ORIGINAL ARTICLE

Eastern Journal of Medicine

East J Med 27(3): 403-409, 2022
DOI: 10.5505/ejm.2022.92489

# Endoscopic Findings in Patients with Chronic Obstructive Pulmonary Disease

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**ABSTRACT**

Although the frequency of reflux esophagitis is increasing in patiens with chronic obstructive pulmonary disease (COPD), there is limited data on how other mucosal pathologies are affected. Therefore, we aimed to examine the various endoscopic findings in patiens with COPD for the first time in the literature.

46 patients (consisting of 22 women=47.8%) with diagnosis COPD who had dyspeptic complaints and underwent upper GI endoscopy for these complaints (COPD group), and 50 patients (consisting of 28 women=56%) with functional dyspepsia were included in the study as the control group (Non-COPD group). Data on demographic characteristics, taken treatments, smoking, alcohol use, endoscopic findings, histopathological findings were documented. Endoscopic findings were compared between COPD and non-COPD groups. In addition, the effect of disease severity on mucosa was investigated.

In the comparison, smoking was statistically significantly higher in COPD group than Non-COPD-group. There was no significant difference in terms of other characteristics (age, gender, body mass index, drug and alcohol use) and presence of helicobacter pylori (HP) between groups ($p>0.05$). When groups are compared in terms of endoscopic findings, the frequency of gastritis, esophagitis, gastric ulcer, duodenal ulcer and barret metaplasia was significantly higher in the COPD group ($p<0.05$). In addition, as the severity of COPD increased, it was observed that pathological mucosal findings increased significantly ($p<0.05$).

Since pathological mucosal findings are significantly higher in patients with COPD, it is important to determine the current situation by performing upper-gastrointestinal system endoscopy and to treat HP infection and pathological endoscopic findings in COPD patients with dyspeptic complaints.

**Keywords**: Chronic obstructive pulmonary disease, hypoxia, reflux esophagitis, ulcer.

## Introduction

Until recently, chronic obstructive pulmonary disease (COPD) was defined as a lung disease characterized by a progressive and irreversible airflow restriction, but it has recently been suggested that airflow restriction is associated with an abnormal inflammatory response, and even systemic effects that are not limited to the lungs have led to a change in the definition of COPD (1,2). According to the renewed GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines; COPD is a preventable and treatable disease with significant extrapulmonary effects that may increase the severity of the disease (2). Airflow restriction in the lungs is usually progressive and is associated with the lung's abnormal inflammatory response to harmful particles and gases, especially tobacco (3-7).

There are many factors affecting the work and functions of the gastrointestinal system (GIS). At the beginning of these factors are nutrition, stress, smoking, alcohol and drugs used, as well as many chronic diseases such as COPD. COPD is divided into two sub-phenotypes, chronic bronchitis and emphysema. In the subtype of emphysema, especially with increased aeration in the lungs, enlargement of the lung volume and secondary to

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**Received:** 06.10.2021, **Accepted:** 25.02.2022

this, reflux and other GIS symptoms are common in patients (8). In addition, COPD is a chronic health problem in which the body remains hypoxic. Hypoxia is a source of stress for the GIS as well as for the whole body. Oxidative stress due to hypoxia and the resulting reactive oxygen products irritate the gastrointestinal mucosa (8-10). Tobacco use, which plays a major role in the development of COPD, is also one of the causes of GIS complaints (10). Apart from these conditions, it is known that drugs used in the treatment of COPD, especially systemic steroids, cause GIS irritation (11,12). Studies in the literature on this subject are mostly on symptomatology. Rarely, only a few studies have examined the incidence of peptic ulcer in COPD patients (8).

Objectively, data on whether endoscopic and histopathological findings differ in COPD patients compared to healthy population is still unclear. Therefore; in our study, we firstly aimed to examine the differences in upper GIS endoscopic findings and the presence of helicobacter pylori (HP) between our patients followed up with a diagnosis of COPD and a healthy control group with functional dyspepsia, and secondly, to examine the relationship between COPD severity and endoscopic findings.

