Sociodemographic characteristics and clinical risk factors of Helicobacter pylori infection and antibiotic resistance in the Eastern Black Sea region of Turkey

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ABSTRACT

Background/Aims: *The aim of this study was to assess the clinical and sociodemographic risk factors of* Helicobacter pylori *infection and antibiotic resistance in the eastern Black Sea region of Turkey.*

Materials and Methods: *In total, 344 patients with dyspeptic symptoms who completed an extended questionnaire were enrolled in the study. Diagnosis of* H. pylori *infection was made by rapid urease test, histopathological investigation, and culture. Susceptibility of* H. pylori *strains was assessed by agar dilution (amoxicillin, tetracycline, metronidazole, levofloxacin) and E-test (clarithromycin) methods.*

Results: *The H. pylori positivity rate was 40.4% (139/344). Logistic regression analysis indicated that age and the presence of duodenal ulcer were independent risk factors associated with* H. pylori *positivity (odds ratio (OR): 0.96, 95% CI: 0.93–0.99, p=0.013; OR: 5.42, 95% CI: 1.96–14.98, p=0.001, respectively). Of 104* H. pylori*-positive cultures, 43 strains (41%) were susceptible to all antibiotics, whereas 61 (59%) were resistant to at least one antibiotic.* H. pylori *resistance rates were 34% for levofloxacin, 31.1% for metronidazole, 28.2% for clarithromycin, 2.9% for amoxicillin, and 1% for tetracycline. Logistic regression analysis indicated that previous use of clarithromycin was the only independent risk factor for* H. pylori *resistance (OR: 6.25, 95% CI: 1.59-24.52, p=0.009).*

Conclusion: *An understanding of the risk factors for* H. pylori *positivity and antibiotic resistance in an extended anamnesis may affect treatment choice and facilitate* H. pylori *eradication. In regions where antibiotic resistance rates are elevated, performing antibiotic susceptibility tests may lead to effective eradication treatment.*

Keywords: Helicobacter pylori, *prevalence, antibiotic resistance*

INTRODUCTION

Helicobacter pylori infection is associated with various upper gastrointestinal system (GIS) disorders, including chronic active gastritis, peptic ulcer disease, intestinal metaplasia, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma (1). More than half of the world's population has *H. pylori* infection, and the incidence of *H. pylori* infection is thought to be associated with age, socioeconomic status, geographical region, and ethnic group (2-4).

H. pylori eradication can reduce the long-term complications of chronic infection, such as peptic ulcer disease, GIS bleeding, and gastric cancer (5). Although the success rate for *H. pylori* eradication with standard treatment was >90% in the past, the success currently varies between 30% and 40% (6-9). One of the most important reasons for *H. pylori* eradication failure is antibiotic resistance (10). Antibiotic resistance is primarily associated with the inappropriate and frequent use of antibiotics, as well as age, gender, concomitant diseases, and demographic characteristics (11-13).

Conflicting results were reported in prior studies that investigated various sociodemographic or clinical risk factors associated with *H. pylori* positivity and antibiotic resistance in different countries (14-16). The primary aim of this study was to investigate the frequency of and risk factors for *H. pylori* infection in patients with dyspeptic symptoms in the eastern Black Sea region of Turkey. The secondary aim was to assess the profile and risk factors for *H. pylori* antibiotic resistance.

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MATERIALS AND METHODS

Patients

This prospective study included adult patients aged 18 years and above who were referred to the Gastroenterology Clinic in the Karadeniz Technical University School of Medicine between July 2010 and December 2011 because of dyspeptic symptoms. Patients with a coagulation disorder, a history of gastric cancer or gastric resection, or who were pregnant were excluded from the study. Of 378 patients screened for inclusion, 34 patients were excluded (23 patients refused endoscopy and 11 patients had relevant medical history). A total number of 344 patients (131 men, 213 women) participated in this study. All patients completed a questionnaire that included questions about dyspeptic symptoms, habits, medical and family history, demographic characteristics, and socioeconomic status. All patients underwent upper GIS endoscopy (Pentax EPK-1000 or EPK-i; Tokyo, Japan) to identify the etiology of the dyspeptic symptoms. Two biopsy samples were obtained from the antrum and the corpus of the stomach during endoscopy and were used for simultaneously performing rapid urease test, histopathological investigations, and *H. pylori* culture. Each biopsy sample was divided into three parts. The first part of the biopsy sample was used for the rapid urease test. Histopathological investigations were performed on the second part of the biopsy sample. Then, the remaining part of the biopsy sample was used for *H. pylori* culture. Patients with a positive culture or with a positive rapid urease test and histopathologically identified microorganisms, even in the absence of a positive culture, were considered to be *H. pylori* positive.

Patients were classified into two groups as *H. pylori* positive or *H. pylori* negative. The *H. pylori*-positive group was then further classified as antibiotic-resistant or antibiotic-susceptible based on the results of antibiotic susceptibility testing. All subjects provided written informed consent for their participation. This study was approved by the ethics committee of Karadeniz Technical University (no. 2010/67).

