JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.952003
J Contemp Med 2021;11(6):761-767

Orjinal Araştırma / Original Article

CagA Positive *Helicobacter pylori* Infection in Coronary Atherosclerosis: Discriminative Value of Lymphocyte to Mean Platelet Volume Ratio

Koroner Aterosklerozda CagA Pozitif *Helicobacter pylori* Enfeksiyonu: Lenfosit Sayısının Ortalama Trombosit Hacmine Oranının Tanısal Değeri

Barış Sensoy[1], Nur Ozer Sensoy[2]

[1] Health Sciences Üniversity Bursa Yüksek İhtisas Training and Research Hospital, Cardiology Clinic, Bursa, Turkey
[2] Mudanya Government Hospital Internal Medicine Clinic, Ankara, Turkey

Abstract

Aim: Potent combined and long-term antithrombotic therapies that predispose to gastric injury are the mainstay of treatment in acute coronary syndromes (ACS). Severe chronic gastric mucosal inflammation due to the *Helicobacter pylori* (*H. pylori*) infection was shown to be associated with higher peripheral blood lymphocytes and lower blood mean platelet volume (MPV) levels. We aimed to investigate the discriminative usefulness of blood lymphocyte to MPV ratio as a simple premise marker for CagA positive *H. pylori* infection before the required advanced diagnostic tests in patients with coronary arterial disease (CAD).

Material and Method: A total of 293 patients' who had undergone elective and urgent coronary angiography due to CAD were included in the study. Serologic *H. pylori* infection status and hematological parameters were determined. Two groups were compared according to CagA serology status. Confounding factors were adjusted by propensity score matching and multivariate logistic regression analysis.

Results: Rates of ACS, male gender, diabetes mellitus, family history of CAD, current smoking and lymphocyte to MPV ratio were higher in seropositive patients according to seronegative patients ($p<0.05$). The ROC curve analysis showed that the lymphocyte to MPV ratio at a cut-off point of 165 had 71% sensitivity and 60% specificity for discriminating patients with positive *H. pylori* serology (AUC=0.71, $p<0.0001$). Lymphocyte to MPV ratio was independently associated with positive *H. pylori* serology.

Conclusion: Lymphocyte to MPV ratio can be helpful for discriminating CagA positive *H. pylori* infected CAD patients requiring advanced confirmatory tests.

Keywords: CagA, coronary arterial disease, *H. Pylori,* lymphocytes, mean platelet volume

Öz

Amaç: Akut koroner sendromlarda (AKS) mideye hasar verebilen uzun süreli güçlü-ikili antitrombotik tedavi kullanılmaktadır. *Helicobacter pylori* (*H. pylori*) enfeksiyonuna bağlı şiddetli kronik gastrik mukozal inflamasyonun, daha yüksek sayıda periferik kan lenfositleri ve daha düşük kan ortalama trombosit hacmi (MPV) seviyeleri ile ilişkili olduğu gösterilmiştir. Koroner arter hastalığı (KAH) olan hastalarda gerekli ileri tanı testlerinden önce CagA pozitif *H. pylori* enfeksiyonu varlığını belirlemede kan lenfosit/MPV oranının öncül belirteç olarak ayırt edici yararlılığını araştırmayı amaçladık.

Gereç ve Yöntem: KAH nedeniyle elektif ve acil koroner anjiyografi yapılan toplam 293 hasta çalışmaya dahil edildi. Serolojik *H. pylori* enfeksiyon durumu ve hematolojik parametreler belirlendi. CagA seroloji durumuna göre iki grup karşılaştırıldı. Etkin faktörler, eğilim skoru eşleştirmesi ve çok değişkenli lojistik regresyon analizi ile ayarlandı

Bulgular: AKS, erkek cinsiyet, diabetes mellitus, ailede KAH öyküsü, halen sigara kullanımı ve lenfosit/MPV oranı seropozitif hastalarda seronegatif hastalara göre daha yüksekti ($p<0.05$). ROC eğrisi analizi, lenfosit/MPV oranının 165 kestirim noktası için pozitif *H. pylori* serolojisi olan hastaları ayırt etmede %71 duyarlılığa ve %60 özgüllüğe sahip olduğunu göstermiştir (AUC=0.71, $p<0.0001$). Lenfosit/MPV oranı bağımsız olarak pozitif *H. pylori* serolojisi ile ilişkiliydi.

