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Analysis of upper gastrointestinal endoscopy results during the COVID-19 pandemic and the impact of SARS-CoV-2 on gastric histopathology: A single-center experience

Aziz Serkan Senger,[1] Mehmet Emirhan Işık[2]

[1]Department of Gastroenterolojic Surgery, University of Health Sciences, Koşuyolu High Specialization Training and Research Hospital, İstanbul, Türkiye
[2]Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences, Koşuyolu High Specialization Training and Research Hospital, İstanbul, Türkiye

ABSTRACT

Introduction: This study was undertaken to compare and analyze changes in the gastroscopy biopsies in infected and non-infected patients performed during the COVID-19 outbreak.

Materials and Methods: A total of 2405 patients who underwent biopsy were obtained from the pathology department. Demographic and pathological characteristics were collected retrospectively from medical records and analyzed, including the patients' age, gender, inflammation, atrophy, intestinal metaplasia, activity, Helicobacter pylori, lymphoid aggregate, and COVID-19 status.

Results: A total of 2405 patients were obtained from the pathology department. In the review of these patients, 294 patients were positive for COVID-19 in the past. COVID-19 was positive in 12.4% of patients with inflammation in the gastric mucosa and 14.9% of those with H. pylori ($p<0.001$ and $p=0.029$, respectively). There was no significant relationship between other variables and COVID-19 positivity. Lymphoid aggregate positivity was statistically significant ($p=0.001$). While the rate of positive lymphoid aggregates in the first 6 months was 60.6%, this rate was 39.4% in the following period. The reliability of the timing of endoscopy after COVID-19 in predicting lymphoid aggregate with the ROC curve is assessed in Table 3, and the cutoff value was 119.5 days (AUC: 0.624, sensitivity and specificity 56.8%, $p<0.001$).

Conclusion: The acute and chronic effects of the disease on the gastrointestinal system are still controversial. It is not yet known what the future consequences of the increase in lymphoid aggregates, which we found in our study, will be.

Keywords: COVID-19, Gastroscopy, Histopathology, Pandemic, SARS-CoV-2

Introduction

Within two decades, there have been three documented highly pathogenic and lethal coronaviruses, namely, severe acute respiratory syndrome-CoV (SARS-CoV), Middle East respiratory syndrome-CoV (MERS-CoV), and SARS-CoV-2.[1] SARS-CoV-2 emerged in the city of Wuhan, China,

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Correspondence: Mehmet Emirhan Işık, M.D., Sağlık Bilimleri Üniversitesi, Koşuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Departmanı, İstanbul, Türkiye
e-mail: emirhan82@gmail.com

and caused an outbreak of unusual viral pneumonia. Being highly transmissible, this novel coronavirus disease, also known as coronavirus disease 2019 (COVID-19), has spread fast all over the world.[2] The clinical spectrum of disease appears from asymptomatic infection to severe viral pneumonia, leading to respiratory failure or even death.[3] The presenting symptoms of COVID-19 often include fever (98%), cough (76%), myalgia/fatigue (44%), and dyspnea (55%).[4]

Gastrointestinal (GI) manifestations are associated but seem less prevalent than in prior SARS or MERS.[5] The frequency of GI symptoms in SARS-CoV-2 patients varied widely from 3.0% to 39.6% in the studies reviewed, and diarrhea was the most frequently reported.[6] Wong et al. reported that the domain of binding receptors on SARS-CoV-2 viruses could bind to the angiotensin-converting enzyme 2 (ACE2) of humans.[7] ACE2 was not restricted to alveolar cells type II in the lung; staining of ACE2 of samples showed positive findings in the cytoplasm of the epithelium lining the stomach, intestine, and cilia.[8] A study has shown that SARS-CoV-2 RNA can be detected in feces for up to a month in 83.3% of patients with a mild infection, raising suspicion of the GI tract as an additional site of viral replication.[9] GI symptomatology tends to be nonspecific and poorly correlates with organic etiology seen on endoscopy.[10]

This study was undertaken to compare and analyze changes in the gastroscopy biopsies of infected and non-infected patients performed during the COVID-19 outbreak.