Microbiology

For the rapid urease test, the biopsy samples were spread on urease medium (Christensen urea agar base [Merck, Germany]+2% urea) and incubated at 37°C for 24 hours. A color change from yellow to pink was considered a positive result. For histopathological investigations, biopsy samples were stained by hematoxylin-eosin and Giemsa stains and evaluated under a light microscope for the presence of *H. pylori* (gram-negative, curved gull-wing shaped bacteria localized in the mucous layer) and morphological changes (inflammation, atrophy, intestinal metaplasia). For *H. pylori* culture, 5% defibrinated sheep/human blood and 10 µg/mL vancomycin, 5 µg/mL trimethoprim, and 1 µg/mL amphotericin B were added into Brucella agar (HiMedia, India) to prepare the medium, and then the plates were incubated for 5-7 days at 37°C in a microaerophilic environment (5% O_2, 10% CO_2, 85% N_2). Bacterial identification was performed based on the presence of uniform, small, translucent colonies, folded bacilli in gram staining, and positivity of urease, oxidase, and catalase.

Susceptibility Testing

The susceptibility of the *H. pylori* strains proliferated on the growth medium to five different antibiotics was tested. The agar dilution method was used for susceptibility testing for four of the antibiotics: amoxicillin, tetracycline, metronidazole, and levofloxacin (17). Bacterial suspensions isolated from the primary plates (McFarland turbidity Standard 2) were prepared in sterile isotonic 0.9% NaCl solution. Brucella agar plates with the antibiotics were prepared by adding 5% sheep/human blood, and different concentrations of the antibiotics (between 0.125 and 128 µg/mL) to each plate. A 3-µL portion of the prepared bacterial suspension was transferred to the plates containing the antibiotics, and the plates were inoculated for 72 hours at 37°C in a microaerophilic environment. The lowest antibiotic concentration that provided complete inhibition of bacterial growth was considered to be the minimum inhibitory concentration value of the tested antibiotic. The cutoffs used for defining susceptibility/resistance to the antibiotics were: 0.5-2/≥8 µg/mL for metronidazole, 0.25-0.50/≥1 µg/mL for levofloxacin, 0.06-0.25/≥1 µg/mL for amoxicillin, and 0.25-2/≥4 µg/mL for tetracycline (18). The E-test method (AB BIODISK, Solna, Sweden) was used for susceptibility testing for clarithromycin. Approximately 0.5 mL of the bacterial suspensions prepared from the primary plates (McFarland turbidity Standard 2) was inoculated into Brucella agar that contained 5% sheep/human blood. After the plates were dried, the E-test strips were placed on the plates and incubated for 72 hours at 37°C in the microaerophilic environment. The E-test results were evaluated based on the recommendations of the manufacturer (antibiotic concentration range: 0.016-256 µg/mL). The cutoff used to define susceptibility/resistance to clarithromycin was: 0.016-0.50/≥1 µg/mL (19). In addition, non-selective Brucella agar plates that contained 5% sheep/human blood were used to check the viability of the *H. pylori* strains in both methods.

Table 1. Clinical characteristics of the H. pylori-negative and H. pylori-positive groups.

Characteristics	*H. pylori*-negative group (n=205)	*H. pylori*-positive group (n=139)	p
Age (years)	40.6±15.8	37.5±15.2	0.079
Gender (male/female)	74/131	57/82	0.357
BMI (kg/m^2)	26.3±4.3	26.0±4.6	0.501
Duration of dyspepsia (months)	43.7±57.6	33.6±53.2	0.101

BMI: body mass index

Statistical Analysis

The Kolmogorov-Smirnov test was used to check whether the parameters compared between study groups were normally distributed. For the assessment of quantitative data, the Student's *t* test was used for comparisons of the parametric variables and the Mann-Whitney-U test was used for comparisons of the non-parametric variables between groups. Qualitative data were analyzed by the chi-square test. Multivariate logistic regression analysis was performed to identify the risk factors that affected *H. pylori* positivity and antibiotic resistance. To perform these analyses, parameters with a p<0.20 in the univariate analysis were considered as independent variables. Results of the applicable model were assessed with the Hosmer-Lemeshow goodness-of-fit test and model fitness tests and were presented as OR (odds ratio) and 95% CI (confidence interval). All data were presented as an arithmetic mean±standard deviation. Statistical analyses were performed using The Statistical Package for the Social Sciences (SPSS) version 13.0 (SPSS Inc., Chicago, IL, USA). A p<0.05 was considered statistically significant.

RESULTS

H. pylori prevalence and risk factors

Of the 344 patients included in this study, 131 (38.1%) were men and 213 (61.9%) were women, with an overall mean age of 39.3±15.6 years (range: 18-82 years). In total, 205 (59.6%) patients were *H. pylori* negative and 139 (40.4%) were *H. pylori* positive (104 patients had positive *H. pylori* cultures, 35 patients had positive rapid urease test and histopathology). Gender, age, body mass index (BMI), and the duration of dyspepsia were not significantly different between the *H. pylori*-positive and *H. pylori*-negative groups (Table 1).

