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HELICOBACTER PYLORI INFECTION AND THE CLINICAL COURSE OF CORONAVIRUS-19 DISEASE

Kubra Ulku KARAMAN [1], Ali ASAN [2], Halil Erkan SAYAN [3], Hakan DEMIRCI [1]

[1] University of Health Sciences, Department of Family Medicine, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey.kan

[2] University of Health Sciences, Department of Infectious Diseases, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey.

[2] University of Health Sciences, Department of Anesthesia and Reanimation, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey.

ABSTRACT

Aim: In this study, we aimed to investigate the effects of the presence of Helicobacter Pylori (*H. Pylori*) infection on the clinical course, prognosis and mortality of Coronavirus-19 disease (COVID-19).

Methods: The research was carried out with 180 volunteer patients hospitalized with a diagnosis of COVID-19 between the dates 25.12.2021 and 25.01.2022. The diagnosis of COVID-19 disease was made by PCR test. *H. Pylori* status of the patients was determined by the Elisa method.

Results: Mortality was observed less in *H. Pylori* positive cases than in negative cases (p=0.015).When the results of multivariate logistic regression analysis were examined, it was determined that a one-unit increase in the level of Blood Urea Nitrogen measurement increased the risk of mortality 1.04 times. The mortality risk of patients classified as severe according to radiological findings was 10.53 times higher than the patient group without findings in the radiological examination. The mortality risk of participants with neuropsychiatric disease was 3.50 times higher than participants without neuropsychiatric disease. In addition, unvaccinated patients were found to have a 2.68 times higher risk of mortality than vaccinated patients.

Conclusion: In this study, as a contribution to the literature, it was seen that among patients hospitalized due to COVID-19, *H. Pylori* positive cases died at a lower rate. Mortality in the *H. Pylori*-positive group may have been affected by confounding factors, but considering that it may still be beneficial in treatment and prevention, the relationship between *H. Pylori* and COVID-19 should be investigated in more detail in further studies.

Keywords: Helicobacter Pylori, COVID-19, prognosis, mortality

Corresponding Author: Kubra Ulku KARAMAN kubraulkuozturk@gmail.com

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INTRODUCTION

Helicobacter Pylori (*H. Pylori*) is known as the most common pathogen in the world. It is observed in 90% of developing countries and more than 50% of developed countries (7). *H. Pylori* is a serious public health problem due to the diseases it causes. It has been shown to be responsible for the etiology of peptic ulcer, stomach cancer, and chronic active gastritis and MALT lymphoma (8, 9).

As of February 1, 2022, there have been more than 383 million confirmed cases in the COVID-19 pandemic worldwide, more than 11 million in Turkey, and more than 87 thousand deaths in Turkey, out of 5 million worldwide (5).

The clinical picture caused by the virus, which is called SARS-CoV-2, has been given the name COVID-19 disease. Clinical symptoms of the disease were observed as fever, dry cough, shortness of breath, weakness, joint pain, headache, sore throat, abdominal pain, vomiting, diarrhea, and loss of taste and smell (6).

SARS-CoV-2 RNA positivity in feces has been reported as 6-83% in COVID-19 disease. The ACE-2 receptors that the SARS-CoV-2 virus uses to enter the cell are highly expressed in the small intestine, and the binding affinity of ACE can affect the infectivity of the virus. There have been studies showing that ACE-2 is highly expressed in the small intestine, especially in the proximal and distal enterocytes (10).For this reason, the digestive tract can be used as an inflow of infection by SARS-CoV-2. *H. Pylori* is one of the most common infections affecting human health, with high prevalence in developing countries. It has been reported that *H. Pylori* plays a role in the pathogenesis of diseases by affecting the expression of ACE-2 receptors in the gastrointestinal tract and is associated with the duration and severity of infection (10). Therefore, it is envisaged that *H. Pylori* may be involved in the prevention of serious infections in COVID-19 infection (11).