Sonuç: Lenfosit/MPV oranı, CagA pozitif *H. pylori* açısından İleri yöntemler ile taranması gereken KAH hastalarını ayırt etmede yardımcı olabilir.

Anahtar Kelimeler: CagA, Koroner Arter Hastalığı, *H. Pylori*, lenfositler, ortalama trombosit hacmi

Corresponding *(İletişim)*: Barıs Sensoy, Health Sciences Üniversity Bursa Yüksek İhtisas Training and Research Hospital, Cardiology Clinic, Bursa, 16100, Turkey
E-mail *(E-posta)*: gs2000bs@yahool.com
Received *(Geliş Tarihi)*: 08.06.2021 **Accepted *(Kabul Tarihi)*:** 11.07.2021

INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is common everywhere in the world, and it affects more than 50% of the world's population.[1] *H. pylori* infection causes variable degrees of mucosal damage in sensitive persons varying from mild gastritis to ulcer, gastrointestinal bleeding and gastric carcinoma.[2,3] Although association between coronary arterial diseases (CAD) and *H. pylori* infection is controversial, factors such as diabetes mellitus and smoking that predispose to both of these diseases, are frequently observed in both CAD and *H. pylori* infection.[3,4] Suggested explanations for the pathogenesis include direct cytotoxic effect and persistent local or systemic inflammatory response due to the microorganism.[2,5] Leukocyte and platelet activation occurs during an inflammatory reaction and mean platelet volume (MPV) is the indicator of platelet reactivity. Recently, MPV has been started to be used as a simple inflammatory indicator in some diseases such as diabetes mellitus, hypertension, atherosclerosis and other inflammatory disorders.[6,7] Also, severe chronic gastric mucosal inflammation due to the *H. pylori* infection was shown to be associated with higher peripheral blood lymphocytes and lower blood MPV levels.[2,8] Besides, positive *H. pylori* CagA serology, accepted as a potent systemic immune-inflammatory response marker, was associated with higher prevalence of acute coronary syndromes (ACS).[9,10]

Potent combined and long-term antithrombotic therapies that predispose to gastric injury are the mainstay of treatment in ACS.[11] Gastrointestinal bleeding after ACS is associated with increased mortality and the role of *H. pylori* infection in gastrointestinal bleeding is well established.[3] Tests required for the diagnosis of the infection; such as endoscopic biopsies, blood serology of *H. pylori* infection or urea breath tests are expensive and are not available everywhere. Therefore especially in CAD patients; a simple, minimally invasive, inexpensive, and widely available diagnostic marker for detecting *H. pylori* infection can be important for clinical practice.

Correlation between inflammatory mediators and the presence of *H. pylori* infection has been determined but the ability of these indicators for discriminating patients with *H. pylori* infection is uncertain.[2,12-15] As *H. pylori* infection was shown to be associated with higher peripheral blood lymphocytes and lower blood MPV levels; we therefore sought to investigate the discriminative usefulness of blood lymphocyte to MPV ratio as a simple premise marker for CagA positive *H. pylori* infection before the required advanced diagnostic tests in patients with CAD.

MATERIAL AND METHOD

Study population

After exclusion of unsuitable patients, a total of 293 subjects undergoing elective and urgent coronary angiography in our Cardiology clinic with various manifestations of ischemic heart disease were included. All of the patients were suspected of having CAD due to clinical symptoms or the results of clinical tests. Subjects with normal coronary arteries and with a disorder associated with acute or chronic infection/inflammation were excluded. None of the subjects included in the study had clinical evidence of connective tissue disease, liver dysfunction, hypothyroidism, severe chronic heart failure (NYHA class III-IV), moderate-severe renal dysfunction (eGFR<60 mL/min/1.73 m^2) and malignant diseases. Additionally, patients with any surgery within the previous 4 weeks, prior upper gastrointestinal tract and coronary arterial bypass surgery, use of nonsteroid anti-inflamatory drugs, blood transfusion during the last three months and incomplete data were excluded. Also none of the 293 individuals recruited had a history of eradication therapy for *H. pylori* infection or had received any antibiotic treatment during the study.

