Original Article

Prevalence of *Helicobacter pylori* infection and its associated factors in patients with COVID-19

Shahriar Nikpour[1], Latif Gachkar[2], Reza Rezaei[3], Mohammad Salehi[4], Farzaneh Futuhi[5], Shahram Sabeti[6], Minoosh Shabani[2], Azam Erfanifar[7*]

[1]Department of Adult Gastroenterology and Hepatology, School of Medicine, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Department of Infectious Diseases and Tropical Medicine, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Student Research Committee, School of Medicine, Shahid Beheshti University of Medical Sciences. Tehran, Iran
[4]Clinical Research Development Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[5]Department of Nephrology, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[6]Department of Pathology, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[7]Department of Internal Medicine, Internal ward, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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Abstract

Background: The severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) attaches to the angiotensin-converting enzyme-2 (ACE-2) receptors for penetrating cells. Because these receptors are extensively distributed in the intestine, coronavirus disease 2019 (COVID-19) may cause gastrointestinal (GI) symptoms. Helicobacter pylori (H. pylori) is known to increase the expression of ACE-2 receptors in the GI tract. This study aimed to investigate the prevalence of H. pylori infection and its associated factors in patients with COVID-19.

Materials and Methods: This cross-sectional study was conducted from February to December 2021. A total of 215 patients who had been diagnosed with COVID-19 infections using a real-time PCR test or a CT scan were included in the study. The enzyme-linked immunosorbent assay (ELISA) test on serum samples was used to evaluate the presence of *H. pylori*.

Results: All 215 positive patients for COVID-19 with a mean age of 59.72±17.23 were evaluated. Among them, 153 patients (71.2%) were *H. pylori*-positive. Moreover, *H. pylori*+/ COVID-19+ group showed higher mean age than *H. pylori*-/ COVID-19+ patients. However, there was no significant difference between the two groups of patients regarding their medical background, drug history, BMI, and disease severity. The prognosis of the patients was severely worse in the *H. pylori*+/ COVID-19+ than in *H. pylori*-/ COVID-19+ patients.

Conclusion: Our study adds to the previous findings and provides evidence regarding the high prevalence of *H. pylori* in COVID-19 patients. These investigations could help us elucidate the relationship between *H. pylori* and respiratory system findings and better understand COVID-19.

Keywords: COVID-19, Gastrointestinal tract, *Helicobacter pylori*

***Corresponding Author:** Azam Erfanifar, MD. Endocrinologist, Internal ward, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran; Email: erfanifarazam@yahoo.com

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Introduction

Coronavirus disease 2019 (COVID-19) became a pandemic just months after it was discovered in December 2019 and led to thousands of deaths worldwide. Massive efforts are being made to better understand the disease's clinical course and the factors influencing mortality risk. Common clinical symptoms include fever, dry cough, acute respiratory failure, dyspnea, pneumonia, pulmonary edema, nausea, vomiting, headache, loss of taste/smell, diarrhea, and abdominal discomfort[1]. Tissue and organ damage caused by a direct viral infection or an over-activated immune response (cytokine storm) are believed to be part of the disease's pathogenesis[2]. The COVID-19 virus interacts with angiotensin-converting enzyme-2 (ACE-2) receptors to enter the cell. These ACE-2 receptors, widely distributed in the intestine, might induce gastrointestinal (GI) manifestations, typical throughout the disease[3, 4]. The virulence of the microorganism and the immune system response is linked to the course and expression of GI and extra-GI problems related to *Helicobacter pylori* (*H. pylori*)[5].

Some evidence suggests that *H. pylori* can cause GI and extra-GI symptoms and complaints, including autoimmune diseases, cardiovascular diseases, and neurological disorders[6]. *H. pylori* is the cause of chronic gastritis and peptic ulcer disease and a key risk factor for functional dyspepsia, peptic ulceration, gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphoma [7]. Infection with *H. pylori* has been associated with various respiratory diseases, including chronic bronchitis[8], asthma, and pulmonary tuberculosis[9]. The immunological and inflammatory responses elicited by *H. pylori* infection are thought to be the principal drivers of extra-GI pathologies[10]. *H. pylori* comprises multiple virulent components, including outer membrane porin proteins, flagella, several 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. These virulence factors activate the host's immune system, causing higher levels of pro-inflammatory cytokines, including TNF-alpha, IL-6, IL-10, and IL-8, resulting in acute and chronic inflammation[11, 12].