## Materials and Methods

**Study Design:** The study included 46 patients with COPD who were followed up with the diagnosis of COPD from the internal medicine outpatient clinic of our hospital between January 2018 and June 2020, who had dyspeptic complaints and underwent upper GIS endoscopy for these complaints, and 50 patients with functional dyspepsia as the control group. Our study was designed retrospectively. Pregnant women, patients who underwent organ transplantation (liver, kidney, bone marrow), those with chronic liver disease and chronic kidney disease, who had an operation related to GIS and patients used proton pump inhibitors were not included in the study. Data on demographic characteristics (age, gender), taken treatments (non-steroidal anti-inflammatory drugs (NSAID), acetylsalicylic acid), smoking, and alcohol use were documented.

**Diagnosis of Chronic Obstructive Pulmonary Disease:** Patients who were newly admitted to our outpatient clinic and whose FEV1/ FVC value was below 0,70 in the pulmonary function test (PFT) were evaluated as COPD. These newly diagnosed patients and those who were previously diagnosed with COPD and received treatment for COPD were included in the study. COPD severity was also determined by performing PFT. Patients with FEV1 ≥ 80% were evaluated as mild COPD, patients with 50% ≤ FEV1 <80% were evaluated as moderate COPD, patients with 30 % ≤ FEV1 < 50% were evaluated as severe COPD, patients with FEV1 < 30% were evaluated as very severe COPD (2). Although emphysema and chronic bronchitis subgroups were intertwined, patients with clinical dyspnea and radiologically supported were classified as emphysematous type, and those with prominent cough and sputum were classified as chronic bronchitis type (2). Functional dyspepsia was diagnosed according to the Rome-IV criteria (Having at least one of the complaints of postprandial fullness, early satiety, epigastric pain and epigastric burning, not having a problem to explain the symptoms, normal upper GIS endoscopy, and symptoms that started at least 6 months ago and the diagnostic criteria have been available for the last three months (13). Endoscopic data were compared between patients with mild COPD and other (moderate, severe and very severe) COPD patients.

**Endoscopic Evaluation:** Endoscopic findings and histopathological data of the patients were documented. The endoscopy of the patients was performed by using the Fujinon EG530WR endoscopy device in the endoscopy unit of our hospital. All patients starved for 6 hours before the endoscopy, and after the local pharyngeal xylocaine anesthesia, the endoscopy procedure was performed. The stomach and duodenum was examined in detail during the endoscopy, and biopsies were taken for helicobacter pylori infection. Endoscopic findings (gastritis, eosophagitis, gastric ulcer, duodenal ulcer, bulbitis, hiatal hernia, les disfunction, alkaline reflux gastritis, barret metaplasia, atrophic gastritis, celiac disease) were documented. The difference between endoscopic findings and histopathological findings between the patients with COPD and the control group diagnosed with functional dyspepsia without any chronic disease was examined. We carefully examined the structure of gastroesophageal junction to assess the Gastroesophageal sphincter incompetency, using a retroflexed view during gastric inflation. The Gastroesophageal sphincter incompetency was graded from I to IV according to the Hill classification (14). Grade 1: The prominent fold of tissue along the lesser curvature apposed closely to the endoscope. Grade 2: The fold was present but less well defined than in grade I, and some periods of opening and rapid closing around the

endoscope were found. Grade 3: The fold was not prominent and often failed to close around the endoscope, gripping it tightly. Grade 4: There was no fold and the lumen of the esophagus was open. The squamous epithelium of the esophagus could be seen below (14).

**Tissue Biopsy and Histopathological Evaluation:** Punch biopsy was taken from the antrum of the patients who underwent endoscopic evaluations using biopsy forceps. The taken biopsy materials were sent to the pathology laboratory in 10% formaldehyde. After routine tissue follow-up procedures, tissue samples embedded in paraffin were cut at 5 micron thickness, stained with routine Giemsa and evaluated under a light microscope. Samples without tissue competence for evaluation were excluded from the study. The materials obtained were evaluated by three experienced, different pathologists without clinical information. An evaluation was made for the presence of HP in the tissue.

**Ethical Statement:** Ethical approval for this study was obtained from the Ethics Committee of our hospital (Approval no: 07/01/2021/2021-01). All procedures were in accordance with the ethical standards of our institution's human experiment committee and the Helsinki Declaration. Written informed consent forms were obtained from all participants in the study.

