The Effect of *Helicobacter pylori* on the Presentation and Clinical Course of Coronavirus Disease 2019 Infection

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ABSTRACT

Objectives: Novel coronavirus 2019 (corona virus disease 2019 [COVID-19]) binds angiotensin-converting enzyme-2 (ACE-2) receptors to enter the cell. These receptors are widely expressed in the intestine, and COVID-19 may cause gastrointestinal symptoms via these receptors during the course of the disease. *Helicobacter pylori* is known to increase the expression of ACE-2 receptors in the gastrointestinal tract. The aim of this study was to investigate the effects of *H pylori* on the presentation and clinical course of COVID-19 infections.

Methods: This study was carried out from June 1 to July 20, 2020. Patients diagnosed with COVID-19 infections by PCR tests were included in the study. Antigen screening tests were performed on stool samples to determine the presence of *H pylori.* All patients were evaluated for manifestations of COVID-19 infection, severity of the course, hospitalized days because of the virus and outcome of the disease process.

Results: Of 108 COVID-19 positive patients evaluated, 31 with a mean age of 49.54 ± 17.94 years were *H pylori*-positive (8 girls [25.8%]) and 77 with a mean age of 47.85 ± 20.51 years; (31 girls [40.3%]) were *H pylori*-negative. Abdominal pain (19.4% vs 2.6%) and diarrhea (32.3% vs 9.1%) were significantly higher in patients with *H pylori* than those without ($P = 0.007$ and $P = 0.006$, respectively). There was no statistically significant difference between *H pylori* positivity and the number of hospitalized days, the severity of the course of COVID-19 infection, or the outcome of the disease ($P > 0.05$).

Conclusion: Our results revealed that the findings of abdominal pain and diarrhea strongly correlated with the presence of *H pylori* in COVID-19 patients.

Key Words: coronavirus 19, gastrointestinal tract, *Helicobacter pylori*

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What Is Known

- Novel coronavirus 2019 binds angiotensin-converting enzyme-2 receptors to enter the cell.
- These receptors are widely expressed in the intestine, and coronavirus 2019 may cause gastrointestinal symptoms via these receptors during the course of the disease.
- *Helicobacter pylori* is known to increase the expression of angiotensin-converting enzyme-2 receptors in the gastrointestinal tract.

What Is New

- Our results revealed that the findings of abdominal pain and diarrhea were strongly correlated with the presence of *Helicobacter pylori* in coronavirus disease-2019 patients.
- We believe this effect is mediated by angiotensin-converting enzyme-2 receptors.

Novel coronavirus disease 2019 (COVID-19) was first described in patients with fever, dry cough, and respiratory failure in Wuhan, China in December 2019. Tissue and organ damage caused by a direct viral attack or an over-activated immune response (cytokine storm) is thought to play a part in the disease pathogenesis. COVID-19 has become a pandemic and killed thousands of people all over the world in less than a year (1,2). Researchers have reported that the virus binds angiotensin-converting enzyme-2 (ACE-2) receptors to enter the cell. These receptors, which are widely expressed in the intestine, can cause gastrointestinal (GI) symptoms frequently experienced during the course of the disease (3).

Helicobacter pylori can cause both GI and extra-GI symptoms and findings. The course and presentation of both GI and extra-GI diseases associated with *H pylori* are related to the virulence of the microorganism and the immune system response (4). *H pylori* has many virulent factors, such as outer membrane porin proteins, flagella, different adherence factors, cytotoxin-associated gene A (*CagA*), vacuolating cytotoxin A (VacA), and a cag pathogenicity island (cag-PAI), to enable colonization and escape from the host's immune response. The host's immune system is triggered by these virulence factors leading to the release of higher levels of pro-inflammatory cytokines, such as TNF-alpha, IL-6, IL-10, and IL-8 causing acute and chronic inflammation (5,6). In addition, *H pylori* has been reported to play a role in the pathogenesis of diseases by increasing the expression of ACE-2 receptors in the GI tract, directly associated with the duration and severity of infection, as well as causing immune dysregulation via its virulent factors (7). The aim of this study was to investigate the effects of the presence of *H pylori* on the presentation and findings associated with COVID-19 infections and the clinical course of the disease.

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TABLE 1. Relationship between coronavirus disease 2019 symptoms and the presence of *Helicobacter pylori*

	H pylori-negative (n = 77)	*H pylori*-positive (n = 31)	*P*
Fever, n (%)	24 (31.2%)	11 (35.5%)	0.665**
Cough, n (%)	41 (53.2%)	13 (41.9%)	0.288**
Dyspnea, n (%)	26 (33.8%)	8 (25.8%)	0.420**
Headache, n (%)	21 (27.3%)	10 (32.3%)	0.604**
Loss of taste/smell, n (%)	3 (3.9%)	4 (12.9%)	0.103**
Nausea/vomiting, n (%)	4 (5.2%)	5 (16.1%)	0.116**
Abdominal pain, n (%)	2 (2.6%)	6 (19.4%)	0.007**
Diarrhea, n (%)	7 (9.1%)	10 (32.3%)	0.006**
Total	77 (100%)	31 (100%)	

H pylori = *Helicobacter pylori*.