The clinical course of COVID-19 infection, risk factors, and factors affecting the prognosis are still the subject of research. Many studies are being conducted to investigate whether there is a relationship between COVID-19 infection and various issues. The fact that the Coronavirus uses ACE-2 receptors for entrance into the cell has again made it a matter of curiosity whether there could be a relationship to *H. Pylori* infection, which affects the ACE receptor pathway in various ways. In our study, we planned to investigate whether the association of *H. Pylori* and COVID-19 infection had an effect on the prognosis of Coronavirus disease and the risk factors that had an effect on the mortality of Coronavirus disease.

METHODS

The University of Health Sciences Bursa Yuksek Ihtisas Training and Research Hospital confirmed the research dated 01.12.2021 with decision number 2011-KAEK-25 2021/12-04.

The study was conducted with 180 patients over the age of 18 who were treated for COVID-19 at Bursa Yuksek Ihtisas Training and Research Hospital between 5.12.2021 and 25.01.2022.Patients who were diagnosed with COVID-19 infection by PCR test were included in the study. A serological test with a sensitivity of 88-95% and specificity of 86-95% was performed to diagnose *H. Pylori* in patients (12). Eradication therapy was not applied to *H. Pylori* positive patients.

Criteria for inclusion in the study for participants:

1. Being over the age of 18.

2. Agreeing to participate in the research.

The research was planned as cross-sectional and prospectively. Patients aged 18 years and over who volunteered for the study were included. *H. Pylori* serology was examined by Elisa method by taking 2-5cc of blood from patients. The blood collection was performed by a nurse. The analyses were performed in the hospital microbiology laboratory on a micro-elisa device. The cost of the 200 micro-elisa kits required for this was met by the clinical research budget of our hospital. The test results were evaluated according to the recommendations of the kit manufacturer. The test results were considered negative for patients with <0.9, suspicious for 0.9-1.1, and positive for patients with >1.1. The clinical course of *H. Pylori* positive and negative patients and the outcome of the disease were followed up and compared from the patient files. Patient age, gender, education status, marital status, income status, smoking, body mass index (BMI), presence of chronic diseases, chronic diseases if any, and COVID vaccination status were recorded using the form containing socio-demographic characteristics. BMI was calculated by dividing body weight (kg) by height squared in meters. Clinical follow-up for patients with COVID symptoms included vital signs, blood tests, radiological imaging reports, need for oxygen, intubation status, clinic and/or the intensive care unit (ICU) stay, discharge and death.

Statistical Analysis

Shapiro Wilk test was used to test the suitability of continuous variables for normal distribution. According to the result of the normality test, variables that showed compliance with normal distribution were reported with mean and standard deviation, and variables that did not show compliance with normal distribution were reported with median, minimum and maximum values. For comparisons between the two groups, t-test was used for an independent double sample if there was a normal distribution, and Mann Whitney U test was used if there was no normal distribution. Categorical variables were compared between the groups using Pearson chi-square test, Fisher's exact chi-square test, and Fisher Freeman-Halton test. Factors affecting mortality were examined by logistic regression analysis. For statistical analysis, SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) Program was used and $p<0.05$ was considered statistically significant.