**Statistical Analysis:** The results of our study were analyzed with the program "The Statistical Package for the Social Sciences 19.0 (SPSS Armonk, NY: IBM Corp.)". Data with continuous values were given as mean ± standard deviation, categorical data as frequency and percentage (n, %). Data were tested for compliance with normal distribution using the Kolmogorov-simirnov test, histogram, and ± standard deviation. Parametric data of the groups were compared using the Student T test and one sample chi-square or Two-Proportions Z test was used to test categorical data. In addition, Fisher's Exact test was used in comparisons with less than 5 observations. The cases with $p < 0.05$ were considered statistically significant.

## Results

The study included 46 COPD patients (consisting of 22 female= 47.8% and 24 male= 52.2%) (COPD group), and 50 functional dyspepsia patients (consisting of 28 female= 56% and 22 male= 44%) as the control (Non-COPD) group. While 28 (60.8%) of COPD patients were emphysematous type, and 18 (39.1%) were chronic bronchitis subgroup. Efforts were made to have similar rates of factors affecting the gastrointestinal system such as smoking, alcohol, drug use, age, gender, and the presence of HP among the groups with and without COPD. In the comparison between COPD and the control groups in terms of demographic characteristics, drug use, smoking and alcohol use; smoking was statistically significantly higher in the COPD group with a diagnosis of COPD ($p$ = 0.002) (Table 1). There was no significant difference between the groups in terms of other demographic characteristics, alcohol and drug use ($p$>0.05) (Table 1). Occupation of the patients with COPD were evaluated; there were 7 farmers, 3 teachers, 8 construction workers and 28 civil servants. Occupation of the patients without COPD were evaluated; there were 8 farmers, 2 teachers, 6 construction workers, 34 civil servants. In the analysis made in terms of factors causing the disease in patients with COPD; It was observed that 25 (54.3%) of the patients smoked and 15 (32.6%) had intense dust exposure. In the comparison between the groups in terms of endoscopic findings; the rate of those who were found to be normal in endoscopic examination was significantly higher in the control group ($p$= 0.021). In addition, gastritis ($p$= 0.021), esophagitis ($p$= 0.026), gastric ulcer ($p$= 0.038), duodenal ulcer ($p$= 0.010), bulbit ($p$= 0.005) and barret metaplasia ($p$= 0.038) were statistically significantly higher in the patient group with COPD, than the group with functional dyspepsia. There was no significant difference in terms of other endoscopic findings and the presence of HP ($p$> 0.05) (Table 2). In addition, esophagitis degrees in both groups were evaluated; while grade of esophagitis A according to Los Angeles classification in all patients in the control group; grade of esophagitis A in 8 patients with COPD, and grade of esophagitis B in 6 patients with COPD.

While 30 (65.2%) patients had mild COPD and 16 (34.8%) patients had moderate, severe and very severe COPD. In the comparison made in terms of COPD severity and endoscopic findings; in the mild COPD group with a FEV1 ≥ 80%, the rate of those who were found to be normal on endoscopic examination was significantly higher ($p$= 0.009). In addition, gastritis ($p$= 0.009), gastric ulcer ($p$= 0.007), duodenal ulcer ($p$= 0.009), bulbit ($p$<0.001), and barret metaplasia ($p$<0.001) were statistically significantly higher in the non-mild COPD group. There was no significant difference

**Table 1.** Comparison of demographic characteristics, habits and drug use of patients with and without COPD

| Drug and demographic characteristics | COPD (n:46) | Non-COPD (n:50) | Total N:96 | p |
|---|---|---|---|---|
| Age (year± SD, range) | 52.7±13.4 (31-72) | 48.1±11.5 (19-65) | 50.2±12.6 (19-72) | 0.068 |
| Sex (Female) | 22 (%47.8) | 28 (%56.0) | 52 (%54.2) | 0.707 |
| BMI | 20.9±4.3 | 21.4±3.6 | 21.1±2.9 | 0.234 |
| Smoker | 25 (%54.3) | 12 (%24.0) | 37 (%38.5) | 0.002 |
| Alcohol user | 5 (%10.9) | 7 (%14.0) | 12 (%12.5) | 0.643 |
| NSAID (user) | 33 (%71.7) | 31 (%62.0) | 64 (%66.7) | 0.312 |
| ASA (user) | 14 (%30.4) | 10 (%20.0) | 24 (%25.0) | 0.238 |