All subjects were screened with a questionnaire. Demographic data and risk factors for CAD were recorded in all participants. Individuals whose income was lower than at least two times of the minimum wage in our country were defined as lower socioeconomic status. The education level was divided into <10 years and ≥10 years. Among the main cardiovascular risk factors, the presence of family history of CAD (in a first-degree relative <55 years of age), hypertension (systolic or diastolic blood pressure >140 and 90 mm Hg, respectively, or pharmacological therapy with antihypertensive drugs), diabetes mellitus (fasting glucose plasma concentrations >126 mg/dL or pharmacological therapy with antidiabetic drugs or insulin), hyperlipidemia (low-density lipoprotein (LDL) cholesterol levels ≥ 130 mg/dl or being treated with lipid-lowering medication) were considered definitions. Current smoking was defined as at least 20 cigarettes per month for more than 6 months. Effort angina was defined by the presence of chest pain on walking that was relieved within 10 minutes after stopping or by ST segment of ECG down-sloping in a standard 12-lead electrocardiogram during chest pain or by positive stress testing. The diagnosis of AMI was established by using American College of Cardiology/European Society of Cardiology criteria.[16] Participation was voluntary, and written, informed consent was obtained from each subject. The study protocol was approved by the ethics committee of our hospital. The inclusion period was from March to September of 2013.

Laboratory Methods

All blood samples were drawn before the procedure after an overnight fasting under standardized conditions. Hematological parameters were measured using a Beckman Coulter LH780 Hematology Analyzer (Beckman Coulter, Inc). Lymphocyte to MPV ratio had calculated from the measurements in the peripheral blood. HsCRP (Siemens BN-II kinetic nephelometry analyzer) was used as a marker of inflammation.

Specific *H. pylori* anti-CagA IgG antibodies were measured by use of a commercial Enzyme-linked immune-sorbent assay (ELISA) (Radim Diagnostics, Rome, Italy) according to

manufacturer's instructions. Titers were defined as positive or negative according to a cutoff value of 30 UR/mL. The sensitivity and specificity of the tests of Radim (TM was 88% and 93.8%, respectively.[17] Patients were divided into 2 groups according to CagA IgG serostatus. All measurements were processed according to standard laboratory practice in a blinded fashion.

Determination of Coronary Arterial Disease

Coronary angiography was performed by a femoral approach using the standard Judkins technique (Axiom Artis zee 2011; Siemens, Munich, Germany). Coronary arteries were opacified with manual injections of 6–8 mL of Iohexol (Omnipaque, Nycomed Ireland, Cork, Ireland) at each position. Coronary artery disease has been defined as stenosis of at least one major epicardial coronary vessel at any degree. Two independent cardiologists who were unaware of the *H. pylori* status of the patients performed visual analysis of the coronary angiograms.

Statistical Analysis

We used the Kolmogorov-Smirnov test to assess the normality of numeric variables and analyzed homogeneity of numeric variables using the Levene test. Continuous variables with a normal distribution were expressed as means with standard deviations. Continuous variables with a skewed distribution (Neutrophils, Lymphocytes, MPV, RDW and Lymphocyte to MPV ratio) were expressed as medians with lower and upper quartiles. The categorical variables were expressed as numbers with percentages. The Student t test, the Mann–Whitney U test and the chi-square ($\chi 2$) tests (or Fisher's exact test if any expected cell count was <5) were used to compare baseline characteristics according to *H. pylori* serology.

Our study groups exhibited significant demographic and atherosclerotic risk factor differences (**Table 1**). To minimize the confounding effect of these factors and to obtain the best balance among groups, we performed a multivariate logistic regression model based on the significant variables.[18] Furthermore, in order to estimate the ability of lymphocyte to MPV ratio for predicting the presence of positive *H. pylori* serology, the receiver–operating characteristic (ROC) curve analysis was done to estimate area under curve (AUC).

Univariate logistic regression was used to investigate the relation between *H. pylori* serologic status and confounding parameters in our entire sample. After performing univariate analysis, significantly obtained variables (female gender, family history of CAD, diabetes mellitus, current smoking, presence of acute coronary syndromes and lymphocyte to MPV ratio higher than 165 (10^3 /μL fL)) were included in multivariate logistic regression analysis. Results were expressed as odds ratio (OR) with 95% confidence intervals (CI).