H. pylori positivity in patients with duodenal ulcer was significantly more frequent compared to frequencies in patients with gastric ulcer/gastritis or non-ulcer dyspepsia (71% vs. 38.1%, and 36.4%, respectively, p=0.001). The rate of *H. pylori* positivity was not significantly different between patients with and without gastric intestinal metaplasia. *H. pylori* positivity in patients with a history of dyspepsia in any of their children was significantly more common compared to the rate in patients whose children were without such a history (73.3% vs. 36.7%, respectively, p=0.011). A history of dyspepsia in mother, father, siblings, husband, or wife did not have a significant effect on *H. pylori* positivity (Table 2).

H. pylori positivity in patients who used proton pump inhibitors (PPIs) was less common than that in patients who did not use PPIs (33.8% vs. 45.2%, respectively, p=0.033). The use of nonsteroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid (ASA) did not have a significant effect on *H. pylori* positivity. Moreover, a history of GIS bleeding, diabetes mellitus (DM), hypertension, congestive heart failure (CHF), coronary artery disease (CAD), cerebrovascular disease (CVD), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), hyperlipidemia, or a parasitic infection was not significantly associated with *H. pylori* positivity (Table 2).

The amount of black tea consumed in the *H. pylori*-positive group was greater than that in the *H. pylori*-negative group (5.7±4.1 cups/day vs. 4.9±2.9 cups/day, respectively, p=0.048). However, coffee or alcohol consumption and smoking were not significantly associated with *H. pylori* positivity (Table 2).

Living in a village, city, either currently or during childhood, was not associated with *H. pylori* positivity. Although the number of current household members (p=0.012) and the number of household members during childhood (p=0.039) were significantly higher, the number of rooms in the current residence (p=0.027) was significantly lower in the *H. pylori*-positive group compared to the results in the *H. pylori*-negative group. *H. pylori* positivity was less frequent in patients who regularly brushed their teeth (p=0.01), but more frequent in patients who had a history of dental treatment (p=0.001). *H. pylori* positivity was more frequent in patients who ate from common plates (p=0.004), hand-washed their dishes (p<0.001), and used well or tap water as drinking water (p<0.001) (Table 2).

Although the patient's or their mother's level of education did not significantly affect the rate of *H. pylori* pos-

Table 2. Risk factors for H. pylori positivity, univariate analysis.

Variable	Patients (n)	*H. pylori* positivity (%)	p
Endoscopic diagnosis			
Duodenal ulcer	31	71	0.001
Gastric ulcer/gastritis	181	38.1	
Non-ulcer dyspepsia	132	36.4	
Intestinal metaplasia	31	48.4	0.449
PPIs use	145	33.8	0.033
NSAIDs use	99	36.4	0.331
ASA use	34	32.4	0.410
DM	30	30	0.307
Hypertension	50	30	0.143
CHF	11	9.1	0056
CAD	5	40	1
CVD	1	100	0.404
CKD	4	25	0.650
COPD	7	57.1	0.447
History of GIS bleeding	7	42.9	1
History of parasitic infection	35	51.4	0.228
History of dyspepsia in mother	100	47	0.117
History of dyspepsia in father	87	42.5	0.659
History of dyspepsia in siblings	70	40	1
History of dyspepsia in spouse	32	46.9	0.404
History of dyspepsia in children	15	73.3	0.011
Alcohol consumption	11	72.7	0.056
Smoking	48	43.8	0.846
Tooth brushing habit			
Never or irregularly	138	48.9	0.01
Regularly, at least once a day	206	35	
History of dental treatment	205	47.8	0.001
Current place of residence			
Village	58	48.3	0.302
Town	110	38.2	
City	176	39.2	
Childhood place of residence			
Village	117	46.2	0.263
Town	116	35.9	
City	111	39.1	
Eating from common plates	52	59.6	0.004
Dishwashing method			
Hand washing	202	48.5	<0.001
Dishwasher	142	28.9	
Drinking water source			
Well water	43	65.1	<0.001
Tap water	205	44.9	
Commercially packed water	96	19.8	
Monthly income			
<500 TRY	50	57	0.049
500–999 TRY	167	40	
1000–1499 TRY	66	38	
≥1500 TRY	61	32	

PPI: proton pump inhibitor; NSAID: nonsteroidal anti-inflammatory drug; ASA: acetylsalicylic acid; DM: diabetes mellitus; CHF: congestive heart failure; CAD: coronary artery disease; CVD: cerebrovascular disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; GIS: gastrointestinal system; TRY: Turkish lira.

itivity, it became less frequent as the level of education of the father increased (p=0.013). The rate of *H. pylori* positivity decreased as the level of monthly income per household member increased (p=0.049) (Table 2).