RESULTS

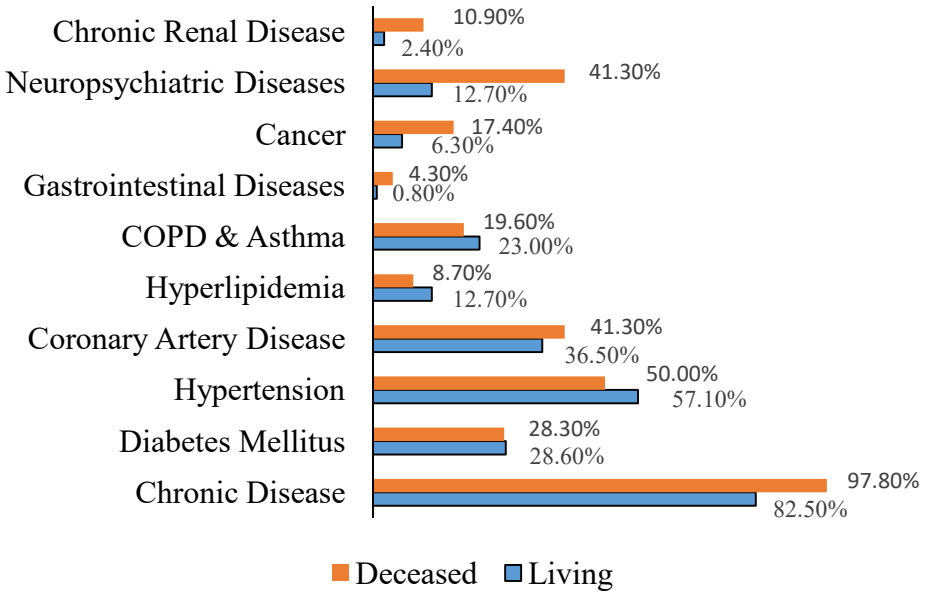
The analysis results for the comparison of general characteristics between patients with and without mortality are given in Table 1. When the table is examined, the median age level is higher in the group with mortality (p=0.002). Marital status was different between the study groups (p=0.006) and the rate of single patients in the group with mortality was higher than the group without mortality. It was determined that the median BMI level of the patient group with mortality was lower (p=0.006). Comparison of patients with and without mortality according to chronic disease distribution is given in Graph 1. It is seen that the incidence of chronic disease is high in patients with mortality (p=0.009). In addition, it is seen that the incidence of cancer is higher in the mortality group (p=0.038). Similarly, the rate of neuropsychiatric disease was found to be higher in patients with mortality (p<0.001).

Table1. Characteristics of the patients with and without mortality

	Total (n=172)	Living (n=126)	Deceased (n=46)	p-value
Gender				
Female	77(%44.80)	58(%46)	19(%41.30)	0.581[a]
Male	95(%55.20)	68(%54)	27(%58.70)	
Age (years)	75(21:98)	68(25:91)	76,50(25:98)	**0.002**[b]
Marital status				
Single	51(%29.80)	30(%24)	21(%45.70)	**0.006**[a]
Married	120(%70.20)	95(%76)	25(%54.30)	
Level of Education				
Not Literate	48(%27.90)	33(%26.20)	15(%32.60)	0.501[a]
Literate & Primary School	76(%44.20)	55(%43.70)	21(%45.70)	
High school and above	48(%27.90)	38(%30.20)	10(%21.70)	
Level of Income				
Poor	119(%69.20)	90(%71.40)	29(%63)	0.292[a]
Good	53(%30.80)	36(%28.60)	17(%37)	
Use of Cigarettes				
Uses	20(%11.60)	14(%11.10)	6(%13)	
Does not use	105(%61)	78(%61.90)	27(%58.70)	0.912[a]
Quit	47(%27.30)	34(%27)	13(%28.30)	
Body Mass Index (kg/m^2)	26.70 (15.60:55.10)	27 (17.60:54.20)	24.90 (15.60:55.10)	**0.006**[b]

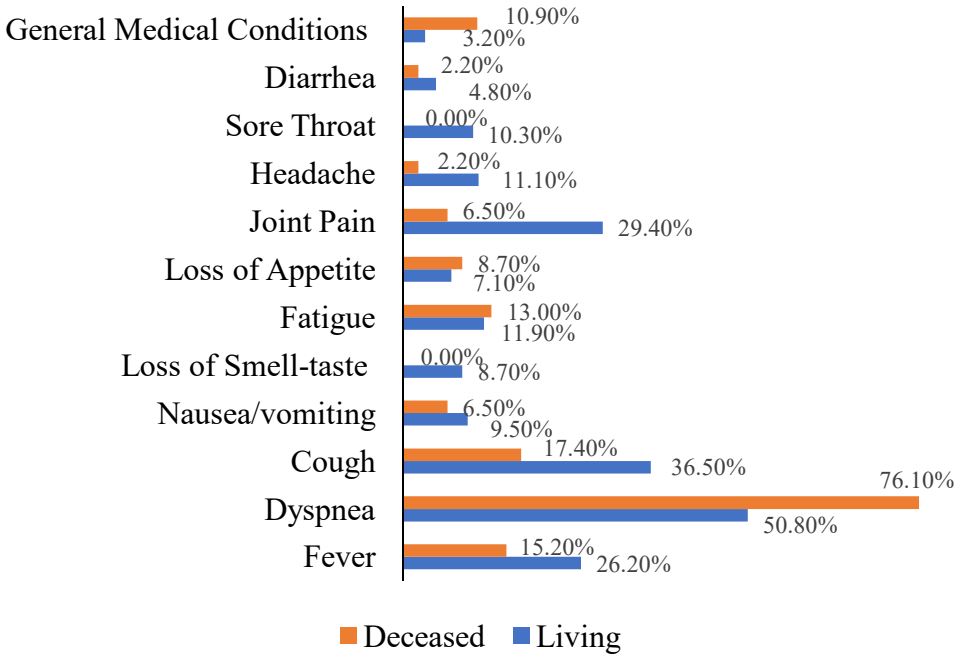
Data are given as median and n%. BMI: Body Mass Index. a: Chi-Square Test, b: Mann-Whitney U Test, c:Fisher-Freeman-Halton Test