Table 1. Demographic, clinical and laboratory characteristics of our entire study group according to *Helicobacter pylori* CagA serology.

	Overall Group n=293	CagA IgG seronegatif n=55	CagA IgG seropositive n=238	p-value
Age, (years)	60±14	60±16	60±14	0.9
Female, n (%)	169 (58)	44 (88)	125 (51)	<0.0001
Family history of CAD, n (%)	174 (59)	22 (44)	152 (63)	0.01
Socioeconomic status, n (%)				
Low	112 (38)	16 (32)	96 (39)	0.32
Middle-High	181 (62)	34 (68)	147 (61)	
School education <10 years, n (%)	140 (48)	27 (54)	113 (46)	0.33
Diabetes, n (%)	129 (44)	10 (20)	119 (49)	<0.0001
Hypertention,n (%)	188 (64)	33 (66)	155 (64)	0.77
Dyslipidemia, n (%)	153 (52)	26 (52)	127 (52)	0.97
Current smoker, n (%)	130 (44)	10 (18)	120 (50)	<0.0001
Dyspepsi, n (%)	172 (59)	30 (54)	142 (60)	0.49
White blood cell count (10^3 /μL)	9.4±3.1	10.2±3.8	9.3±2.9	0.07
Platelets (10^3 /μL)	228±61	211±56	231±62	0.03
Neutrophils (10^3 /μL)	6.3 (4.8-7.9)	7.4 (5.0-8.1)	5.6 (4.8-7.8)	0.04
Lymphocytes (10^3 /μL)	1.8 (1.3-2.4)	1.4 (1.2-1.8)	1.9 (1.4-2.7)	<0.0001
MPV, fL	8.8 (7.8-9.4)	9.1 (8.2-9.3)	8.6 (7.7-9.5)	0.20
RDW, %	14.0 (13.4-15.1)	14.1 (13.2-15.1)	13.9 (13.4-15.0)	0.83
HsCRP,	5.9±4.0	6.7±4.2	5.8±4.0	0.13
Haemoglobin, g/dL	13.9±1.7	14.1±1.6	13.8±1.8	0.29
Creatinine, mg/dL	1.0±0.3	1.1±0.3	1.0±0.3	0.23
Lymphocytes/MPV (10^3 /μL fL)	214 (140-307)	154 (123-197)	228 (147-307)	<0.0001
Lymphocytes/MPV>165 (10^3 /μL fL)	190 (65)	22 (40)	168 (71)	<0.0001
CagA IgG titer UR/mL	115±91	8±7	137±85	<0.0001
CAD type, n (%)				
Stable CAD	213 (73)	48 (87)	165 (69)	0.02
ACS	80 (27)	7 (13)	73 (31)	

ACS, acute coronary syndrome; CAD, coronary arterial disease; Cag A, cytotoxin-associated gene product; HsCRP, high sensitive C-reactive protein; IgG, immunoglobulin G; MPV, mean platelet volume; RDW, red cell distribution width.

The sample size was sufficient to detect odds ratios for an association between the *H. pylori* serology and confounding parameters with 80% power at the 5% level of significance. A P-value ≤0.05 was considered statistically significant. Statistical tests were two-sided. All analyses were performed with IBM SPSS 15 software (SPSS version 15.0, SPSS, Chicago, IL, USA).

RESULTS

Clinical variables, coronary atherosclerotic disease and *H. pylori* infection.

The general features of patients according to *H. pylori* serology status for both entire and matched samples are summarized in **Table 1** and **2.** Tests for CagA-positive strains of *H. pylori* infection were performed in all subjects with positive results in 81.2%. Prevalence of male gender, diabetes mellitus, family history of CAD and current smoking was higher in seropositive patients than the seronegative ones (p<0.05). Also presence of acute coronary syndromes, lymphocyte counts and lymphocyte to MPV ratio were higher in patients with positive serology according to seronegative patients (p<0.05). The odds ratio of positive serology for the presence of acute coronary syndromes was 3.0 (95% CI (1.3-7.0); p=0.007).

The ROC curve analysis showed that the lymphocyte to MPV ratio at a cut-off point of 165 had 71% sensitivity and 60% specificity to determine positive *H. pylori* serology (AUC=0.71, p<0.0001).

