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Analysis of upper gastrointestinal endoscopy results during the Covid-19 pandemic. A high-volume single-Center experience.

PURPOSE: *The histopathological effects of the COVID-19 period on the upper gastrointestinal system are not clearly known. This study is the first in the literature to compare the results of upper endoscopic biopsy before and during the COVID-19 period.*
METHODS: *Data of 10510 patients who underwent upper endoscopy with a given biopsy sample during the procedure between March 2019 and March 2021 were retrospectively scanned. Patients are divided into two groups as the pre-pandemic period patients and the COVID-19 pandemic period patients. The pathological data of these patients were statistically analyzed according to the Sydney classification.*
RESULTS: *Group 1 comprised of 6,787 patients with 3,915 females and 2872 males (F:M=1.3:1), while Group 2 with 1,734 females and 1,455 males (F:M=1.2:1), and this gender difference between the two groups was statistically significant (p=0.002). A comparison of the patient groups in terms of the inflammation, activation, intestinal metaplasia, and presence of H. pylori revealed a significant difference, with higher rates recorded in the COVID-19 period than in the pre-pandemic period (p < 0.05).*
CONCLUSION: *In the pandemic period, the results of the upper endoscopic biopsy are adversely affected by various factors compared to the pre-pandemic period.*

KEY WORDS: Biopsy, COVID-19, Sydney classification, Upper endoscopy

Introduction

After first appearing in Wuhan, China in December 2019, the COVID-19 outbreak, which affects the lower respiratory tract, has resulted in over 153 million cases and over 3.2 million deaths worldwide [1]. Soon after the appearance of this novel virus, the World Health Organization (WHO) declared the outbreak a global pandemic on March 11, 2020 [2]. This was an unprecedented situation with extremely restrictive considerations [3]. The specialized care required by the infected who required hospitalization and mechanical ventilation has affected significantly the routine operation of healthcare facilities in the most affected countries, including the roles of endoscopy units [4,5]. Since gastrointestinal (GI) endoscopy represents a potential source of SARS-CoV-2 transmission among healthcare workers, the European Society of Gastrointestinal Endoscopy (ESGE) recommended postponing or prioritizing elective procedures to reduce COVID-19-related morbidity/mortality.
Accordingly, it was recommended that GI endoscopy be performed or rescheduled within less than 12 weeks in patients with neoplastic lesions with suspicion for high-grade dysplasia/early cancer [4].

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Global adverse events such as natural disasters can lead to both physical damage and psychological distress[6], although it may be difficult to objectively assess the severity of emotional stress in a person, and more so than physical stress [7]. The present study examines the impact of emotional stress and changing habits on the upper gastrointestinal system during the COVID-19 pandemic, for which our experiences and histopathological data are presented. To the best of our knowledge, this is the first study in literature to compare gastroscopic findings during the COVID-19 pandemic with the pre-pandemic period, making use of the updated Sydney classification [8].

Materials and Methods

In this observational study, we make a retrospective analysis of the data of patients who underwent an upper gastrointestinal endoscopy and biopsy during the procedure at the Kanuni Sultan Süleyman Training and Research Hospital, University of Health Sciences between March 2019 and March 2021. Patients under the age of 18, pregnant women, patients with insufficient procedural or biopsy results, and patients lacking updated Sydney classification records were excluded from the study [8]. The patients were classified into two groups for assessment, being those from the pre-COVID-19 pandemic period (11.03.2019-11.03.2020) and those from the COVID-19 pandemic period (12.03.2020-12.03.2021). All patients underwent an upper gastrointestinal endoscopy by experienced specialist clinicians with endoscopy certificates. During the procedure, a total of 4-5 biopsy samples were collected from the patients' gastric antrum and corpus. The presence of tumors was evaluated in the first statistical assessment, and these patients were excluded from the second statistical assessment. Using the updated Sydney classification [8], the level of neutrophilic infiltration of the lamina propria was graded based on the presence of H. pylori activity, chronic inflammation, intestinal metaplasia and atrophy. Ethical approval for the study was granted by the hospital in which the procedures were performed (IRB No: 2021.04.137). Since this was a COVID-19 study, permission was also obtained from the provincial health directorate on behalf of the Turkish Ministry of Health. All patients included in the study submitted an informed consent form.