Furthermore, *H. pylori* has been linked to disease pathogenesis by increasing ACE-2 receptor expression in the GI tract. It is directly associated with the severity and duration of infection and causes immunological dysregulation through its virulent components[13, 14]. In addition, a correlation between *H. pylori* infection and chronic respiratory disorders has been discovered in various meta-analysis studies[15, 16]. In COVID-19 patients, Balamtekin *et al*. found that ACE-2 receptors mediate the association between *H. pylori* infection and stomach pain and diarrhea[17]. Since COVID-19 patients frequently develop GI complications, the current study aimed to evaluate H-pylori prevalence and its associated factors in patients with COVID-19.

Methods

The ethics committee approved this cross-sectional study at Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1399.1015). From February to December 2021. This assessment was conducted at Loghman Hakim hospital (Tehran, Iran) on adult patients over 18 years old diagnosed with COVID-19 infections by CT-scan imaging or Real-Time PCR and physician assessment. Informed consent was obtained from each subject and/or caregiver(s).

Blood samples of the patients were sent to the laboratory under appropriate conditions. Anti *H.pylori* antibody levels were measured according to the manufacturer's instructions (Pishtaz Teb ELISA kits, Iran). Patients with a history of antibiotic therapy for *H. pylori* infection were excluded from the study. Clinical features, medical history, and serum biochemical variables were compared between COVID-19+/*H. pylori*+ and COVID-19+/*H. pylori*- groups of patients. Statistical analysis was performed using SPSS Statistics 25.0 (Chicago, Illinois, USA). The data were represented using frequency and percentage, mean and standard deviation. The normal distribution of variables was performed using the Kolmogorov-Smirnov test. The Chi-square independent test or Fisher's test was used to examine the relationship between qualitative variables between groups. The T-test was used to compare quantitative variables. $P<0.05$ was considered statistically significant for all analyses, and $P<0.07$ was considered borderline significance.

Results

This study aimed to determine the frequency of *H. pylori* and its associated factors in COVID-19 patients at Loghman Hakim Hospital. In this descriptive cross-sectional study, 215 patients were referred to the hospital with acute respiratory symptoms, such as fever, cough, and other coronary symptoms. Their infection was confirmed using CT-scan imaging, a real-time PCR test, and a specialist doctor's diagnosis. *H. pylori* was found in 153 (71.2%) of the samples (COVID-19+/*H. pylori*+), whereas the rest were negative (COVID-19+/*H. pylori*-). The clinical findings of patients between these two groups were compared. Table 1 provides the demographic characteristics of the patients with COVID-19.

The differences in medical history variables have been assessed between the COVID-19+/*H. pylori*+ and COVID-19+/*H. pylori*- groups (Table 2). The 100% frequency refers to the prevalence of patients mentioned in the same category. Variables, such as having a history of cardiovascular disease, hypertension, lung diseases, GI disorders, renal failure, diabetes, and other endocrine diseases, were not significantly different between the two groups of COVID-19+/*H. pylori*+ and COVID-19+/H. pylori- patients (Table 2). Also, we compared the variables related to the medications used by patients, and the results are shown in Table 3. It seems that there is no significant difference between COVID-19+/*H. pylori*+ and COVID-19+/*H. pylori*- patients.

In Table 4, we examined the laboratory findings between the two COVID-19+/*H. pylori*+ and COVID-19+/*H. pylori*- patients. Among the mentioned variables, respiratory rate (P=0.07) and titer of *H. pylori* (P<0.001) showed a significant difference between the two groups. The respiratory rate was remarkably higher in COVID-19+/*H. pylori*+ (20.75±4.51) in compare to COVID-19+/*H. pylori*- (19.63±3.37) patients. Positive participants had a mean *H. pylori* titer of 54.65±44.2, while negative subjects had a mean titer of 9.18±10.48 (P=0.001).