After balancing the groups for significant confounding CAD risk factors and coronary syndrome type; higher lymphocyte to MPV ratio, higher rates of male gender and current smoking remained significant in seropositive subjects compared to seronegatif ones (p<0.05) (**Table 2**).

Medical treatments

Treatment rates with ACEİ, beta-blocker, calcium channel blocker and statin were similar between the groups according to *H. pylori* CagA serology (p>0.05). Only rate of treatment with angiotensin converting enzyme blockers differed between the groups in our matched samples (79% vs. 54%; p<0.02; for negative and positive serology respectively).

Regression analysis

After univariate analysis, independent association of *H. pylori* serology with significant confounding clinical features was investigated by multivariate analyses. In our entire sample after controlling for female gender, family history of CAD, diabetes mellitus, current smoking and presence of acute coronary syndromes; lymphocyte to MPV ratio higher than 165 (10^3 /μL fL) remained positively associated with *H. pylori*

Table 2. Demographic, clinical and laboratory characteristics of our matched study group according to *Helicobacter pylori* CagA serology.

	Overall Group n=78	CagA IgG seronegatif n=39	CagA IgG seropositive n=39	p-value
Age, (years)	61±15	60±17	58±13	0.67
Female, n (%)	72 (92)	39 (100)	33 (85)	0.03
Family history of CAD, n (%)	32 (41)	15 (38)	17 (44)	0.64
Socioeconomic status, n (%) Low Middle-High	 31 (40) 47 (60)	 12 (31) 27 (69)	 19 (49) 20 (51)	 0.10
School education <10 years, n (%)	33 (42)	16 (41)	17 (44)	0.82
Diabetes, n (%)	11 (14)	5 (13)	6 (15)	0.74
Hypertention,n (%)	49 (63)	28 (72)	21 (54)	0.10
Dyslipidemia, n (%)	43 (55)	21 (54)	22 (56)	0.82
Current smoker, n (%)	9 (12)	1 (3)	8 (21)	0.03
Dyspepsi, n (%)	43 (55)	19 (49)	24 (61)	0.25
White blood cell count (10^3 /μL)	10.3±3.6	10.7±3.8	9.5±3.0	0.14
Platelets (10^3 /μL)	221±70	215±61	225±72	0.53
Neutrophils (10^3 /μL)	7.1 (5.4-8.1)	7.7 (6.5-9.2)	6.6 (4.7-7.9)	0.013
Lymphocytes (10^3 /μL)	1.8 (1.3-2.3)	1.4 (1.1-2.1)	2.1 (1.4-2.7)	0.002
MPV, fL	8.8 (7.5-9.1)	9.1 (7.8-9.1)	8.2 (7.2-9.1)	0.07
RDW, %	14.1 (13.4-15.0)	14.1 (13.1-15.1)	14.1 (13.6-15.0)	0.57
HsCRP,	6.8±3.9	6.9±4.1	6.5±3.6	0.65
Haemoglobin, g/dL	14.7±1.4	14.6±1.2	14.8±1.5	0.52
Creatinine, mg/dL	1.1±0.2	1.1±0.2	1.1±0.2	0.87
Lymphocytes/MPV (10^3 /μL fL)	191 (140-307)	154 (134-261)	247 (154-325)	0.005
Lymphocytes/MPV>165 (10^3 /μL fL)	44 (56)	16 (41)	28 (72)	0.006
CagA IgG titer UR/mL	49±60	7±5	118±74	<0.0001
CAD type, n (%) Stable CAD ACS	 64 (82) 14 (18)	 32 (82) 7 (18)	 32 (82) 7 (18)	 1

ACS, acute coronary syndrome; CAD, coronary arterial disease; Cag A, cytotoxin-associated gene product; HsCRP, high sensitive C-reactive protein; IgG, immunoglobulin G; MPV, mean platelet volume; RDW, red cell distribution width.

Table 3. Multivariable regression analysis of *Helicobacter pylori* CagA serology and potential associated variables in our entire and matched sample groups.