During the pre-COVID-19 period between March 11, 2019 and March, 11 2020, a total of 7,047 patients underwent EGD, of which 6,885 were considered eligible for the study. The pathologies of 98 patients were reported as malignant, but as these patients were not assessed according to the Sydney classification, a total of 6,787 patients were evaluated in Group 1. During the COVID-19 period between March 12, 2020 and March 12, 2021, a total of 3,463 patients underwent EGD, of which 3,257 were considered eligible for the study. The pathology of 68 patients was reported as malignant, and after the exclusion of these patients, a total of 3,189 (Fig. 1): The total number of study patients and the distribution of the number of patients by groups.

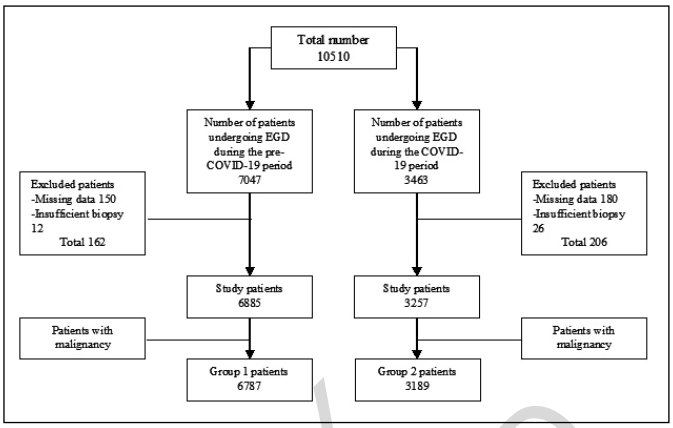

Fig. 1:. The total number of study patients and the distribution of the number of patients by groups.

Statistical Analysis

The software IBM® SPSS® (Statistical Package for the Social Sciences) version 22 (IBM Corp. Armonk, NY, USA) was used for statistical analysis. Qualitative data were presented as frequency and percentage. According to the Kolmogorov-Smirnov test, the age with non-normal distribution was given as median (Interquartile Range-IQR). The association of the COVİD-19 period with categorical variables was analyzed using the Chi-square test. The Mann-Whitney-U test was used to evaluate the relationship between numerical data and the COVID-19 period. A p-value of less than 0.05 was considered significant.

Results

Table I summarizes the demographic data of the patients with detected tumors from the two time periods. Tumors were detected in 98 patients in the pre-COVID-19 period, compared to 68 patients in the pandemic period ($p = 0.014$). There was no significant between-group difference in the age distribution or gender of the patients with tumors ($p = 0.234$). The rate of tumoral diseases was observed to be higher in elderly patients, being those in the ≥65 years age group, than in the non-elderly group during the COVID-19 period (Group 1 = 1.4%; Group 2 = 2.1%), although the difference was statistically insignificant ($p = 0.709$).

The demographic and histopathologic data of the non-tumor patients are presented in Table II. In Group 1,

TABLE I - *Number of patients undergoing EGD in one year*

		The Pre-COVID-19 Period n. (6885)	The COVID-19 Period n. (3257)	P
Tumor	Absent	6787 (98.6%)	3189 (97.9%)	0.014*
	Present	98 (1.4%)	68 (2.1%)	
Demographic data of 166 patients with tumors				
Age (years)	Median (IQR)	65 (54–74)	62 (52–71)	0.234**
Age, n (%)	<64 years	49 (50.0%)	36 (52.9%)	0.709*
	≥65 years	49 (50.0%)	32 (47.1%)	
Gender, n (%)	Male	69 (70.4%)	47 (69.1%)	0.859*
	Female	29 (29.6%)	21 (30.9%)	

*Chi-Square test, **Mann-Whitney U test

TABLE II - *Relationship between demographic and pathological data of 9,976 non-tumorous patients*