Finally, we investigated the severity of the COVID-19 (mild, moderate, severe, and critical)/ *H. Pylori* infection and found no significant correlation (P=0.219, Table 5). As shown in Table 5, 9.8% of *H. Pylori*

Table 1: Demographic background of Covid-19 patients.

			Helicobacter		
		Total	**positive**	**Negative**	**p value**
Age	Mean SD	59.72 ± 17.23	61.24 ± 17.24	56.1 ± 16.8	0.048€
	Median (Range)	61 (20,100)	63 (20,100)	54.5 (23,90)	
Sex	female	78 (36.3%)	56 (36.6%)	22 (35.5%)	0.877*
	male	137 (63.7%)	97 (63.4%)	40 (64.5%)	
Education	Illiterate	38 (22.5%)	28 (23.9%)	10 (19.2%)	0.205*
	Primary	99 (58.6%)	71 (60.7%)	28 (53.8%)	
	Academic	32 (18.9%)	18 (15.4%)	14 (26.9%)	
Marital	married	131 (89.1%)	88 (88.9%)	43 (89.6%)	0.461*
	Widow	10 (6.8%)	8 (8.1%)	2 (4.2%)	
	divorced	6 (4.1%)	3 (3.0%)	3 (6.3%)	
Smoking		31 (21.1%)	19 (19.8%)	12 (23.5%)	0.672*
Cigarettes	Daily	9 (90.0%)	8 (88.9%)	1 (100.0%)	0.725*
	Weekly	1 (10.0%)	1 (11.1%)	0 (0.0%)	
Hookahs	Daily	4 (57.1%)	3 (60.0%)	1 (50.0%)	0.809*
	Weekly	3 (42.9%)	2 (40.0%)	1 (50.0%)	
Alcohol		24 (15.5%)	16 (15.4%)	8 (15.7%)	0.961*

€ Based on t-test

*Based on chi-square and fisher Exact test

Table 2: The differences in medical history variables between the H. pylori + and H. pylori -.

		Helicobacter		
	Total	**Positive**	**Negative**	***P*-value***
Myocardial Infarction	10 (100.0%)	9 (100.0%)	1 (100.0%)	0.333
Angina	9 (100.0%)	6 (100.0%)	3 (100.0%)	0.727
Hypertension	65 (100.0%)	49 (100.0%)	16 (100.0%)	0.507
Heart Failure	8 (100.0%)	7 (100.0%)	1 (100.0%)	0.4
Chronic Lung Diseases	1 (100.0%)	1 (100.0%)	0 (0.0%)	__
Asthma	6 (100.0%)	4 (100.0%)	2 (100.0%)	0.75
Gastroesophageal Reflux	3 (100.0%)	1 (100.0%)	2 (100.0%)	0.8
Stomach Peptic Ulcer	7 (100.0%)	5 (100.0%)	2 (100.0%)	0.666
Inflammatory Heart Diseases	0 (0.0%)	0 (0.0%)	0 (0.0%)	__
Diabetes	61 (100.0%)	49 (100.0%)	12 (100.0%)	0.412
Hypothyroid	7 (100.0%)	4 (100.0%)	3 (100.0%)	0.888
Hyperlipidemia	4 (100.0%)	2 (100.0%)	2 (100.0%)	__
Hyperthyroid	2 (100.0%)	2 (100.0%)	0 (0.0%)	__
Renal Failure	7 (100.0%)	6 (100.0%)	1 (100.0%)	0.444

* Based on chi-square and fisher Exact test

patients had a mild COVID-19 infection, 43.1% had a moderate infection, 32.0% had a severe infection, and 15.0% had an acute infection. Disease with *H. Pylori*, on the other hand, was linked to a poor prognosis in patients with COVID-19 (P=0.044). The results demonstrate that 68% in the *H. pylori*+ group were discharged, 32% expired, 82.3% in the *H. pylori*- group were discharged, and 17.7% expired (Table 5).

Table 6 shows the relationship between *H. pylori* infection and BMI, respiration rate, pulse rate, systolic blood pressure, and diastolic blood pressure. The findings revealed that there is not any significant

Table 3: Comparison of variables related to the medications used by patients in the two groups.