Materials and Methods

Patients

A retrospective analysis was made of 3020 patients who underwent gastroscopy between April 2019 and September 2021. The results of 2405 patients who underwent biopsy were obtained from the pathology department. Exclusion criteria were age <18, immunosuppressive patients, previous gastric surgery, and COVID-19 polymerase chain reaction (PCR) test results that could not be reached. The study was approved by the Clinical Research Ethics Committee of Koşuyolu High Specialization Training and Research Hospital Institution. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or the national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Data

Demographic and pathological characteristics were collected retrospectively from medical records and analyzed, including the patients' age, gender, inflammation, atrophy, intestinal metaplasia, activity, Helicobacter pylori, lymphoid aggregate, and COVID-19 status. ROC curve analysis was performed to assess the timing of endoscopy after COVID-19 test PCR positivity.

Statistical Analysis

The IBM Statistical Package for the Social Sciences (SPSS) Statistics software package, version 22 for Windows (SPSS Inc., Chicago, IL, USA), was used for the study's statistical analyses. Shapiro–Wilk test preferred the count of the study group was 2 and the count of the study group 3 or higher, Kolmogorov–Smirnov test was preferred. Qualitative data were presented as frequency and percentage, and quantitative data were expressed as mean±SD if the data were normally distributed and as median (min-max) (interquartile range) if not normally distributed.

The patients were divided into two groups positive and negative, according to the PCR test results. Pearson Chi-square test was used to evaluate the relationship between demographic and histopathological data. As a subgroup analysis, the Chi-square test will be used to evaluate the relationship of COVID-19-positive patients (n=294) with chronic damage to the gastric mucosa. The ROC curve was used to determine the cut-off value of the endoscopy time after COVID-19 had passed. $P<0.05$ was considered statistically significant.

Results

A total of 2405 patients were obtained from the pathology department. In the review of these patients, 294 patients were positive for COVID-19 in the past. The distribution of demographic and histopathologic data of patients who underwent gastroscopy during the pandemic period according to their COVID-19 status is given in Table 1. The median age of patients with positive COVID-19 was 49 (39–60) and 52 (41–61) in negative patients, and the age variable was statistically significant between the two groups ($p=0.006$). COVID-19 was positive in 12.4% of patients with inflammation in the gastric mucosa and 14.9% of those with H. pylori ($p<0.001$ and $p=0.029$, respectively). There was no significant relationship between other variables and COVID-19 positivity ($p>0.005$).

Table 1. Patients variables according to COVID-19 status in the pandemic period

Variables	COVID-19 status				
	Positive (n=294, 12.9%)		Negative (n=1979, 87.1%)		
	n	%	n	%	p
Age, years, median (IQR)	49 (39-60)		52 (41-61)		0.006
Gender					
Male	137	12.8	945	87.2	0.899
Female	157	13.1	1034	86.9	
Inflammation					
Absence	59	14.9	320	85.1	<0.001
Present	235	11.2	1658	88.8	
Atrophy					
Absence	261	12.5	1819	87.5	0.072
Present	33	17.1	160	82.9	
Intestinal metaplasia					
Absence	234	12.8	1596	87.2	0.670
Present	60	13.5	383	86.5	
Activity					
Absence	162	12.0	1185	88.0	0.120
Present	132	14.3	794	85.7	
H. pylori					
Absence	166	11.7	1248	88.3	0.029
Present	128	14.9	731	85.1	
Lymphoid aggregate					
Absence	156	12.1	1136	87.9	0.161
Present	138	14.1	843	85.9	

IQR: Interquartile Range.