		Group 1 (The Pre-COVID-19 Period)		Group 2 (The COVID-19 Period)		
		n (6787)	%	n (3189)	%	P
Age, years, median (IQR)		48 (37–60)		45 (34–57)		<0.001
Age Years	<65	5642	83.1%	2763	86.6%	<0.001
	≥65	1145	16.9%	426	13.4%	
Gender	Male	2872	42.3%	1455	45.6%	0.002
	Female	3915	57.7%	1734	54.4%	
Gastritis	Inactive	2676	39.4%	1111	34.8%	<0.001
	Active	4111	60.6%	2078	65.2%	
Inflammation	Absent	0	0.0%	0	0.0%	<0.001
	Mild	3894	57.4%	1645	51.6%	
	Moderate	2307	34.0%	1217	38.2%	
	Severe	586	8.6%	327	10.3%	
Activation	Absent	2662	39.2%	1111	34.8%	<0.001
	Mild	2696	39.7%	1183	37.1%	
	Moderate	1289	19.0%	762	23.9%	
	Severe	140	2.1%	133	4.2%	
Lymphoid aggregate	Absent	5073	74.7%	2383	74.7%	0.861
	Present	1714	25.3%	806	25.3%	
Atrophia	Absent	6583	97.0%	3097	97.1%	0.564
	Mild	163	2.4%	75	2.4%	
	Moderate	37	0.5%	13	0.4%	
	Severe	4	0.1%	4	0.1%	
H. pylori	Absent	3243	47.8%	1329	41.7%	<0.001
	Mild	1603	23.6%	694	21.8%	
	Moderate	1284	18.9%	642	20.1%	
	Severe	657	9.7%	524	16.4%	
Intestinal metaplasia	Absent	5995	88.3%	2845	89.2%	0.046
	Mild	381	5.6%	180	5.6%	
	Moderate	304	4.5%	106	3.3%	
	Severe	107	1.6%	58	1.8%	

the 6,787 patients comprised 3,915 females and 2872 males (F:M=1.3:1), while in Group 2, the 3,189 patients comprised 1,734 females and 1,455 males (F:M=1.2:1), and this gender difference between the two groups was statistically significant (p=0.002). The median age was 48 (37-60) years in Group 1 and 45 (34-57) years in Group 2 (p<0.001). Admission was found to decrease significantly among female patients during the pandemic period (p=0.02). The proportion of patients over 65 years of age in the control group was higher in the pre-COVID-19 pandemic period than in the pandemic period (16.9% vs. 13.4, respectively) (p<0.001). A comparison of the patient groups in terms of the, inflammation, activation, intestinal metaplasia and presence of H.

pylori revealed a significant difference, with higher rates recorded in the COVID-19 period than in the pre-pandemic period ($p<0.05$). There was no significant difference in lymphoid aggregate and atrophic gastritis between the groups ($p>0.05$).
Severe inflammation was significantly more common in the COVID-19 period than in the pre-pandemic period (10.3% vs. 8.6, respectively) ($p<0.001$). Similarly, the severity of activation was 4.2% in the pandemic period compared to 2.1% in the pre-pandemic period ($p<0.001$). In addition, the rate of severe H. pylori was significantly higher in the pandemic period than in the pre-COVID period ($p<0.001$), while severe intestinal metaplasia was observed to be less affected by the pandemic than the other parameters, although the difference was still significant ($p=0.046$).