Variables	Entire sample n=293		Matched Sample n=78	
	Multivariate OR (95% CI)	P value	Multivariate OR (95% CI)	P Value
Male gender	4.3 (1.7-10.8)	0.002	-	-
Family history of CAD	2.7 (1.3-5.7)	0.010	-	-
Diabetes mellitus	2.5 (1.1-5.7)	0.037	-	-
Current smoker	4.3 (1.8-10.3)	0.001	4.8 (0.4-55.1)	0.20
Acute coronary syndromes	6.8 (2.5-18.7)	<0.0001	-	-
Lymphocytes/MPV>165 (10^3 /μL fL)	3.8 (1.9-7.8)	<0.0001	4.1 (1.5-11.2)	0.007

*Adjusted for Lymphocytes/MPV>165 (10^3 /μL fL), female gender and current smoking CAD, coronary arterial disease; CI, confidence interval; MPV, mean platelet volume; OR, odds ratio.

serology (OR:3.8; 95% CI (1.9-7.8); p<0.0001). İn our matched sample, after controlling for female gender and current smoking, multivariable regression analysis showed the independent association of lymphocyte to MPV ratio higher than 165 (10^3 /μL fL) with *H. pylori* serology (OR:4.1; 95% CI (1.5-11.2); p<0.007) (**Table 3**).

DISCUSSION

This propensity score match observational study has confirmed that in CAD patients, CagA positive *H. pylori* infection prevalence is high. Also positive *H. pylori* CagA serology is found to be associated with higher prevalence of diabetes mellitus, current smoking, family history of CAD and acute coronary syndromes. The major and novel finding of this study is the independent positive association of lymphocyte to MPV ratio with CagA positive *H. pylori* infection in CAD patients.

H. pylori infection is common everywhere in the world, and it affects more than 50% of the world's population.[1] Association between CAD and *H. pylori* infection is suggested to be effected by factors predisposing to both of these diseases.[3,4] Major factors responsible for increasing rate of CAD occurrence like diabetes mellitus and smoking were linked with higher prevalence of *H. pylori* infection.[4] Therefore, investigating the relation between *H. pylori* infection and stable or unstable forms of cardiac syndromes is complicated and related trials are controversial.[9,10,19-23] Population-based cohort studies have not observed a significant association of *H. pylori* infection and CAD.[20,21] However, such a significant, positive association between positive anti-CagA IgG serology and the occurrence of ACS was concluded in a meta-analysis and in a prospective, case-control study with a 12-year follow-up period.[9,10,21] In line with these studies ACS was associated with positive CagA *H. pylori* serology in our study. Reasons for the differences with the previous reports may be due to study designs, heterogeneous patient populations, validity of exposure information and differences in treatment modalities. Our study tried to solve these limitations at least partly by balancing the groups. Similar to the literature, female gender, family history of CAD, history of diabetes mellitus and current smoking were the covariates associated with positive anti-CagA IgG serology in our study. Also, positive *H. pylori* CagA serology, a potent systemic immune-inflammatory response marker, was associated with higher prevalence of acute coronary syndromes. The induction of thrombotic processes by the maintenance of a low grade general inflammatory response is recognized as one of the potential mechanisms linking *H. pylori* infection to ACS occurrence.[5] By observing a positive association between CagA IgG seroprevalence and lymphocyte count, we have supported this finding.

Gastrointestinal bleeding after ACS is associated with increased mortality and the role of *H. pylori* infection (especially CagA positive strains) in the pathogenesis of gastrointestinal bleeding is well established.[3] Also, potent combined and long-term antithrombotic therapies that predispose to gastric injury are the mainstay of treatment in ACS. When the frequent association of CAD risk factors with *H. pylori* infection and the high serologic prevalence of virulent *H. pylori* infection are taken into account, the necessity of diagnosis and treatment of infection should be emphasized in patients with CAD; especially in subjects with ACS. Currently *H. pylori* testing and eradication therapy for gastrointestinal primary bleeding prevention is recommended for patients at risk.[11,24] In addition, tests required for the diagnosis of the infection; such as endoscopic biopsies, blood *H. pylori* serology or urea breath tests are expensive and are not available everywhere. Therefore, a simple, minimally invasive, inexpensive, and widely available diagnostic marker for *H. pylori* infection can be important for clinical practice especially in CAD patients. As the appropriate markers; leukocytes, platelets and MPV levels, that are routinely reported during a complete blood count analysis, were investigated regarding the intensity and severity of inflammation in patients with *H. pylori* infection.[2,12]