Distribution of the participants according to symptoms is given in Graph 2. It is seen that the rates of dyspnea, cough, and loss of smell-taste, joint pain and sore throat differ between patients with and without mortality. The rate of dyspnea was higher in patients with mortality (p=0.013). Accordingly, the rate of patients with cough complaint was higher in the patient group without mortality (p=0.017). It was determined that the rate of odor-taste loss was higher in patients without mortality (p=0.038). The proportion of patients reporting joint pain was also higher in the non-mortality group (p=0.002). In addition, it was determined that complaints of sore throat were higher in patients without mortality (p=0.021).



Graph 1. Distribution of patients with and without observed mortality according to their chronic disease

When Table 2 is examined, it is seen that there is a difference between the groups according to median hemoglobin measurements (p=0.020). The median Hgb measurement of patients with mortality was lower. On the other hand, the median reticulocyte measurement was found to be higher in the group without mortality (p=0.050).



Graph 2. Distribution of patients with and without observed mortality according to their symptoms.

Table2. Complete blood count values and mortality

	Total (n=172)	Living (n=126)	Deceased (n=46)	p- value[b]
White Blood Cells	9.37(0.58:45.97)	8.86(1.49:27.91)	10.82(0.58:45.97)	0.118
Neutrophils	7.039(0.31:42.79)	6.94(0.54:23.97)	8.66(0.31:42.79)	0.128
Lymphocytes	1.15(0.14:19.59)	1.15(0.19:19.59)	095(0.14:11.21)	0.125
Hemoglobin	12.17±2.19	12.50(6.20:17.90)	11.20(7.30:15.60)	**0.020**
Red Blood Cells	4.27(1.51:5.99)	4.32(1.51:5.99)	3.98(2.48:5.24)	**0.050**
Mean Corpuscular Volume	89.05(58.10:122.50)	89(58.10:122.50)	89.65(63.60:105)	0.318
Platelets	233(16:605)	240(34:605)	226(16:456)	0.077

Data are given as median (minimum: maximum). b: Mann-Whitney U Testi

Table 3 includes intergroup comparisons of biochemical tests of patients included in the study. It is seen that the biochemical measurements did not differ between the study groups. When Table 3 is examined, it is seen that the median chloride level is higher in patients with mortality (p=0.033). Bilirubin measurement was also higher in the patient group with mortality (p=0.027).

Table3. The relationship of biochemical measurements of participants with mortality

	Total (n=172)	Living (n=126)	Deceased (n=46)	p-value[b]
Fasting Blood Glucose	132(63:720)	128(63:687)	139.50(70:720)	0.303
Sodium	137(119:173)	137(119:173)	138.50(128:164)	0.055
Potassium	4.40(2.30:6.80)	4.40(2.30:6.80)	4.40(2.30:5.60)	0,619
Chloride	103(81:141)	102(81:141)	104(90:134)	**0.033**
Alanine Aminotransferase	21(6:1038)	20.50(6:298)	21(6:1038)	0.826
Aspartate Aminotransferase	29(7:326)	28(7:326)	30(11:292)	0.697
Direct Bilirubin	0.27(0.06:7.80)	0.24(0.06:7.80)	0.30(0.08:2.49)	**0.027**
Blood Urea Nitrogen	22(5:128)	20.50(7.60:74)	30(5:128)	**<0.001**
Creatinin	0.92(0.28:15.92)	0.92(0.28:2.94)	1.05(0.30:15.92)	0.215