Logistic regression analysis indicated that age and the presence of duodenal ulcer were independent risk factors for *H. pylori* positivity. The presence of duodenal ulcer increased the rate of *H. pylori* positivity 5.4-fold compared to the rate with the presence of non-ulcer dyspepsia (OR: 5.42, 95% CI: 1.96-14.98, p=0.001). Each 1 year increase in a patient's age decreased the rate of *H. pylori* positivity 0.96-fold (OR: 0.96, 95% CI: 0.93-0.99, p=0.013) (Table 3).

H. pylori antibiotic resistance and risk factors

Of 104 *H. pylori*-positive cultures, 43 (41%) were susceptible to all antibiotics, and 61 (59%) were resistant to at least one antibiotic. *H. pylori* resistance rates were 34% for levofloxacin, 31.1% for metronidazole, 28.2% for clarithromycin, 2.9% for amoxicillin, and 1% for tetracycline.

Univariate analysis showed that the mean age of patients with levofloxacin-resistant *H. pylori* was greater than the mean age of patients with levofloxacin-susceptible *H. pylori* (41.7±15.5 vs. 35.2±15.7 years, respectively, p=0.045). Levofloxacin resistance was also more common in patients with a history of upper GIS bleeding, DM, and previous use of levofloxacin compared to resistance in patients without such histories (100% vs. 31.7%, p=0.036; 71.4% vs. 30.9%, p=0.041; 84.6% vs. 26.4%, p<0.001, respectively). Metronidazole resistance was more common in patients with a history of upper GIS bleeding, DM, and previous use of metronidazole compared to patients without such histories (100% vs. 28.7%, p=0.027; 71.4% vs. 27.8%, p=0.027; 80% vs. 28.3%, p=0.03, respectively). Clarithromycin resistance was more frequent in patients with DM and previous use of clarithromycin compared to patients without such histories (71.4% vs. 24.7%, p=0.017; 71.4% vs. 16.9%, p<0.001, respectively). However, no significant relation was found between antibiotic resistance and gender; BMI; duration of symptoms; endoscopic diagnosis; use of PPIs, NSAIDs or ASA; smoking; tea, coffee, or alcohol consumption; history of parasitic disease, hypertension, CHF, CAD, CVD, or COPD; history of dyspepsia in mother, father, siblings, husband or wife; frequency of tooth brushing; history of dental treatment; education level; place of current residency; level of income per household member; number of individuals or rooms in the current place of residence; source of drinking water; habit of eating from a common plate; and method of dishwashing (Tables 4 and 5). As the

Table 3. Risk factors for H. pylori positivity, multivariate analysis.

Variable	OR	95% CI	p
Age	0.96	0.93-0.99	0.013
Duration of dyspepsia	1	0.99-1.00	0.167
The number of household members during childhood	1.05	0.92-1.20	0.488
Gender			
Male	1		
Female	0.89	0.38-2.13	0.800
Endoscopic diagnosis			
Non-ulcer dyspepsia	1		
Duodenal ulcer	5.42	1.96-14.98	0.001
Gastric ulcer/gastritis	1.37	0.78-2.40	0.268
Smoking			
No	1		
Quit smoking	0.58	0.20-1.69	0.320
Yes	1.04	0.45-2.39	0.926
PPI use			
No	1		
Yes	0.82	0.47-1.43	0.484
Hypertension			
No	1		
Yes	0.79	0.34-1.83	0.581
History of parasitic infection			
No	1		
Yes	2.00	0.83-4.84	0.122
History of dental treatment			
No	1		
Yes	1.73	0.97-3.07	0.063
Eating from common plates			
No	1		
Yes	1.35	0.64-2.87	0.429
Monthly income			
<500 TRY	1		
500-999 TRY	0.56	0.25-1.25	0.155
1000-1499 TRY	0.49	0.19-1.29	0.146
≥1500 TRY	0.44	0.15-1.24	0.121
Education level			
Not literate	1		
Primary school graduate	1.19	0.40-3.53	0.750
Secondary school graduate	0.61	0.14-2.56	0.496
High school graduate	0.26	0.06-1.07	0.062
University graduate	0.29	0.06-1.42	0.126
Education level of mother			
Not literate	1		
Primary–secondary school graduate	1.23	0.62-2.46	0.559
High school–university graduate	0.31	0.07-1.40	0.128
Education level of father			
Not literate	1		
Primary–secondary school graduate	0.90	0.39-2.10	0.813
High school–university graduate	0.32	0.09-1.06	0.063

OR: odds ratio; CI: confidence interval; PPI: proton pump inhibitor; TRY: Turkish lira.

Table 4. Clinical characteristics of antibiotic resistant group and antibiotic susceptible group.