		Helicobacter		
	Total	**positive**	**negative**	**P-value***
ACEs & ARBs	49 (100.0%)	37 (100.0%)	12 (100.0%)	0.509
Calcium Channel Blocker	19 (100.0%)	15 (100.0%)	4 (100.0%)	0.967
Metformin	32 (100.0%)	24 (100.0%)	8 (100.0%)	0.524
Insulin	43 (100.0%)	32 (100.0%)	11 (100.0%)	0.533
Remdesivir	119 (100.0%)	77 (100.0%)	42 (100.0%)	0.71
Favipiravir	15 (100.0%)	11 (100.0%)	4 (100.0%)	0.588
Kaletra	5 (100.0%)	5 (100.0%)	0 (0.0%)	___
Recigen	180 (100.0%)	126 (100.0%)	54 (100.0%)	0.604
Dexamethasone	65 (100.0%)	44 (100.0%)	21 (100.0%)	0.656
Arbidol	10 (100.0%)	8 (100.0%)	2 (100.0%)	0.5
Methylprednisolone	102 (100.0%)	74 (100.0%)	28 (100.0%)	0.557
Actemra	26 (100.0%)	17 (100.0%)	9 (100.0%)	0.7143
Prednisolone	9 (16.1%)	7 (20.6%)	2 (9.1%)	0.283

ACE, Angiotensin converting enzyme inhibitors and ARBs, Angiotensin II Receptor Blockers inhibitors.
**P*-value based on Fisher Exact and Chi-square

Table 4: Comparison of quantitative variables related to the medications used by patients in the two groups.

	Total		Helicobacter				*p* value€
			Positive		Negative		
			Mean ± SD	Median (Range)	Mean ± SD	Median (Range)	
Height	170.23 ± 11.18	171 (116,190)	169.34 ± 10.74	170 (116,190)	172 ± 11.92	175 (120,189)	0.189
Weight	82.02 ± 19	80 (47,188)	81.4 ± 19.57	78 (47,188)	83.26 ± 17.98	80 (56,140)	0.589
BMI	28.42 ± 6.66	27.23 (17.71,56.47)	28.32 ± 6.75	27.08 (17.71,56.47)	28.63 ± 6.53	27.34 (20.28,47.1)	0.803
RR	20.43 ± 4.23	20 (12,39)	20.75 ± 4.51	20 (12,39)	19.63 ± 3.37	19 (14,31)	0.07
PR	86.04 ± 14.59	85 (49,149)	86.65 ± 14.39	86 (49,149)	84.53 ± 15.09	80 (50,130)	0.337
SBP	124.67 ± 18.94	120 (80,195)	125.02 ± 19.74	120 (80,195)	123.82 ± 16.9	125 (85,162)	0.676
DBP	76.01 ± 11.25	78 (50,100)	75.52 ± 11.67	75 (50,100)	77.23 ± 10.12	80 (50,100)	0.25
T	37.37 ± 0.78	37.1 (32.5,40.5)	37.35 ± 0.82	37 (32.5,40.5)	37.41 ± 0.68	37.25 (36,39.5)	0.638
Cr	1.44 ± 1.01	1.2 (0.5,11)	1.44 ± 1.11	1.2 (0.5,11)	1.45 ± 0.72	1.2 (0.8,4.4)	0.963
Na	135.28 ± 10.1	135 (10.1,161)	134.96 ± 11.83	135 (10.1,161)	136.05 ± 3.05	136 (130,144)	0.486
FBS	181.84 ± 98.25	144 (46,553)	187.69 ± 106.29	143.5 (46,553)	167.8 ± 74.76	144 (85,366)	0.255
HbA1c	9.01 ± 1.85	9.2 (6.2,11.2)	9.01 ± 1.85	9.2 (6.2,11.2)	___	___	___
AST	63.89 ± 40.29	54 (4,239)	66.04 ± 42.95	55 (18,239)	58.5 ± 32.48	48.5 (4,150)	0.265
ALT	45.08 ± 36.61	34.5 (2,299)	46.77 ± 39.66	35 (11,299)	40.91 ± 27.56	33.5 (2,117)	0.342
ALP	188.73 ± 96.52	164 (3.9,717)	193.18 ± 92.72	176 (3.9,525)	178.01 ± 105.38	151 (73,717)	0.367
ESR	46.16 ± 25.52	44.5 (3,124)	47.12 ± 26	46 (3,124)	43.96 ± 24.47	40 (3,99)	0.453
CRP	77.59 ± 337.18	45.7 (0.6,4613)	87.42 ± 401.61	45.75 (0.6,4613)	54.34 ± 35.93	43.7 (1.3,124.7)	0.543
Ferritin	419.36 ± 215.82	437 (12.42,1242)	416.41 ± 185.74	409 (16,920)	426.65 ± 278.96	453.5 (12.42,1242)	0.782
D Dimer	52.97 ± 229.07	0.85 (0.13,1052)	78.83 ± 280.3	0.96 (0.15,1052)	1.24 ± 1.09	0.85 (0.13,3.3)	0.479
Duration of ICU hospitalization	7.25 ± 4.61	6 (2,28)	7.14 ± 4.73	6 (2,28)	7.73 ± 4.17	7 (3,21)	0.657
Ward add	0.03 ± 0.16	0 (0,1)	0.04 ± 0.19	0 (0,1)	0 ± 0	0 (0,0)	0.17
Duration of ward hospitalization	5.54 ± 2.68	5 (1,25)	5.42 ± 2.75	5 (1,25)	5.78 ± 2.52	5 (2,16)	0.427
Titer. H. Pylori	41.54 ± 42.96	26.4 (2,286)	54.65 ± 44.2	36.4 (12,286)	9.18 ± 10.48	6.75 (2,57)	<0.001

