation (>0.3 mg/dL and >0.1 mg/dL, respectively). *H. pylori* seropositivity was not associated with serum CRP levels of >0.1 mg/dL (Table 2). In that analysis, the elevated serum CRP levels were associated with BMI, current smoking, fasting glucose level, hypertension, and diabetes mellitus, while regular exercise and high-density lipoprotein cholesterol protected against elevated serum CRP levels. *H. pylori* seropositivity was also not associated with serum CRP levels of >0.3 mg/dL.

The relationship between *H. pylori* infection and systemic inflammation was evaluated based on NLR, PLR, and CRP levels using multiple linear regression analysis (Table 3). *H. pylori* seropositivity was not associated with higher CRP levels when they were treated as a continuous variable. However, CRP levels were significantly associated with older age and BMI, while high-density lipoprotein cholesterol was inversely associated with CRP levels. *H. pylori* seropositivity was not associated with NLR values when they were treated as a continuous variable. However, NLR values were significantly associated with male sex and BMI, while regular exercise was inversely associated with NLR values. *H. pylori* seropositivity was not associated with PLR values when they were treated as a continuous variable.

We evaluated the correlation between *H. pylori* antibody titers and various inflammatory markers (CRP, NLR and PLR) using Pearson's correlation coefficient. *H. pylori* antibody titers were not significantly correlated with any of the inflammatory markers, although they were significantly correlated with each other (Table 4).

DISCUSSION

Cross-sectional data from a large sample of asymptomatic men and women undergoing routine health check-ups were used to investigate the association of *H. pylori* infection with systemic inflammation, which is a potential mechanism linking *H. pylori* infection to extra-gastric disease. However, our results revealed that *H. pylori* infection was not associated with the three inflammatory markers (CRP, NLR and PLR). This result was consistent among the inflammatory markers and persistent regardless of high or low cut-off values for defining systemic inflammation.

The hypothesis that systemic inflammation is induced by chronic *H. pylori* infection remains controversial. Several studies have revealed the association between *H. pylori* infection and systemic inflammation.[16-18,20] A study of 81 healthy Japanese men revealed that serum CRP levels were significantly higher in cases with *H. pylori* seropositivity.[17] Furthermore, a cross-sectional population-based study of 2,361 English participants identified *H. pylori* infection as a significant risk factor for systemic inflammation.[16] Another study of 1,157 healthy participants revealed that *H. pylori* infection is a risk factor for elevated CRP levels.[21] In contrast, however, a population-based study of 1,834 healthy men and women revealed that *H. pylori* infection was unrelated to CRP levels and leukocyte counts.[18] Another study of 489 dyspeptic patients did not detect an association between *H. pylori* infection and systemic inflammation based on serum CRP levels.[20] These inconsistent results may be due to the variation in each study's limited sample sizes, heterogeneous participant groups, and often incomplete control of confounding factors. In particular, most previous studies did not control for socioeconomic status, which can have a significant influence on both *H. pylori* infection and systemic inflammation, as *H. pylori* infection is related to living in crowded conditions with poor hygiene and low socioeconomic status,[2,3] while systemic inflammation and cardiovascular disease are also related to socioeconomic status.[22,23] Thus, the present study carefully accounted for potential confounding factors, including age, sex, BMI, smoking status, alcohol intake, physical activity, and education level as a surrogate for socioeconomic status. Our findings confirmed that individuals with *H. pylori*

infection had lower education levels than those without *H. pylori* infection.

Recent studies have indicated that NLR or PLR are potential biomarkers and prognostic factors for various diseases, including cardiovascular disease, malignancy, rheumatological disorders, and other inflammatory diseases.[24-26] Systemic inflammation is associated with alterations in the quantity and composition of circulating blood cells, which are usually associated with neutrophilia, thrombocytosis, and lymphopenia.[27] Thus, the features of circulating blood cell components can be used to assess inflammatory activity.[28] Furthermore, NLR is derived from routine complete blood count data, which makes it an inexpensive and readily available marker in daily practice (especially relative to CRP testing). Only one study has evaluated the association between NRL and *H. pylori* infection,[29] revealing a significant correlation between *H. pylori* infection and systemic inflammation based on NLR. However, that study was limited by its small sample size (50 participants) and a lack of control for potential confounding factors. In contrast, the present study revealed that *H. pylori* infection was not associated with systemic inflammation based on NLR or PLR.

The present study has several strengths. First, a large sample size and adjustment for potential confounding factors allowed us to minimize temporal bias. Additional strengths include the use of high-quality standardized anthropometric measurements, incorporation of an epidemiological questionnaire regarding lifestyle factors, and use of various high-quality laboratory tests. However, there are also several limitations that should be considered when interpreting our findings. First, the *H. pylori* infection status was solely evaluated based on serum IgG results from an enzyme-linked immunosorbent assay, without other laboratory tests, such as the urease breath test or rapid urease test. Serological results cannot differentiate between current and past infections. Nevertheless, serological testing for IgG to *H. pylori* is a highly sensitive and inexpensive mass screening tool that can be easily used in areas with a high prevalence of *H. pylori* infection. Furthermore, the Korean prevalence of *H. pylori* infection in a nationwide multicenter study was 59.6%,[30] which agrees with our prevalence of 58.2%. Second, we cannot exclude the possibility of residual or unmeasured confounding, despite the adjustment for several important confounding factors in the multivariable analysis. Third, we cannot exclude the possibility that unmeasured low-grade inflammation was induced by chronic *H. pylori* infection. Finally, we evaluated the data from healthy participants who underwent routine health check-ups, therefore our results may be difficult may be difficult to generalize our findings to other populations.

In conclusion, this study revealed that *H. pylori* infection was not associated with three inflammatory markers (CRP, NLR and PLR) after adjusting for potential confounding factors. This result was consistent for all three inflammatory markers and at different CRP cut-off values for defining systemic inflammation. Further investigation is needed to clarify the interaction among *H. pylori* infection, systemic inflammation, and extra-gastric disease.

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