The acute/chronic effects of SARS-CoV-2 in the gastric mucosa in patients who underwent endoscopy are examined in Table 2. The patients were divided into two groups. The first group consisted of patients who underwent gastroscopy within 6 months after COVID, while the second group consisted of patients who underwent gastroscopy within 6 months after COVID. Only lymphoid aggregate positivity was statistically significant (p=0.001). While the rate of positive lymphoid aggregates in the first 6 months was 60.6%, this rate was 39.4% in the following period.

The reliability of the timing of endoscopy after COVID-19 in predicting lymphoid aggregate with the ROC curve is assessed in Table 3, and the cutoff value was 119.5 days (AUC: 0.624, sensitivity and specificity 56.8%, p<0.001) (Fig. 1).

Discussion

It is known that COVID-19 infection not only infects the respiratory system but also the GI tract.[11] In our study, it was found that lymphoid aggregates were significantly detected and inflammation increased in patients who underwent gastroscopy within the first 6 months. ROC curve analysis revealed that the cutoff value was 119.5 days, sensitivity and specificity 56.8%, p<0.001.

During the SARS-CoV outbreak, 30–70% of patients had GI involvement. MERS-CoV patients had high levels of GI involvement. GI manifestations are reported in 11.4–61.1% of individuals with COVID-19.[12] SARS-CoV-2 uses the transmembrane serine protease 2 receptor in addition to the ACE2 receptor. ACE2 receptors, which the virus uses to gain cellular entry, are expressed in both the respira-

Table 2. Demographic and histopathological features of the COVID-19 positive patients according to endoscopy timing

Variables	Endoscopy timing after COVID-19 infection				
	<6 months		≥6 months		
	n	%	n	%	p
Age, years, Median (IQR)	49 (39-60)		49 (39-57)		0.457
Gender					
Male	106	76.8	32	23.2	0.222
Female	110	70.5	46	29.5	
Inflammation					
Absence	22	75.9	7	24.1	0.759
Present	194	73.2	71	26.8	
Activity					
Absence	118	72.8	44	27.2	0.786
Present	98	74.2	34	25.8	
Intestinal Metaplasia					
Absence	172	73.5	62	26.5	0.979
Present	44	73.3	16	26.7	
Atrophy					
Absence	188	72.9	70	27.1	0.532
Present	28	77.8	8	22.2	
Helicobacter Pylori					
Absence	121	72.9	45	27.1	0.798
Present	95	74.2	33	25.8	
Lymphoid Aggregate					
Absence	136	84.0	26	16.0	<0.001
Present	80	60.6	52	39.4	

IQR: Interquartile Range.

tory tract and GI tract epithelium, creating the potential for viral replication in the GI tract. These receptors are expressed in the lung, esophagus, stomach, small intestine, and colon.[13,14] Fever and cough were the dominant symptoms, and GI symptoms were uncommon, suggesting a difference in viral tropism compared with SARS-CoV, MERS-CoV, and seasonal influenza.[15] Depending on previous investigations conducted on SARS-CoV, the most important evident histopathological finding was the depletion of mucosa-associated lymphoid tissue in the oropharynx, appendix, and parts of the small intestine. In contrast, the stomach tissue each had not revealed apparent evident histological changes.[16]

Studies demonstrated that MERS-CoV and SARS-CoV

Table 3. Assesment of the reliability of post-COVID-19 endoscopy timing in predicting lymphoid aggregate with ROC curve

	AUC	95% CI	Cut off	Sensitivity %	Specificity %	Youden Index	p
Post-COVID endoscopy timing/day	0.624	0.559-0.689	119.5	56.8	56.8	0.136	**<0.001**

AUC: Area Under Curve; CI: Confidence Interval.