€ Based on t-test

correlation between COVID-19+/*H. pylori*+ and COVID-19+/*H. pylori*- patients (0.576, 0.380, 0.805, 0.689, 0.445, and 0.441, respectively).

Table 5: Comparison of the severity and prognosis of the COVID-19 disease related to H. Pylori infection.

			Helicobacter		
		Total	Positive	Negative	p value*
Severity	Mild	20 (9.3%)	15 (9.8%)	5 (8.1%)	0.219
	Moderate	102 (47.4%)	66 (43.1%)	36 (58.1%)	
	Severe	65 (30.2%)	49 (32.0%)	16 (25.8%)	
	Critical	28 (13.0%)	23 (15.0%)	5 (8.1%)	
Outcome	Discharge	155 (72.1%)	104 (68.0%)	51 (82.3%)	0.044
	Expire	60 (27.9%)	49 (32.0%)	11 (17.7%)	

**p* value based on chi-square test

Table 6: Comparison of Vital sign variables in COVID-19 patients in the two groups of H. pylori + and H. pylori -.

			Helicobacter		
		Total	positive	negative	p value*
BMI	<25	45 (33.3%)	30 (33.3%)	15 (33.3%)	0.576
	(25 - 30)	52 (38.5%)	33 (36.7%)	19 (42.2%)	
	(30 -35)	20 (14.8%)	16 (17.8%)	4 (8.9%)	
	(35-40)	10 (7.4%)	7 (7.8%)	3 (6.7%)	
	>=40	8 (5.9%)	4 (4.4%)	4 (8.9%)	
RR	=<16	28 (13.0%)	18 (11.8%)	10 (16.1%)	0.380
	>16	187 (87.0%)	135 (88.2%)	52 (83.9%)	
PR	<=100	193 (89.8%)	138 (90.2%)	55 (88.7%)	0.805
	>100	22 (10.2%)	15 (9.8%)	7 (11.3%)	
SBP	<=140	179 (83.3%)	126 (82.4%)	53 (85.5%)	0.689
	>140	36 (16.7%)	27 (17.6%)	9 (14.5%)	
DBP	<=90	195 (90.7%)	137 (89.5%)	58 (93.5%)	0.445
	>90	20 (9.3%)	16 (10.5%)	4 (6.5%)	
Temperature	<=37.5	131 (60.9%)	96 (62.7%)	35 (56.5%)	0.441
	>37.5	84 (39.1%)	57 (37.3%)	27 (43.5%)	