MATERIALS AND METHODS

This study was carried out from June 1 to July 20, 2020 in SBU Gulhane Training and Research Hospital COVID-19 Unites, Ankara, Turkey. Adult patients diagnosed with COVID-19 infections by PCR tests were included in the study. Endoscopy was not performed on COVID-19-positive patients because of the risk of transmission. An *H pylori* stool antigen test [Premier Platinum HpSA (Meridian Diagnostics, Cincinnati, OH) ELISA kit], which has a sensitivity of 87.2% and a specificity of 44%, was performed on all patients. In those diagnosed with COVID-19/*H pylori*, we did not administer *H pylori* eradication treatment based on *H pylori* stool antigen test positivity without histopathological/immunohistochemical studies. Clinical characteristics and the course of COVID-19 were compared between *H pylori*-positive and -negative patients.

Patient samples were transferred to the laboratory under appropriate conditions and handled according to the product instructions for the extraction of SARS-CoV-2 (2019-NCover) with the Bio-speedy COVID-19 RT-qPCR Detection Kit (Bioeksen, İstanbul/Turkey). Samples prepared with the PCR Bio-Rad CFX96 were amplified on TouchTM or QIAGENRotor-Gene (QIAGEN, Germany) devices. Rapid diagnosis was accomplished by 1-step reverse transcription (RT) and quantitative real-time PCR (RT-qPCR) targeting the RdRp (RNA-dependent RNA polymerase) gene fragment. The results were evaluated according to the recommendations of the kit manufacturer.

All the patients in the study (COVID-19+/*H pylori*+) and control groups (COVID-19+/*H pylori*-) were examined for the presence of classic findings of the COVID-19 infections (fever, dry cough, dyspnea, headache, loss of taste and smell) complaints and findings related to GI involvement (nausea, vomiting, abdominal pain, diarrhea) and the results were recorded. Patients were classified according to the severity of the disease as; mild (no pneumonia and no hospitalization), moderate (hospitalized without pneumonia), moderate/severe (hospitalized with pneumonia), or severe (admitted to the intensive care unit because of difficulty in breathing because of pneumonia). The number of hospitalized days, whether they received ventilation support therapy because of COVID-19, and the outcome of the disease process were determined for each patient.

In addition, all the patients were evaluated for the presence of comorbid diseases like hypertension and diabetes mellitus and the medications they received for these diseases.

Continuous variables were expressed as mean ± standard deviation, whereas categorical data were expressed as numbers and percentages. Normality analyses were performed with the Kolmogorov–Smirnov goodness-of-fit test in the cross-group analysis of continuous variables. The independent samples *t* test was used in the evaluation of the groups that fit the normal distribution of continuous variables. Cross-group comparisons of variables not eligible for normal distribution were performed with Mann-Whitney *U* tests. The chi-square test was used in the comparison of categorical data. The analyses were performed with the SPSS software program version 24.0 (IBM Corporation, Armonk, NY). The statistical significance level was set at $P < 0.05$.

RESULTS

A total of 108 patients were diagnosed as having COVID-19 infection, 31 with a mean age of 49.54 ± 17.94 years which were *H pylori*-positive [8 girls (25.8%)] and 77 with a mean age of 47.85 ± 20.51 years, which were *H pylori*-negative (31 girls [40.3%]) were *H pylori*-negative.

There was no significant difference in terms of fever, dry cough, dyspnea, headache, nausea/vomiting, and loss of taste/smell between patients with and without *H pylori* infection. Abdominal pain (19.4% vs 2.6%) and diarrhea (32.3% vs 9.1%) were significantly higher in patients with *H pylori* than those without *H pylori* ($P = 0.007$ and $P = 0.006$, respectively) (Table 1). There was no statistically significant relationship found between comorbid disease presence and *H pylori* positivity ($P > 0.05$). The presence of *H pylori* also did not affect days of hospitalization, severity, or outcome of COVID-19 infections (Table 2).