Leukocyte and platelet activation occurs during an inflammatory reaction and MPV is the indicator of platelet reactivity.[7] Recently, MPV has been started to be used as a simple inflammatory indicator in some diseases such as diabetes mellitus, hypertension, atherosclerosis and other inflammatory disorders.[6] Few studies have also shown a correlation between inflammatory mediators and the presence of *H. pylori* infection.[2,12-15] Particularly, CRP levels were observed to be increased in *H. pylori* infection.[15] Also, value of neutrophil to lymphocyte ratio and MPV levels for the detection of *H. pylori* were reported.[2,12-14] The results of these studies were different from our findings. Farah et al.[12] determined the clinical importance of lower lymphocyte

counts and Topal et al.[2] demonstrated the impracticability of MPV levels for detecting *H. pylori* infection and severity of inflammation. In our study, lymphocyte to MPV ratio higher than 165 (10^3 /µL fL) detected positive *H. pylori* CagA serology with 71% sensitivity and 60% specificity. These conflicting results about inflammatory parameters in *H. pylori* infected patients might be partially explained by different patient selections (such as age, sample size, inclusion of patients with comorbidity) and different diagnostic criteria. In contrast to mentioned studies; in the present study, sample size was larger, all of the patients had CAD, detection of *H. pylori* was by serology and only CagA positive strains were evaluated. Actually, presence of lymphoid follicles in patients with *H. pylori* infection related chronic mucosal inflammation was shown to be associated with higher peripheral blood lymphocytes and lower blood MPV levels.[2,8] This finding suggests that, agent accepted to be responsible for more severe inflammation, can be important by influencing mirror indicators of advanced inflammatory status in blood. But due to the study designs, the rate of patients infected with pathogenic CagA strain was obscure in those studies.

Strengths of our study include the large sample size relative to similar studies and fully matched compared samples for probable confounders. Limitations are *H. pylori* diagnosis based on serology, which may reflect not only present but also recent or past *H. pylori* infection. So, association of acute *H. pylori* infection with the presence of acute coronary syndromes is uncertain. On the other hand, *H. pylori* status was determined among all cases with the same method reducing internal variability, and, although the test showed good correlation with previous *H. pylori* tests used in former studies, no specific local validation was performed. Our measurements of subsequent markers were based on a single determination and the time-course alterations cannot be extrapolated from the study. Observational studies are always open to residual confounding that cannot always be completely controlled. Here, we reported estimates of OR adjusted by most widely recognized independent risk factors.

CONCLUSION

We suggest that lymphocyte to MPV ratio can be an inexpensive premise test for the classification of CagA positive *H. pylori* infected patients with CAD who require advanced confirmatory tests. Nevertheless, future studies going deeper in this discussion are required for investigating the importance of the blood lymphocyte to MPV ratio.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ministry of Health and the ethics committee of Ankara Training and Research Hospital institution, and our study was carried out in accordance with Principles of the Helsinki Declaration (Decision no:4123 13/03/2013).