BMI, Body Mass Index; RR, respiratory rate; PR, pulse rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.
**p* value based on chi-square test

Discussion

Although new details about the symptoms and treatment of COVID-19 disease are released daily, our information on COVID-19 infection and treatment is still limited[18]. The link between the presence of *H. pylori*, the world's most frequent infection, and the COVID-19 virus is investigated in this study. We observed that the frequency of *H. pylori* among 215 COVID-19 positive patients was 71.2%. Patients with *H. pylori* had a higher mean age. and showed an increased level of *H. pylori* titer compared to *H. pylori*- patients. We did not observe any significant difference in gender, education, or other demographic characteristics between *H. pylori*+ and *H. pylori*- infection in COVID-19 patients. Likewise, medical history of previous disease and used medications were not significantly different between the two groups of COVID-19 patients with *H. pylori*+ and *H. pylori*- infection.

Additionally, our findings showed that *H. pylori* infection was correlated to the COVID-19 severity. However, it seems that *H. pylori* infection is a detrimental factor for the prognosis of the patients. Our study adds to the previous findings and provides evidence regarding the high prevalence of *H. pylori* in

COVID-19 patients.

The prevalence of *H. pylori* ranges between 7% to 87% worldwide, with lower rates in studies conducted in European nations[19]. *H. pylori* infection is more common in developing countries compared to developed communities. Numerous studies in various nations have found that the prevalence of *H. pylori* infection ranges from 20% in European countries[20] to over 80% in some Eastern Mediterranean countries[21]. Variations in the predicted prevalence rates were also observed in research carried out in Iran. According to Moosazadeh *et al*. meta-analysis, the prevalence of *H. pylori* infection in the general population of Iran is estimated to be 54%[22]. However, the prevalence of *H. pylori* infection in the Iranian population has decreased in recent years [23]. In the previous studies, inconsistent findings have been observed between non-COVID-19 viral and *H. pylori* infection[24-26]. As reported in a prior study, patients with chronic bronchitis showed considerably higher *H. pylori* seropositivity than controls (83.3% *vs.* 60%; P=0.007)[27].

Furthermore, patients with chronic obstructive pulmonary disease (COPD) had a higher rate of *H. pylori* seropositivity than healthy controls (54.7% *vs.* 23.5%, P=0.026)[28]. Similarly, chronic bronchitis has been identified as the leading cause of death in patients with peptic ulcers[29]. These findings imply that *H. pylori* infection may enhance the chance of chronic bronchitis. In the study by Ebule et al., the prevalence of *H. pylori* was 41.9% among tuberculosis patients[30]. According to Genc *et al*., *H. pylori*-positive was found in 27.35 % of COVID-19 patients[18]. In this regard, our results showed that the prevalence of *H. pylori* was 71.2% among 215 patients with COVID-19.

GI symptoms vary between 2 and 50%, with an average of 10% related to COVID-19 infection[31]. Previously, it has been shown that diarrhea and abdominal pain did not affect the severity of the length of covid-19 hospitalization[32]. Although the exact cause of diarrhea in COVID-19 infection is unknown, ACE-2 receptors, located throughout the GI tract, are considered mainly involved. *H. pylori* and its toxins have increased ACE-1, ACE-2, renin, and chymase protein production in human and animal models[33, 34]. Additionally, *H. pylori*-associated ACE-2 overexpression has been linked to bacterial virulence factors[35]. According to the reports, the virus may cause diarrhea after entering the cell, inducing malabsorption and increased intestinal permeability. Furthermore, it has been suggested that intestinal inflammation and dysbiosis caused by ACE-2 alterations in intestinal homeostasis may lead to diarrhea[3]. Further evaluation is needed to find the correlation between GI manifestations in COVID-19 patients and *H. pylori* infection and the modifications of the signaling pathways, such as ACE-2 receptors in the GI tract.

Age, sex, and socioeconomic status have all been linked to H. pylori infection[36] and the risk of chronic bronchitis[37]. The mean age of the patients in our study was 59.72±17.23 years. We observed that the *H. pylori*-positive group had a significantly higher average age (61.24 ± 17.24) than the *H. pylori*-negative (56.1 ± 16.8) group. Age is closely related to the propensity of COVID-19 comorbidities, contributing to the severity of the disease[38]. Therefore, it suggests that *H. pylori* infection can be a risk factor for older infected patients by covid-19.