Variable	Antibiotic resistant group	Antibiotic susceptible group	p
Age (years)			
Levofloxacin	41.7±15.5	35.2±15.7	0.045
Metronidazole	38.2±15	37±16.3	0.732
Clarithromycin	36.7±16.1	37.6±15.9	0.793
BMI (kg/m^2)			
Levofloxacin	25.9±3.1	26±5.1	0.930
Metronidazole	25.2±4.3	26.3±4.6	0.283
Clarithromycin	25.2±4.3	26.2±4.6	0.309
Duration of dyspepsia (months)			
Levofloxacin	39.1±58.2	33.3±58	0.631
Metronidazole	41±58.7	32.6±57.7	0.498
Clarithromycin	40±61.4	33.7±56.8	0.604

BMI: body mass index

number of patients with *H. pylori* resistant to amoxicillin or tetracycline was limited, the factors that affected resistance to these two antibiotics could not be evaluated.

Logistic regression analysis indicated that previous use of clarithromycin was an independent risk factor for *H. pylori* resistance and increased the risk of resistance about 6.3-fold (OR: 6.25, 95% CI: 1.59-24.52, p=0.009) (Table 6).

H. pylori dual and multiple antibiotic resistances

Dual resistance and resistance to at least three antibiotics were noted in *H. pylori* from 23 (22.1%) and seven (6.8%) patients, respectively. Of *H. pylori* with dual antibiotic resistance, five strains (8.2%) were resistant to both clarithromycin and metronidazole, six (9.8%) were resistant to both clarithromycin and levofloxacin, 11 (18.0%) were resistant to both metronidazole and levofloxacin, and 1 (1.6%) was resistant to both amoxicillin and levofloxacin. Of *H. pylori* with resistance to at least three antibiotics, five strains (8.2%) were resistant to clarithromycin, metronidazole, and levofloxacin; one (1.6%) was resistant to amoxicillin, clarithromycin, metronidazole, and levofloxacin; and one (1.6%) was resistant to all antibiotics (amoxicillin, clarithromycin, tetracycline, metronidazole, and levofloxacin).

Table 5. Risk factors for H. pylori resistance, univariate analysis.

Variable	Patients (n)	Levofloxacin resistance (%)	Metronidazole resistance (%)	Clarithromycin resistance (%)
Variable	Patients (n)	Levofloxacin resistance (%)	Metronidazole resistance (%)	Clarithromycin resistance (%)
Gender				
Male	36	37.2	34.9	25.6
Female	68	31.1	27.9	29.5
Endoscopic diagnosis				
Duodenal ulcer	19	47.4	21.1	15.8
Gastric ulcer/gastritis	49	30.6	30.6	28.6
Non-ulcer dyspepsia	36	30.6	36.1	33.3
PPI use				
No	66	27.3	27.3	27.3
Yes	38	44.7	36.8	28.9
NSAID use				
No	77	33.8	29.9	24.7
Yes	27	33.3	33.3	37
ASA use				
No	95	33.7	29.5	25.3
Yes	9	33.3	44.4	55.6

Table 5. Risk factors for H. pylori resistance, univariate analysis. (Continue)

Variable	Patients (n)	Levofloxacin resistance (%)	Metronidazole resistance (%)	Clarithromycin resistance (%)
DM				
No	97	30.9*	27.8*	24.7*
Yes	7	71.4*	71.4*	71.4*
Hypertension				
No	93	33.3	31.2	28
Yes	11	36.4	27.3	27.3
CHF				
No	103	33.3	31.1	28.2
Yes	1	100	0	0
CAD				
No	102	32.4	29.4	27.5
Yes	2	100	100	50
CVD				
No	103	34	31.1	28.2
Yes	1	0	0	0
COPD				
No	102	34.3	31.4	28.4
Yes	2	0	0	0
History of GIS bleeding				
No	101	31.7*	28.7*	27.7
Yes	3	100*	100*	33.3
History of parasitic infection				
No	90	35.6	33.3	30
Yes	14	21.4	14.3	14.3
History of dyspepsia in mother				
No	67	32.8	31.3	23.9
Yes	37	35.1	29.7	35.1
History of dyspepsia in father				
No	73	34.2	31.5	31.5
Yes	31	32.3	29	19.4
History of dyspepsia in siblings				
No	79	36.7	31.6	27.8
Yes	23	26.1	30.4	26.1
History of dyspepsia in husband or wife				
No	58	36.2	34.5	24.1
Yes	11	45.5	36.4	27.3
History of dyspepsia in children				
No	53	47.2*	35.8	28.5
Yes	11	0*	27.3	9.1

Table 5. Risk factors for H. pylori resistance, univariate analysis. (Continue)