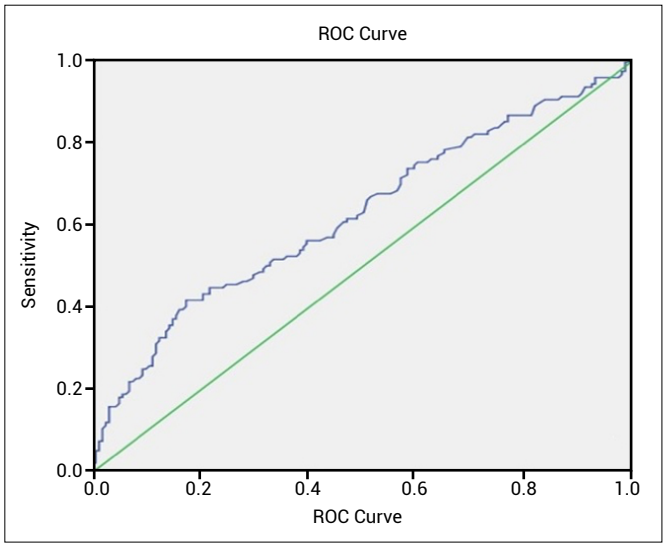

Figure 1. Assesement of the reliability of post COVID-19 endoscopy timing in predicting lymphoid aggregate with ROC.

could invade the human digestive system. MERS-CoV uses dipeptidyl peptidase-4 receptors and causes inflammation and degradation of the intestinal epithelium. On the other hand, SARS-CoV uses ACE2 as the receptor for entry into cells and infection of the body.[17] Studies reported that coronaviridae were detected in the stool for a long time. Kopel et al. found that the SARS-CoV-2 RNA can still be detected in the stool for more than 10 weeks after initial symptoms. Although the respiratory symptoms of CoVs are well-known, the GI symptoms and continual viral shedding in the feces are often overlooked.[18] Cai et al.'s study has shown that SARS-CoV-2 RNA can be detected in feces for up to a month in 83.3% of patients with a mild infection, raising suspicion for the GI tract as an additional site of viral replication.[9] Another study demonstrated that 23.3% of those patients had positive stool samples even after the viral RNA cleared from their respiratory tract.[19]

SARS-CoV-2 RNA has been found in biopsies from the esophagus, stomach, duodenum, and rectum. These findings further support the evidence of replication of infectious virions occurring within the GI tract.[20] Entry of SARS-CoV-2 into host cells may trigger an inflammatory response. Histology shows occasional lymphocyte infiltration in the esophagus and partial epithelial degradation, necrosis, and mucosal shedding in the stomach.[12] There could be a direct injury to the GI system due to an inflammatory response.[20]

In an article from Italy, 38 patients who underwent endoscopy were evaluated. About 37% had esophagitis, erosive gastritis, or peptic ulcer, and 5 patients (13%) had ischemic or hemorrhagic colitis.[21] A study from New York City was comprising 84 COVID-19-positive cases identified esophagitis, peptic ulcer, or gastritis in 31% of cases and colitis in 8%.[22]

In a study including 95 patients with prominent GI symptoms, six patients underwent endoscopy. While SARS-CoV-2 RNA was detected in the esophagus, stomach, duodenum, and rectum in two patients with severe disease, the virus was detected in the duodenum in only one patient with mild disease.[23] In addition, in the study in which it was stated that endoscopy was performed in 73 patients due to upper GI bleeding, it was found that only mucosal damage was observed in the esophagus. No abnormality was observed in the stomach, duodenum, colon, and rectum. Histological findings were edema, plasma cell, and lymphocyte infiltration in the lamina propria of the stomach, duodenum, and rectum.[24]

Limitations

The primary limitation of our study is the problems that may arise from the nature of retrospective studies. Another limitation of the study is single centered. Third, evaluation by different endoscopists and pathologists can be counted. However, even with the limitations of this study, there are still important implications that can be made. In addition, the amount of biopsy taken from each site was variable, and less biopsy in patchy diseases may result in underdiagnosis.

Conclusion

COVID-19, which has been in our lives for the past 2 years, is not only a respiratory system disease but also affects the GI system. The issue of the acute and chronic effects of the disease on the GI system is still controversial. It is not yet known what the future consequences of the increase in lymphoid aggregates, which we found in our study, will be. For this, studies are needed to determine the long-term effects.

Disclosures

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