Informed Consent: Written consent was obtained from all patients who participated in the study and their relatives.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Murray LJ, Bamford KB, O'Reilly DP, McCrum EE, Evans AE. *Helicobacter pylori* infection: relation with cardiovascular risk factors, ischaemic heart disease, and social class. Br Heart J 1995;74(5):497-501.
2. Topal F, Karaman K, Akbulut S, et al. The relationship between mean platelet volume levels and the inflammation in *Helicobacter pylori* gastritis. J Nat Med Assoc 2010;102(8):726-30.
3. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of *Helicobacter pylori* infection--the Maastricht IV/ Florence Consensus Report. Gut. 2012;61(5):646-64.
4. Marietti M, Gasbarrini A, Saracco G, Pellicano R. *Helicobacter pylori* infection and diabetes mellitus: the 2013 state of art. Panminerva medica. 2013;55(3):277-81.
5. Elizalde JI, Pérez-Pujol S, Heras M, Sionis A, Casanovas N, Martorell T, et al. Effects of *Helicobacter pylori* eradication on platelet activation and disease recurrence in patients with acute coronary syndromes. Helicobacter. 2004;9(6):681-9.
6. Sansanayudh N, Anothaisintawee T, Muntham D, McEvoy M, Attia J, Thakkinstian A. Mean platelet volume and coronary artery disease: a systematic review and meta-analysis. Int J Cardiol 2014;175(3):433-40.
7. Borissoff JI, Spronk HM, ten Cate H. The hemostatic system as a modulator of atherosclerosis. New Eng J Med 2011;364(18):1746-60.
8. Karttunen TJ, Niemela S, Kerola T. Blood leukocyte differential in *Helicobacter pylori* infection. Digestive diseases and sciences. 1996;41(7):1332-6.
9. Franceschi F, Niccoli G, Ferrante G, et al. CagA antigen of *Helicobacter pylori* and coronary instability: insight from a clinico-pathological study and a meta-analysis of 4241 cases. Atherosclerosis. 2009;202(2):535-42.
10. Ikeda A, Iso H, Sasazuki S, Inoue M, Tsugane S, Group JS. The combination of *Helicobacter pylori*- and cytotoxin-associated gene-A seropositivity in relation to the risk of myocardial infarction in middle-aged Japanese: The Japan Public Health Center-based study. Atherosclerosis. 2013;230(1):67-72.
11. Singla S, Sachdeva R, Uretsky BF. The risk of adverse cardiac and bleeding events following noncardiac surgery relative to antiplatelet therapy in patients with prior percutaneous coronary intervention. J Am Coll Cardiol 2012;60(20):2005-16.
12. Farah R, Khamisy-Farah R. Association of neutrophil to lymphocyte ratio with presence and severity of gastritis due to *Helicobacter pylori* infection. J Clin Lab Anal 2014;28(3):219-23.
13. Guclu M, Agan AF. Association of Severity of *Helicobacter pylori* Infection with Peripheral Blood Neutrophil to Lymphocyte Ratio and Mean Platelet Volume. Euroasian J Hepato-Gastroenterol 2017;7(1):11-16.
14. Umit H, Umit EG. *Helicobacter pylori* and mean platelet volume: a relation way before ımmune thrombocytopenia? Eur Rev Med Pharmacol Sci. 2015 ;19(15):2818-23.
15. Jha HC, Prasad J, Mittal A. High immunoglobulin A seropositivity for combined Chlamydia pneumoniae, *Helicobacter pylori* infection, and high-sensitivity C-reactive protein in coronary artery disease patients in India can serve as atherosclerotic marker. Heart and Vessels. 2008;23(6):390-6.
16. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Circulation. 2012;126(16):2020-35.

17. Matsukura N, Onda M, Tokunaga A, Kato S, Yamashita K, Ohbayashi M. Detection of *Helicobacter pylori* DNA in gastric juice by the polymerase chain reaction: comparison with findings in bacterial culture and the detection of tissue IgA and serum IgG antibodies against *Helicobacter pylori*. J Gastroenterol 1995;30(6):689-95.
18. Rubin DB. The design versus the analysis of observational studies for causal effects: parallels with the design of randomized trials. Stat Med 2007;26(1):20-36.
19. Kowalski M. *Helicobacter pylori (H. pylori*) infection in coronary artery disease: influence of *H. pylori* eradication on coronary artery lumen after percutaneous transluminal coronary angioplasty. The detection of *H. pylori* specific DNA in human coronary atherosclerotic plaque. J Physiol Pharmacol. 2001;52(1 Suppl 1):3-31.
20. Haider AW, Wilson PW, Larson MG, et al. The association of seropositivity to *Helicobacter pylori*, Chlamydia pneumoniae, and cytomegalovirus with risk of cardiovascular disease: a prospective study. J Am Coll Cardiol 2002;40(8):1408-13.
21. Strachan DP, Mendall MA, Carrington D, et al. Relation of *Helicobacter pylori* infection to 13-year mortality and incident ischemic heart disease in the caerphilly prospective heart disease study. Circulation. 1998;98(13):1286-90.
22. Niccoli G, Franceschi F, Cosentino N, et al. Coronary atherosclerotic burden in patients with infection by CagA-positive strains of *Helicobacter pylori.* Coron Artery Dis. 2010;21(4):217-221.
23. Furuto Y, Kawamura M, Yamashita J, Yoshikawa T, Namikawa A, Isshiki R, et al. Relationship Between *Helicobacter pylori* Infection and Arteriosclerosis. Int J Gen Med. 2021 23;14:1533-1540.
24. Abraham NS, Hlatky MA, Antman EM, et al. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. A Report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. J Am Coll Cardiol 2010;56(24):2051-66.