Additionally, several studies have revealed that male gender, some ethnic groups, and patients with type 2 diabetes and other chronic diseases might be at increased risk of adverse outcomes following severe COVID-19 infection[39-41]. Ibrahim *et al.* investigated the gender differences in the prevalence of *H. pylori* infection in pediatric and adult populations. They revealed that gastric cancer, the most prevalent complication of *H. pylori* infection, was more common in men. Male has been related to a higher frequency of *H. pylori* infection in children and adults[42]. However, Ashtari *et al. reported* no correlation between sex and *H. pylori* infection[23]. Chronic bronchitis was more common in H. pylori IgG seropositive females than non-infected females, as shown in a study of 3608 Chinese adults[43]. Our study showed no significant difference between the two groups of *H. pylori*-positive and negative patients.

In contrast, it has been reported that the male gender is more easily attacked by COVID-19 and more likely to enter severe cases[38]. Regarding the previous research findings, further studies with a large sample size are recommended to evaluate the effects of gender differences on COVID-19 patients infected with *H. pylori*. Furthermore, there was no remarkable difference between the two groups of *H. pylori*-positive

and negative patients regarding smoking status. In a prior meta-analysis conducted by Vardavas and Nikitara[55], it was reported that the smokers were 1.4 times more likely to have severe symptoms of COVID-19 and 2.4 times more likely to be admitted to an intensive care unit (ICU), need mechanical ventilation, or die compared to nonsmokers. It may be linked to an increased ACE2 gene expression in smokers[44].

Obesity is considered a risk factor for *H. pylori* infection, and its prevalence is higher in obese people. Furthermore, data suggests a link between BMI and the severity of COVID-19 and mortality[45-47]. Obesity (BMI 30 kg/m2) is also associated with a higher incidence of COVID-19 acute infection and COVID-19 in-hospital mortality[48]. Similarly, Palaiodimos *et al.* found that severe obesity (BMI 35 kg/m2) was associated with a higher mortality[49]. Meanwhile, ACE2 is extensively expressed in adipose tissue. These may cause obese individuals vulnerable to COVID-19[50]. Some studies examined the potential association outcomes of patients admitted to hospital and compared progression to ICU or death with obesity. Because either obesity itself or the severity of COVID-19 disease could prompt admission to a hospital, the association between these factors might be spurious. A large population-based study found that BMI>30 kg/m^2 was linked to an increased COVID-19 mortality rate than a BMI<30 kg/m^{2,} [39]. In a community-based cohort study, Gao *et al*. found that the hazard ratio of severe outcomes following COVID-19, such as admission to hospital, admission to ICU, or death increases gradually in BMI>23 kg/m^2, which was not attributable to excess risks of related diseases, such as type 2 diabetes. They found that BMI was a more significant risk factor for younger people aged 20–39 than older people (≥80 years)[51]. In our current study, the mean BMI of COVID-19 patients was 28.42±6.66, and we did not find any significant difference between *H. pylori*+/ COVID-19+ (28.32 ± 6.75) and *H. pylori*-/ COVID-19+ (28.63 ± 6.53) groups (P = 0.803). On the other hand, respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature did not show a significant difference between the two *H. pylori*+/ COVID-19+ and *H. pylori*-/ COVID-19+ groups. We did not notice any significant alterations in both *H. pylori* + and *H. pylori* - Covid-19 patients.