Variable	Patients (n)	Levofloxacin resistance (%)	Metronidazole resistance (%)	Clarithromycin resistance (%)
Alcohol consumption				
No	98	34.7	30.6	26.5
Yes, at least once a week	6	16.7	33.3	50
Smoking				
No	75	34.7	26.7	30.7
Quit smoking	10	20	30	20
Yes	19	36.8	47.4	21.1
Tooth brushing habit				
Never or irregularly	51	35.3	29.4	25.5
Regularly, at least once a day	53	32.1	32.1	30.2
History of dental treatment				
No	30	23.3	43.3	40
Yes	74	37.8	25.7	23
Current place of residence				
Village	25	36	16	24
Town	33	30.3	39.4	30.3
City	46	34.8	32.6	28.3
Childhood place of residence				
Village	25	32.6	23.3	20.9
Town	32	29	38.7	35.5
City	47	40	33.3	30
Eating from common plates				
No	78	35.9	30.8	24.4
Yes	26	26.9	30.8	38.5
Dishwashing method				
Hand-washing	71	32.4	28.2	28.2
Dishwasher	33	36.4	36.4	27.3
Drinking water source				
Well water	25	43.5	17.4	30.4
Tap water	32	30.9	38.2	27.9
Commercially packed water	47	30.8	15.4	23.1
Monthly income				
<500 TRY	9	32	29	38
500-999 TRY	55	30	28	26
1000-1499 TRY	20	44	40	40
≥1500 TRY	20	34	34	8
Education level				
Not literate	13	36.4	18.2	27.3

Table 5. Risk factors for H. pylori resistance, univariate analysis. (Continue)

Variable	Patients (n)	Levofloxacin resistance (%)	Metronidazole resistance (%)	Clarithromycin resistance (%)
Primary school graduate	37	35	35	22.5
Secondary school graduate	7	41.7	41.7	16.7
High school graduate	26	31.6	21.1	36.8
University graduate	21	27.3	31.8	36.4
History of levofloxacin use				
No	102	26.4*	28.6	28.6
Yes	2	84.6*	46.2	23.1
History of metronidazole use				
No	101	32.3	28.3*	26.3
Yes	3	60	80*	60
History of clarithromycin use				
No	84	30.1	32.5	16.9*
Yes	20	47.6	23.8	71.4*

PPI: proton pump inhibitor; NSAID: nonsteroidal anti-inflammatory drug; ASA: acetylsalicylic acid; DM: diabetes mellitus; CHF: congestive heart failure; CAD: coronary artery disease; CVD: cerebrovascular disease; COPD: chronic obstructive pulmonary disease; GIS: gastrointestinal system; TRY: Turkish lira. Asterisks indicate statistical significance (p<0.05)

Validity of the diagnostic tests (rapid urease test, histopathology, culture)

The validity of each diagnostic method was evaluated. Sensitivities of the rapid urease test, histopathological examination, and *H. pylori* culture were 66.9%, 89.2%, and 74.8%; specificities were 100.0%, 86.8%, and 100.0%; positive predictive values were 100.0%, 82.1%, and 100.0%; and negative predictive values were 81.7%, 92.2%, and 85.4%, respectively.

DISCUSSION

Although the prevalence of *H. pylori* infection is around 30% in developed countries, it increases to 70%-90% in developing countries. This difference is considered to be associated with ethnic origin, geographical conditions, socioeconomic status, and hygiene (2, 20). Although previous studies in Asian countries reported the *H. pylori* prevalence as 50%-70%, the prevalence in Turkey was 71% (16, 21). In the present study, the rate of *H. pylori* positivity in patients who reside in our region and present with dyspeptic symptoms was 40.4%. This rate was lower than the rates previously reported in developing countries.

The prevalence of *H. pylori* is known to increase with age (1, 2). The multivariate analysis in this study indicated that the rate of *H. pylori* positivity showed a slight but statistically significant decrease with age. This finding, which was contradictory to the results previously reported in the literature, could be attributed to the frequent prescription of *H. pylori* eradication treatments in our region.

H. pylori infection results in the development of upper GIS disorders, such as duodenal ulcer, gastric ulcer, intestinal metaplasia, and gastric cancer (22-24). In a previous study performed by Boyanova et al. (14), duodenal ulcer, gastric ulcer, and gastritis/non-ulcer dyspepsia were noted in 28%, 10%, and 62% of *H. pylori*-positive patients, respectively. In a study by Agarwal et al. (25), chronic gastritis was detected in 20.37%, duodenal ulcer in 53.7%, gastric ulcer in 12.9%, and non-ulcer dyspepsia in 12.9% of patients with *H. pylori* infection. In the present study, *H. pylori* positivity in patients with duodenal ulcer was more common than that in patients with gastric ulcer/gastritis or non-ulcer dyspepsia. Moreover, the multivariate analysis indicated that the rate of *H. pylori* positivity was 5.4-fold higher in patients with duodenal ulcer. However, the rate of *H. pylori* positivity was not significantly different between patients with and without intestinal metaplasia. Shi et al. (26) reported a higher *H. pylori* prevalence in subjects with a family history of upper GIS disorders. In the present study, although there was no relation between the dyspeptic symptoms of the mother, father, siblings, husband, or wife and *H. pylori* positivity, the rate of *H. pylori* positivity in patients who had a child with dyspeptic symptoms was higher than the rate in those whose children did not have dyspeptic symptoms.