Data are given as median (minimum: maximum). b: Mann-Whitney U Test

Table 4 includes comparisons of disease and treatment characteristics between patient groups with and without mortality. It is seen that there is a difference between patients with and without mortality according to the radiology results (p<0.001). There were also differences between the groups according to the equipment used to deliver oxygen to the patient (p<0.001). High Flow O2 usage rate was higher in the patient group with mortality (7.10% vs. 54.30%; p<0.05). It was determined that the rate of patients who did not need oxygen was higher in the group without mortality (18.30% vs. 4.30%; p<0.05). The rate of intubated patients also differed between groups, and mortality was higher in the observed group (p<0.001). The rate of hospitalization in the ICU was also higher in the mortality group (p<0.001). It was determined that the rate of patients using steroids did not differ between the groups (p=0.427). There was also a difference between

the groups according to the number of days spent in the service (p=0.016). While the median value for the number of days spent in the service was 12 days in the mortality group, it was 9 days in the non-mortality group.

Table4. Comparison of disease and treatment characteristics between patients with and without observed mortality.

	Total (n=172)	**Living (n=126)**	**Deceased (n=46)**	**p-value**
Result of Radiology				
• Light & Medium	112(%65.10)	90(%71.40)	22(%47.80)	**<0.001[a]**
• Heavy	36(%20.90)	14(%11.109	22(%47.80)	
• Education	24(%14)	22(%17.50)	2(%4.30)	
O_2				
• Mask O_2	104(%60.50)	85(%67.50)	19(%41.30)	**<0.001[a]**
• High Flow O_2	34(%19.80)	9(%7.10)	25(%54.30)	
• Continuous positive airway pressure - Bilevel positive airway pressure	9(%5.20)	9(%7.10)	0	
• No	25(%14.50)	23(%18.30)	2(%.430)	
Intubation				
• Intubated	49(%28.50)	10(%7.90)	39(%84.80)	**<0.001[a]**
• No Intubation	123(%71.50)	116(%92.10)	7(%15.20)	
Intensive Care Unit Hospitalization				
• Yes	89(%51.70)	45(%35.70)	44(%95.70)	**<0.001[a]**
• No	83(%48.30)	81(%64.30)	2(%4.30)	
Steroid Therapy				
• Yes	131(%76.20)	94(%74.60)	37(%80.40)	0.427[a]
• No	41(%23.80)	32(%25.40)	9(%19.60)	
	Total (n=142)	**Living (n=121)**	**Deceased (n=21)**	**p-value**
Days of Clinical Hospitalization	9(1:73)	9(1:73)	12(1:33)	**0.016[b]**
	Total (n=89)	**Living (n=45)**	**Deceased (n=44)**	**p-value**
Days of Intensive Care Unit Hospitalization	9(2:60)	7(2:60)	16(2:59)	0.061[b]

Data are given as median and n%. BMI: Body Mass Index. a: Chi-Square Test, b: Mann-Whitney U Test, c: Fisher-Freeman-Halton Test

Multivariate logistic regression analysis was performed to identify independent risk factors thought to have an effect on mortality. Analysis results are presented in Table 5. It was determined that a one-unit increase in the Blood Urea Nitrogen (BUN) measurement level increased the risk of death 1.04 times. When examined in terms of radiological findings, it was determined that the risk of death in patients classified as severe according to radiological findings was 10.53 times higher than the patient group without findings in the radiological examination, but no additional risk was observed. Mortality was higher in patients with mild and moderate radiological findings than in patients without findings on examination. It was determined that the risk of

death of participants with neuropsychiatric disease was 3.50 times higher than those without neuropsychiatric disease. In addition, it was determined that the risk of death was 2.68 times higher in unvaccinated patients than in vaccinated patients.