Discussion

Our retrospective analysis of histopathological data on EGD was carried out for a single tertiary center, and is the first study to compare the histopathological results and assessments of upper gastrointestinal endoscopy procedures performed during the COVID-19 pandemic and those from the pre-pandemic period.
During this period, healthcare workers of endoscopy units have been exposed to COVID-19 through the contact of saliva droplets with their faces and respiratory tracts [9]. It is estimated that 10% of workers in this unit have been infected [10], and so various measures have been adopted and procedures have been put in place in accordance with recommendations.
As is the case in endoscopy centers all over the world, precautions have been taken to ensure work is carried out in accordance with the requirements of the pandemic conditions during the COVID-19 period. One such measure is limiting the number of procedures carried out in the presence of only limited indications [4]. While most centers cancelled endoscopic procedures during this period, such procedures continued to be performed in tertiary centers in the presence of limited indications. The limits placed on the procedures of endoscopy units have varied according to the restrictions imposed by individual countries during the pandemic. Compared to the assessment period of our study, the active service provided during the one-year period of the pandemic was found to be 49% of our EGD capacity. This rate was observed to vary from month to month, depending on restriction-related decisions, although a significant decrease has been recorded in the number of procedures during the complete lockdown periods, especially in the first three months of the pandemic, and such restrictions have been reported also in developed Western countries such as the United Kingdom [11]. A decrease in absolute numbers has been recorded in countries such as the United States [12], the United Kingdom [11], the Netherlands [13], China [14] and Romania [15]. In Turkey, during the complete lockdowns that started to be imposed across the country on March 21, elective endoscopic procedures were canceled altogether [16]. The restrictions imposed in this period as a necessity reduced the number of procedures, leading to delays in the diagnosis and treatment of cancer, and this delay was of great concern. In a recent modeling study, it was found that a 3-6 month delay in the treatment of cancer patients has a significant impact on survival, especially in stage 2 and 3 tumors [17]. Although there was a decrease in the number of procedures in our study, there was no reduction in incidences of cancer. In fact, the rate of new cases of cancer in this period was found to be significantly higher than in the previous period (Table I), which is believed to result from the presentation of patients to our hospital, which is a referral center, with suspicious symptoms due to the postponement of procedures by various centers. Most endoscopy units around the world are currently working toward the resumption of elective GI endoscopies that have been postponed due to the COVID-19 restrictions [15].
When our data is examined, the first remarkable finding related to demographic data is the significant decrease in the number of patients over 65 years old, who applied to hospitals especially during the COVID-19 pandemic compared to the previous period (16.9% vs. 13.4%). This is believed to result from the restrictions that are specifically imposed on those over the age of 65 years in Turkey [18]. The incidence of cancer is known to be generally high among patients in this age group [19]. Although this significant decrease was not reflected in the comparison of cancer rates in our study, we believe that delays were experienced in diagnosis and treatment. The results of the aforementioned study on the treatment modalities also underlined the importance of this delay [17].
In the present study, the rate of absent activation in the histopathological assessment of chronic gastritis in the two groups based on the updated Sydney classification was significantly higher in the pre-COVID-19 period (39.2% vs. 34.8%; $p<0.001$), while the increase in the severity of activation was greater in the COVID-19 period (2.1% vs. 4.2%).
Alam et al. reported this increase in activation severity to be correlated with the increase in bacterial density [20]. Our study data also revealed the density of H. pylori to be consistent with this situation, and there have been studies suggesting that it may be attributable to a virulent strain of bacteria [21]. Another reason may be the low dietary intake of antioxidant vitamins [22,23]. Considering that people's dietary habits change considerably during periods such as this, diet and the presence of Helicobacter pylori may affect the results.
A prospective randomized study by Capelle et al demonstrated that the atrophy severity was correlated with the severity of gastritis activation [24]. H. pylori virulence,

environmental factors and the presence of accompanying associated lesions are well-known risk factors for atrophy [25-29], although in the present study, no significant difference in atrophy between the two groups could be established.

We believe that this may be attributable to several reasons. Since the development of atrophy, as a precancerous lesion, takes time, the results may be reflected in clinical presentations in the future. The significantly greater presence and the increasing severity of Helicobacter pylori during the COVID-19 period are findings that support those of the present study. Helicobacter pylori has been reported to be a major risk factor for atrophic gastritis [30], and while it usually spreads by the fecal-oral route, it is also likely to be transmitted by the oral-oral route and through contaminated secretions [31]. It is mostly acquired in childhood and occurs in people living under conditions of poverty, overcrowding and poor hygiene [32].

The impact of this global pandemic on society varies according to the level of development. Developed industrial countries sought to alleviate the negative economic effects of the pandemic on people through the provision of financial support [33], while developing and economically weak countries experienced more dramatic impacts, with rises in unemployment, suicide and depression [34,35]. Organizations such as the International Labor Organization (ILO) reported increased unemployment and rising poverty in society during this period [35].

The impact of these conditions is more obvious in underdeveloped and developing countries, and the high mortality rates during the pandemic can be considered proof of this [1]. Given that H. pylori infection increases under these adverse conditions, it may be considered a source of the difference established in the present study.

Our study data reveals that the COVID-19 period has had a negative impact on the gastric mucosa due to the effects of H. pylori, and the direct and indirect effects of stress-based mechanisms. H. pylori infection is also the main etiological agent in chronic active gastritis, peptic ulcer and gastric cancer, and it is estimated that half of the global population carries this bacterium [36]. The reported prevalence in our country is 53% [37] in asymptomatic individuals and 86% [38] in symptomatic individuals, although rates may vary from country to country, and there have been reports of different rates in different regions of the same country [39]. In our study, the rate of Helicobacter pylori was 52.2% in the pre-COVID-19 period and 58.3% in the COVID-19 period (Table II).