Table 6. Risk factors for H. pylori resistance profile, multivariate analysis.

Variable	OR	95% CI	p
Age	1	0.97-1.03	0.834
Duration of dyspepsia	1	0.99-1.01	0.952
Gender			
Male	1		
Female	0.63	0.20-2.01	0.431
Endoscopic diagnosis			
Non-ulcer dyspepsia	1		
Duodenal ulcer	1.32	0.33-5.32	0.696
Gastric ulcer/gastritis	0.90	0.32-2.51	0.842
Smoking			
No	1		
Quit smoking	0.26	0.04-1.60	0.146
Yes	1.39	0.41-4.80	0.598
PPI use			
No	1		
Yes	1.47	0.56-3.90	0.434
History of levofloxacin use			
No	1		
Yes	4.76	0.88-25.91	0.710
History of clarithromycin use			
No	1		
Yes	6.25	1.59-24.52	0.009

OR: odds ratio; CI: confidence interval; PPI: proton pump inhibitor

Long-term PPI use in patients with dyspeptic symptoms may complicate the diagnosis of *H. pylori* infection by causing the translocation of *H. pylori* from the antrum to the corpus (1, 2). In this study, the univariate analysis showed that the rate of *H. pylori* positivity in patients who used PPIs was lower than the rate in those who did not, which may be associated with the effects of PPI use on the diagnostic tests performed for *H. pylori*.

Different results have been reported in the literature regarding the relation between *H. pylori* infection and smoking or alcohol consumption. Zhang et al. (27) found no relation between *H. pylori* infection and smoking, whereas alcohol consumption was found to increase *H. pylori* prevalence 9-fold in patients with functional dyspepsia. However, Kim et al. (28) reported that smoking and alcohol consumption had no significant effect on *H. pylori* prevalence. In contrast, Gao et al. (29) determined that moderate alcohol consumption facilitated elimination of *H. pylori*. In the present study, the rate of *H. pylori* positivity in patients with regular alcohol consumption was higher than the rate in those without, but the difference was not statistically significant, which is probably because of the limited number of patients with regular alcohol consumption. On the other hand, smoking had no significant effect on *H. pylori* positivity. The studies that investigated the relation between tea consumption and *H. pylori* prevalence were mostly performed in the East Asian countries; they showed that consumption of green tea provided protection against *H. pylori* infection (30). Similarly, Boyanova et al. (31) reported that the consumption of green and black tea reduced the risk of *H. pylori* infection. In contrast to the previous studies in the literature, black tea consumption in the *H. pylori*-positive group was higher than that in the *H. pylori*-negative group in this study.

Besides the stomach tissue, *H. pylori* is also present in the saliva, feces, oral cavity, dental plaque, and tonsil tissue. Thus, reinfections may still occur despite previously successful *H. pylori* eradication (2, 16, 32). Jia et al. (33) found that the rate of *H. pylori* positivity in individuals who had regular dental visits for plaque cleaning was lower than the rate in individuals who did not. In the present study, the rate of *H. pylori* positivity in patients who regularly brushed their teeth was lower than the rate in those who did not regularly brush their teeth or did not brush at all. Moreover, our data indicated that the rate of *H. pylori* positivity in patients with a history of dental treatment was higher than that in patients without dental treatment. This may be associated with insufficient sterilization of the reusable medical tools that are used within the oral cavity during the dental procedures.

Insufficient health care services, failure to provide safe drinking water, and, in particular, living in crowded households during childhood are among the important factors associated with the increased prevalence of *H. pylori* infections in developing countries (1, 2, 16, 34). Fialho et al. (35) reported that the number of household members per room and the number of children in the household were independent risk factors for *H. pylori* infection. In line with the data in the literature, the number of cur-

rent household members and the number of household members during childhood were higher and the number of rooms in the current household was lower in the *H. pylori*-positive group than in the *H. pylori*-negative group in this study. *H. pylori* infection is known to be transmitted through environmental contamination, such as contamination of drinking water, particularly in rural areas. In a study performed by Ahmed et al. (36) in South India, the incidence of *H. pylori* infection in individuals who were drinking well water was greater than that in individuals who were drinking tap water. In this study, *H. pylori* positivity in patients who were drinking well or tap water was more common than that in patients who were drinking commercially packed water.

Socioeconomic status is one of the most significant factors that affects *H. pylori* prevalence. Nouraie et al. (37) showed that a higher level of education of individuals and their parents reduced the rate of *H. pylori* positivity. Graham et al. (38) reported that the rate of *H. pylori* positivity increased with decreasing monthly income and education level. In the present study, the univariate analysis indicated that the level of education of the patients or their mothers had no significant effect on *H. pylori* positivity, whereas *H. pylori* positivity decreased as the level of education of the father increased, which is consistent with the results in the literature. In keeping with the literature, *H. pylori* positivity decreased as the monthly income per household member increased in this study. In addition, comparison of the preferred methods for dishwashing showed that *H. pylori* positivity in patients who preferred hand-washing was higher than that in patients who used a dishwasher. When all data collected were considered as a whole, it seems reasonable to suggest that, because of the position of the father in a Turkish family in relation to the patriarchal structure of the Turkish population, the level of education and monthly income of the father directly affected the socioeconomic status of the family and indirectly affected the hygiene habits of all family members.