Table5. Risk factors having an impact on mortality

	Wald	p	OR	%95 (CI)	
				Lower	Upper
Age	0.02	0.894	1	0.97	1.04
Body Mass Index	0.01	0.941	0.99	0.91	1.10
Chronic Disease					
• Yes	0.68	0.409	2.56	0.28	23.72
Joint Pain					
• Yes	2.99	0.084	0.24	0.05	1.21
Hemoglobin	0.11	0.744	0.96	0.77	1.20
Blood Urea Nitrogen	8.14	**0.004**	1.04	1.01	1.06
Radiological Findings					
• Light and Medium	0.12	0.728	1.35	0.25	7.34
• Heavy	7.10	**0.008**	10.53	1.87	59.50
H. Pylori					
• Positive	0.52	0.469	0.69	0.25	1.88
Neuropsychiatric Disease					
• Yes	5.48	**0.019**	3.50	1.23	10.01
Vaccination Status					
• Vaccination-free	4.23	**0.040**	2.68	1.05	6.88
Model χ^2=70.64; **p<0.001**					
Hosmer and Lemeshow Testi: p=0.462					

OR: Odds ratio, CI: Confidence Interval

DISCUSSION

From the results of the study, in patients hospitalized due to COVID-19, the presence of *H. Pylori*, age, marital status and body mass index were found to be associated with mortality. It was found that the presence of chronic diseases was associated with mortality. Of the symptoms, dyspnea, cough, loss of smell/taste, joint pain and sore throat were associated with mortality. Radiological findings, O2 treatment, intubation, number of days in the ICU and clinic, and mortality were other related variables. In the regression analysis, the factors affecting mortality were BUN value, presence of radiological findings, presence of neuropsychiatric disease and vaccination status.

One of the first study in the literature to examine the relationship between *H. Pylori* and COVID-19 infection was conducted by Balamtekin et al. In their study, they found that there was a positive relationship between *H. Pylori* and gastrointestinal symptoms (13). They argued that the basis of this relationship is due to the changes that *H. Pylori* causes in the ACE receptor pathway that COVID-19 uses to enter the cell. However, in our study, we did not observe a significant difference between *H. Pylori* positive and negative patients in terms of gastrointestinal symptoms. We thought

that this difference may be a result of sampling and that the *H. Pylori* diagnostic tests used were different.

In contrast to our findings, several studies on iron deficiency anemia and *H. Pylori* have shown that there is a correlation between *H. Pylori* and iron deficiency anemia (14). In one study, it was found that there is a stronger relationship in children than in adults (15). As a result of increasing the demand for iron by increasing the intake of lactoferrin from neutrophils by gastric colonization of *H. Pylori*, it is argued that this mechanism leads to iron deficiency. Another mechanism described is the disruption of iron absorption as a result of low acid secretion due to atrophic gastritis and a decrease in ascorbic acid in gastric juice, especially in the elderly (14, 15).

There are limited studies conducted in the literature on COVID-19 mortality associated with *H. Pylori* and there is not much data on this issue. The study of Balamtekin et al. was the first to be conducted on this subject (13). Although the mortality rate of *H. Pylori* positive patients was lower in their study; this was not found to be statistically significant. It is thought that the immune stimulation caused by the toxins of *H. Pylori* may play a role in extra-gastrointestinal diseases. There is an increasing amount of research examining the relationship of *H. Pylori* with lung diseases. Regarding this, it has been suggested that by aspirating the stomach contents, these toxins can cause lung damage by increasing inflammatory mediators in the respiratory system. However, studies on the effects of *H. Pylori* on the respiratory system have not been able to establish an exact result (13).

In many studies, it has been shown that advanced age increases the likelihood of developing a serious COVID-19 infection (16, 17). In our study, the results are compatible with the literature and we think that advanced age increases mortality. In our study, marital status was found to be associated with COVID-19 infection mortality. We thought that the reason for the higher rate of single patients in the group where mortality was observed may be due to the overabundance of widowed patients in the older age group. Two studies conducted in Italy and America also support our data. They considered that widows, divorcees and bachelors have worse health status than married people. Older people have a higher risk of mortality, which may be a result of couples encouraging each other to seek medical help and treatment (18, 19).

In a study conducted with smoking, it was found that patients with a history of smoking have an increased risk of hospitalization with severe infection, followed by an increased risk of in-hospital mortality (20). On the other hand, there are studies in which there was no significant relationship between smoking and the severity of the disease, which agrees with our study (21). Smoking, peribronsial respiratory tract inflammation, disruption of the respiratory epithelium and alveolar clearance of corruption can cause a decline in the capacity of phagocytic macrophages, and both the severity and mortality of bacterial and viral infections may increase (22).