According to early findings, arterial hypertension is linked to increased susceptibility to SARS-CoV-2 infection, a more severe course, and more COVID-19–related mortality. A meta- analysis by Zhu et al. showed that patients suffering from hypertension or underlying cardiovascular diseases have a high risk of developing severe manifestations of COVID- 19[52]. After investigating the clinical characteristics of older patients with COVID-19, Niu *et al*. discovered that 15% of patients had hypertension, 5% had coronary heart disease, and only 3% of all patients had diabetes[53]. Furthermore, COVID-19 may be influenced by major pathophysiological hypertension mechanisms such as stimulation of the renin-angiotensin system (RAS). Angiotensin-converting enzyme 2 (ACE2) is a key receptor for SARS-CoV-2 to enter host cells, forming a link between COVID-19 and RAS[54]. Patients with severe COVID-19 may present with a status of systemic hyper-inflammation or cytokine storm[55]. In different retrospective cohorts, severity and mortality-associated risk factors have been reported[56], and acute kidney injury (AKI) is described in up to 25% of patients[57]. Different studies highlight the importance of an elevation of inflammatory mediators as the pathogenic basis for the development of AKI, produced by endothelial dysfunction, microangiopathy, and tubular damage[58]. Our results did not show any significant difference in the medical history of myocardial infarction, angina, heart failure, and hypertension between two groups of *H. pylori*+/ COVID-19+ with *H. pylori*-/ COVID-19+.

H. pylori infection may be responsible for various endocrine[59]. According to recent research,[60] patients with diabetes mellitus had a worse prognosis when infected with COVID-19. Endothelial dysfunction is considered a critical event for the infection and severity of vascular damage in the patient infected with the COVID-19. Type 2 diabetes mellitus should be viewed as a relevant factor for endothelial damage in patients infected with COVID-19[61]. However, we observed no significant differences between *H. pylori*-positive and *H. pylori*-negative regarding the diabetes history.

Furthermore, it should be noted that we also did not find any correlation between pulmonary disease background and *H. pylori* infection in COVID-19 patients. Chronic activation against *H. pylori* and its toxins has been

postulated to play a role in the etiology of lung and GI malignancies; however, research has failed to establish conclusive evidence of this function[62]. The importance of virulent factors, particularly VacA and CagA, has been discovered in investigations studying the involvement of *H. pylori* in acute lung diseases[63]. Nakashima *et al.* revealed the presence of *H. pylori* VacA in human lung tissues, causing vacuolation and the generation of IL-8 and IL-6 by airway epithelial cells[64]. However, the pathogenic mechanisms underlying *H. pylori*'s pulmonary effects are primarily unknown[7].

Furthermore, recent research provided evidence that the presence of *H. pylori* was not correlated with the clinical severity of COVID-19 disease, the requirement for ventilation support therapy, or the length of hospitalization in patients with COVID-19 infection[65]. Balamtekin *et al.* discovered that the severity of COVID-19 infections' symptoms and mortality rates are strongly related to the degree of pulmonary system involvement. According to their research, there was no correlation between the prevalence of *H. pylori* and the severity of pulmonary system disease linked with COVID-19 infections[17]. However, our study's findings showed a significant correlation between the *H. pylori* infection and the outcome of COVID-19 patients, but not the clinical severity of the disease. The correlation between *H. pylori* and extra-GI problems is based on acute and chronic immune activation and an unbalanced immune response to the bacteria and toxins[66]. Accordingly, further evaluation is needed to find the correlation between COVID-19 and *H. pylori* infection and the alterations of the signaling pathways, such as ACE-2 receptors in the GI tract.

Conclusion

Since *H. pylori* infection rates vary by geographic area, age, and ethnicity, we designed a cross-sectional study in Iran, where *H. pylori* infection is prevalent. We evaluated the frequency of H. pylori in COVID-19 positive patients and studied its correlation with other associated factors. Our results revealed a 71.2% frequency of *H. pylori* infection in COVID-19 subjects. ACE-2 receptors can mediate this effect. However, further research is needed to evaluate the signaling pathways. The variable of age was strongly higher in *H. pylori* +/COVID-19+ patients. This lack of correlation can be related to the small sample size. Our findings showed that *H. pylori* infection was significantly correlated with the prognosis of the disease. There is an urgent need for further studies with a large sample size investigating the presence of *H. pylori* and the covid-19 manifestations and underlying mechanisms. Likewise, it is needed to evaluate the effects of *H. pylori* on the requirement for ventilation support therapy or the length of hospitalization in patients with COVID-19 infection. These investigations can help us fully reveal the mechanism of GI symptoms in COVID-19 disease, elucidate the relationship between GI and respiratory system findings, and better understand COVID-19, which is still a terrible enigma.

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