Antibiotic resistance is one of the most significant causes of insufficient *H. pylori* eradication (14). In a meta-analysis performed by Kuo et al. (39), the rates of primary antibiotic resistance in the Asia-Pacific region were reported as 17% for clarithromycin, 44% for metronidazole, 18% for levofloxacin, 3% for amoxicillin, and 4% for tetracycline. In addition, the resistance rates for clarithromycin and levofloxacin increased over time, whereas the rates for other antibiotics remained stable (39). In a meta-analysis of results reported for Turkey, the primary antibiotic resistance rates of *H. pylori* were amoxicillin 0.9%, clarithromycin 24.8%, metronidazole 33.7%, tetracycline 3.5%, and levofloxacin 23.7% (40). In another study conducted in Turkey, resistance rates of *H. pylori* were clarithromycin 36.7%, metronidazole 35.5%, and levofloxacin 29.5% (41). In the present study, the rates of clarithromycin and levofloxacin resistance were higher than those previously reported in the literature. Boyanova et al. (42) reported that the rate of triple (amoxicillin+metronidazole+clarithromycin) antibiotic resistance was 0.4%. Based on our data, the frequency of triple antibiotic resistance in our region was 8.2%, which could be an indicator of serious treatment failures for *H. pylori* eradication that we may encounter in the future.

The increase in quinolone resistance is considered to be frequently associated with the increase in the use of new-generation quinolones (15). Various factors, such as age, the region of residence, clarithromycin or metronidazole resistance, urinary tract infections, and a history of antibiotic use within the last year may lead to the development of quinolone resistance (14, 15, 43). It was previously shown that clarithromycin resistance was associated with previous use of macrolide antibiotics, age, female gender, ethnic origin, presence of non-ulcer dyspepsia, smoking, and geographical region, whereas metronidazole resistance was associated with previous use of nitroimidazole antibiotics, female gender, geographical region, development level, socioeconomic factors, and ethnic origin (11, 13, 15, 43-46). In our study, levofloxacin resistance increased with age. The rate of levofloxacin resistance was also higher in patients with previous use of levofloxacin or a history of DM or upper GIS bleeding. Clarithromycin resistance was found to be associated with previous use of clarithromycin or a history of DM, whereas metronidazole resistance was more common among those with previous use of metronidazole or a history of DM or upper GIS bleeding. The resistance to quinolone antibiotics may be elevated because they are a preferred treatment option (having broad-spectrum, once-daily usage, and easy transition from intravenous to oral treatment), in particular for the treatment of urinary tract infections (10, 14). Frequent use of macrolide antibiotics for *H. pylori* eradication and respiratory tract infections and frequent use of nitroimidazoles for parasitic, dental, and gynecologic infections may be associated with the increase in resistance rates for these drug classes. Moreover, the gastric microvascular and drug absorption changes in patients with a history of DM and GIS bleeding may affect the development of antibiotic resistance. The common use of antibiotics to treat gastropa-

resis and infections in DM patients may also be a factor for the development of resistance in *H. pylori* (47). Similarly, Demir et al. (48) previously reported that the rate of clarithromycin resistance in *H. pylori* increased 1.8-fold in DM patients.

This study had some limitations. Sampling performed by consecutive enrollment of patients with dyspepsia who were referred to our gastroenterology outpatient clinics within a defined time interval appeared to be the most appropriate method among "non-probability" sampling techniques, as it allowed an evaluation of the overall regional population through investigation of individuals enrolled in this study within a reasonable timeframe. However, the estimated rates of *H. pylori* positivity and antibiotic resistance may not be applicable to the overall population in our region. Moreover, because the number of positive cases was small for some of the risk factors evaluated, statistically significant differences may not have been effectively detected even though marked differences were noted regarding the percentages for some risk factors.

In conclusion, although the results of the univariate analysis showed that several factors affected *H. pylori* positivity and primary antibiotic resistance, logistic regression analysis demonstrated that age and the presence of duodenal ulcer were independent risk factors for *H. pylori* positivity and that previous use of clarithromycin was an independent risk factor for *H. pylori* antibiotic resistance. An understanding of the risk factors for *H. pylori* positivity and antibiotic resistance may facilitate eradication of *H. pylori*. In regions where antibiotic resistance rates are elevated, performing antibiotic susceptibility tests may lead to an effective eradication treatment.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Karadeniz Technical University (Decision date: 28.06.2010, Decision no.: 2010/67).

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

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