Further research is needed to identify the underlying mechanisms by which COVID-19 occurs with more severe symptoms and increases mortality in smokers (22).

The negative impact of comorbid diseases on the prognosis of COVID-19 infection has been estimated. In a study conducted on this issue, it was found that the mortality risk of patients with COVID-19 from cardiovascular disease, cancer, hypertension, diabetes, chronic kidney disease and chronic heart disease is increased (23). Our study supports these results. The chronic diseases that we found to be associated with mortality were cancer, neuropsychiatric diseases and chronic kidney disease. We thought that this may be due to immunosuppression caused by treatments such as chemotherapy and surgery in cancer patients. A study has shown that there is a 2.5-fold increase in the severity of COVID-19 and increased mortality rates in patients with cerebrovascular disease. Researchers have tried to explain this by massive cytokine release and endothelial activation that can lead to vascular damage, causing lung damage (24). In chronic kidney patients, increased levels of pro-inflammatory cytokines leading to oxidative stress and the resulting immune system damage may increase susceptibility to bacterial and viral infections and may be the main reason for the increased risk of pulmonary inflammation (25).

It is believed that COVID-19 vaccines are effective in preventing disease and reducing morbidity and mortality from severe infections. Studies on vaccines are still ongoing. A study has shown that a single dose of the Pfizer-BioNTech vaccine is about 80% effective in preventing hospitalizations with COVID-19 and 85% effective in preventing death from COVID-19 (26). In another study, it was shown that the Pfizer/BioNTech vaccine is highly effective in preventing symptomatic COVID-19, hospitalization, severe illness and mortality (27). Another study in Brazil with those over the age of 75, mortality in patients with the Oxford-AstraZeneca vaccine or CoronaVac-COVID 19 after a single dose Sinovac was associated with an important reduction. Application of two doses of the vaccine showed higher rates of protection (28). Our study also supports this data. It was observed that the rate of vaccinated patients was higher in the group where mortality was not observed.

When we examine the relationship between COVID symptoms and mortality, in a study conducted on this subject, dyspnea complaints were associated with high mortality and support our data (29). The presence of respiratory system symptoms in hospitalized patients, especially dyspnea, may be a guide in terms of prognosis.

There are studies evaluating the relationship between abnormal kidney function markers and mortality in patients with COVID-19. It has been shown that high creatinine and BUN values and kidney disease increase in-hospital mortality (30). The researchers explained this with the fact that expression of ACE-2 in the kidney is about 100 times higher than in the lung, and that the Coronavirus can enter kidney cells in an ACE-2-dependent way and cause kidney damage. Another

mechanism is thought to be that virus-derived cytokines may have indirect effects on kidney tissue with hypoxia and rhabdomyolysis. Our study determined that a one-unit increase in the level of BUN measurement, similar to the literature, increased mortality risk 1.04 times.

Many studies have been conducted with radiological findings in COVID-19. Studies have shown that bilateral lung involvement and consolidation is associated with high mortality. It is observed more frequently in the late stages of the disease, and lung involvement increases with the progression of the disease (31). Similarly, in our study we found that the mortality risk of patients classified as severe according to their radiological findings was 10.53 times higher than that of the patients with no findings in the radiological examination.

H. Pylori positivity was determined by serological test. Although the test has high reliability, the gold standard investigation for *H. Pylori* is histopathological examination of endoscopic biopsy material. In this aspect our research is limited. Our research also includes only hospitalized patients. We cannot comment on *H. Pylori* positivity in milder cases of COVID-19 outpatients, which limits our study.

In conclusion, in this study, as a contribution to the literature, it was seen that patients hospitalized due to COVID-19 in *H. Pylori* positive cases died at a lower rate. Mortality in the *H. Pylori* positive group may have been affected by confounding factors, but considering that it may still be beneficial in the understanding of treatment and prevention, the relationship between *H. Pylori* and COVID-19 should be investigated in more detail in further studies.

Competing interests: There are no conflicts of interest

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