DISCUSSION

COVID-19 infection became a pandemic a short time after it was identified in December 2019 and is responsible for the deaths of

TABLE 2. The relationship between *Helicobacter pylori* and the clinical course of coronavirus disease 2019

	H pylori-negative (n = 77)	*H pylori*-positive (n = 31)	*P*
Days of hospitalization (mean ± SD)	5.18 ± 1.27	5.22 ± 1.31	0.741*
Severity of COVID-19 symptoms, n (%)			
Mild	24 (31.2%)	7 (22.6%)	0.666**
Moderate	36 (46.8%)	17 (54.8%)	
Moderate/severe	9 (11.7%)	5 (16.1%)	
Severe	8 (10.4%)	2 (6.5%)	
Intubation, n (%)	7 (9.1%)	2 (6.5%)	1.000**
Outcome of COVID-19 disease, n (%)			
Exitus	7 (9.1%)	1 (3.2%)	0.171**
Discharged with recovery	70 (90.9%)	29 (93.5%)	
Transported to another hospital	0 (0.0%)	1 (3.2%)	
Total	77 (100%)	31 (100%)	

COVID-19 = coronavirus disease 2019; *H pylori* = *Helicobacter pylori*.

thousands of people all over the world. Enormous efforts are ongoing to understand the clinical presentation of the disease and the factors affecting mortality rates. Patients present clinically with fever, dry cough, dyspnea, pneumonia, pulmonary edema, acute respiratory failure, headache, loss of taste/smell, nausea/vomiting, abdominal pain, and diarrhea (8). In this study, the relationship between the presence of *H pylori*, the most common infection in the world, and COVID-19 infection was investigated. Our results revealed that the presence of abdominal pain and diarrhea strongly correlated with the presence of *H pylori* in COVID-19 patients. In terms of other manifestations, no difference was found between the study groups. There are reports that the incidence of diarrhea is between 2% and 50% with an average of 10% associated with COVID-19 infection (3). Although the mechanism of diarrhea in COVID-19 infection is not entirely known, it is strongly believed that it is through ACE-2 receptors commonly found throughout the GI tract. Human and animal model-based research showed that *H pylori* and its toxins are closely correlated with increased ACE-1, ACE-2, renin, and chymase protein expression (9–11). Furthermore, *H pylori*-associated ACE-2 over-expression has been shown to be related to virulent factors of the bacteria (9,12).

It has been reported that the virus may be responsible for diarrhea after entering the cell, causing malabsorption and an increase in intestinal permeability. In addition, it has been argued that intestinal inflammation and dysbiosis caused by disruption of intestinal homeostasis with ACE-2 changes may cause diarrhea (3). This study is the first in the literature to examine the relationship between *H pylori* and COVID-19. Our results suggest that *H pylori* increases diarrhea and abdominal pain in COVID-19 infection via over-expression of the ACE-2 receptors in the GI tract, thereby causing more virus to enter enterocytes. We observed that diarrhea and abdominal pain did not affect the severity of the clinical course or length of hospital stay, as reported in the literature (3,13).

In patients with COVID-19 infection, the presence of *H pylori* was not statistically significantly associated with the clinical severity of the disease, the need for ventilation support therapy, or the length of hospitalization. We now clearly know that the severity of the clinical course and mortality rates of COVID-19 infections directly correlate with the degree of pulmonary system involvement (8). Our results suggest that there is no relationship between the presence of *H pylori* and the degree of pulmonary system disease associated with COVID-19 infections. Acute and chronic immune stimulation and abnormal immune response to the bacteria and its toxins are the basis of the relationship between *H pylori* and extra-GI diseases (4,5). Recently, there has been a remarkable increase in the number of studies investigating the effect of *H pylori* on lung diseases. The bacteria reach the lung directly through aspiration of contaminated gastric content or inhalation of particles in the air, and through toxins. Lung damage may be associated with increased production of inflammatory mediators and endothelial dysfunction markers in the respiratory system cells (14,15). It has been suggested that chronic stimulation against *H pylori* and its toxins may play a role in the pathogenesis of lung cancer as well as gastrointestinal cancers; however, research has failed to show a definitive conclusion concerning this role (16,17). Studies investigating the role of *H pylori* in acute diseases of lung revealed importance of virulent factors, especially toxin VacA and CagA (18). Nakashima et al reported that *H pylori* VacA was present in human lung tissues and induced vacuolation and production of IL-8 and IL-6 by airway epithelial cells. VacA could play a role in the pathogenesis of respiratory diseases and/or collagen vascular disease-associated interstitial pneumonia (14).

CONCLUSIONS

Our results revealed that the findings of abdominal pain and diarrhea were strongly correlated with the presence of *H pylori* in COVID-19 patients. We believe this effect is mediated by ACE-2 receptors. From this point of view, it is obvious that there is an urgent need for studies investigating the presence of *H pylori* and the expression of ACE-2 receptors in the lungs and upper respiratory system. These investigations can help us fully reveal the mechanism of diarrhea in COVID-19 infections, elucidate the relationship between GI and respiratory system findings, and gain a better understanding of COVID-19, which is still a terrible enigma.

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