Another influential factor is the fluctuation of gastric acid levels due to the increase in psychological stressors during the COVID-19 period, and the associated effect on the gastric mucosa. The relationship between gastric acid secretion and emotional state was first reported by Beaumont in 1833 [40]. The response to stress varies from person to person [41], and it can be very severe at certain times - for example, the risk of peptic ulcer perforation was found to increase during the air raids on London in World War II[42]. In another study, it was reported that an increase in bleeding ulcers occurred following the Hanshin-Awaji earthquake in Japan [43]. In such cases, the damage caused by the reaction of the body manifests itself in the gastrointestinal tract, and the findings of the present study showed that the COVID-19 period had led to an increase in the number of gastrointestinal tract problems reported that were attributable to many reasons.

The fact that our findings were taken from patients selected during the restriction period leads to some bias in the study. As can be seen from the results, however, environmental, physical and psychological factors that manifest under extraordinary conditions can have highly significant effects on the gastrointestinal tract. The health of this tract, which has been referred to as the second brain, affects all body functions.

A literature review revealed our study to be the first to compare histopathological findings of upper gastrointestinal endoscopy from the COVID-19 and pre-COVID-19 periods, although the correlation of the results with those recorded in studies of other extraordinary situations reveals the need for a multidisciplinary approach to the development of treatment modalities.

The limitations of this study included its retrospective single-center design, the assessment of histopathological findings alone, rather than in coordination with clinical and laboratory findings, and the lack of assessment of the stress experienced by the patients during the COVID-19 period.

Conclusion

Patients undergoing biopsy during EGD in the pandemic period were found to be younger, and in this period, the number of male patients was found to have increased when compared to the previous year. Despite the decreased number of procedures in tertiary centers during the COVID-19 period, no correlation with gastric tumor detection at the same rate was identified - that is, a greater proportion of patients with gastric cancer were detected in the pandemic period. The study also highlighted an increase in the incidence and severity of H. pylori, activation and intestinal metaplasia among non-tumor patients during the COVID-19 period. Multicenter studies are needed to validate these results.

Conflict of interest: The authors declare that they have no conflicts of interest.

Ethics approval: Yes. The Institutional Review Board (IRB) of our hospital approved this study (approval numbers 2021.04.137), which was conducted in accordance with the ethical standards of the Declaration of Helsinki, as revised in 2013.

Consent to participate: Not applicable.

Riassunto

Non sono chiaramente noti gli aspetti istopatologici del sistema gastrointestinale superiore del periodo COVID-19. Questo studio è il primo in letteratura a confrontare i risultati della biopsia endoscopica del tratto digerente superiore prima e durante il periodo COVID-19.
Sono stati scansionati retrospettivamente i dati di 10.510 pazienti sottoposti a indagine endoscopica del tratto digestivo superiore tra marzo 2019 e marzo 2021sono stati scansionati retrospettivamente su un campione bioptico. I pazienti sono stati divisi in due gruppi, cioè i pazienti del periodo pre-pandemia e i pazienti del periodo pandemico COVID-19. I dati isto-patologici di questi pazienti sono stati analizzati statisticamente secondo la classificazione di Sydney.
Risultati: Il Gruppo 1 comprendeva 6.787 pazienti con 3.915 donne e 2872 uomini (F:M=1,3:1), mentre il Gruppo 2 comprendeva 1.734 donne e 1.455 uomini (F:M=1,2:1), e questa differenza di genere tra i due gruppi era statisticamente significativo (p=0,002). Un confronto dei gruppi di pazienti in termini di infiammazione, attivazione, metaplasia intestinale e presenza di H. pylori ha rivelato una differenza significativa, con tassi più elevati registrati nel periodo COVID-19 rispetto al periodo pre-pandemia (p<0,05).
Conclusione: Nel periodo pandemico, i risultati della biopsia endoscopica superiore sono influenzati negativamente da vari fattori rispetto al periodo pre-pandemia.

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