COPD: Chronic obstructive pulmonary disease, BMI: body mass index, NSAID: non-steroidal anti Inflammatory drug, ASA: acetyl salicylic acid

**Table 2.** Comparison of Endoscopic Findings of Patients with and without COPD

| Endoscopic findings | COPD (n:46) | Non-COPD (n:50) | Total N:96 | p |
|---|---|---|---|---|
| Normal (n,%) | 10 (%21.7) | 22 (%44.0) | 32 (%33.3) | 0.021 |
| Gastritis (n,%) | 36 (%78.3) | 28 (%56.0) | 64 (%66.7) | 0.021 |
| Esophagitis (n,%) | 14 (%30.4) | 6 (%12.0) | 20 (%20.8) | 0.026 |
| Gastric ulcer (n,%) | 6 (%13.0) | 1 (%2.0) | 7 (%7.3) | 0.038 |
| Duodenal ulcer (n,%) | 8 (%17.4) | 1 (%2.0) | 9 (%9.4) | 0.010 |
| Bulbitis (n,%) | 9 (%19.6) | 1 (%2.0) | 10 (%10.4) | 0.005 |
| Hiatal hernia (n,%) | 4 (%8.7) | 4 (%8.0) | 8 (%8.3) | 0.902 |
| LES disfunction (n,%) | 6 (%13.0) | 7 (%14.0) | 13 (%13.5) | 0.891 |
| Alkaline reflux gastritis (n,%) | 2 (%4.3) | 1 (%2.0) | 3 (%3.1) | 0.509 |
| Barret metaplasia (n,%) | 6 (%13.0) | 1 (%2.0) | 7 (%7.3) | 0.038 |
| Atrophic gastritis (n,%) | 0 (%0) | 0 (%0) | 0 (%0) | - |
| Celiac disease (n,%) | 0 (%0) | 0 (%0) | 0 (%0) | - |
| HP (n,%) | 27 (%58.7) | 31 (%62.0) | 58 (%60.4) | 0.741 |

LES: Less Eosophageal Sphincter, HP: Helicobacter Pylori

in terms of other endoscopic findings and the presence of HP ($p$> 0.05) (Table 3).

## Discussion

COPD is a disease that has multisystemic effects and can permanently cause chronic sequelae. COPD affects most of the other systems besides the lungs, especially the circulatory system (5-7). Although its systemic effects are common, the most known effects on GIS; reflux oesophagitis, stress ulcers and ulcer bleeding. When the studies are analyzed; reflux complaints due to hyperinflation secondary to emphysema are seen in the vast majority of patients (4,8). Benson et al. suggested that 26% of COPD patients had reflux symptoms and they were more common in women (15). Similarly, Kim et al. evaluated 253 COPD patients by performing esophagogastroduodenoscopy and they detected reflux esophagitis in 30% of the patients. In the multivariate analysis performed to determine the factors affecting the development of reflux esophagitis; age (odds ratio [OR], 0.950; 95% confidence interval [CI], 0.918 to 0.983; $p$= 0.003), smoking pack-years (OR, 1.015; 95% CI, 1.004 to 1.025; $p$= 0.006), and inhaled anticholinergics (OR, 0.516; 95% CI, 0.271 to 0.982; $p$= 0.044) have been shown to be an independent risk factor (16). In the study of Iliaz et al. itwas reported that although 53.6% of the patients had reflux symptoms clinically, 73.9% of the patients had reflux with 24 h pH impedance (17). We think that the occurrence of such different results in studies may be due to the different prevalence of some risk factors affecting the development of reflux esophagitis among societies. In our study, where demographic characteristics such as age, gender, and factors such as body mass index (BMI) and NSAID use were taken equally between the groups, it was found that the frequency of reflux esophagitis was 30.4% in the COPD group and this

**Table 3.** Comparison of Endoscopic Findings, Demographic Characteristics and Hp Presence By FEV1

| Endoscopic findings | FEV1 ≥80 (n:30) | FEV1<80 (n:16) | Total (n:46) | p |
|---|---|---|---|---|
| Normal (n,%) | 10 (%33.3) | 0 (%0) | 10 (%21.7) | 0.009 |
| Gastritis (n,%) | 20 (%66.7) | 16 (%100) | 36 (%78.3) | 0.009 |
| Eosophagitis (n,%) | 8 (%26.7) | 6 (%37.5) | 14 (%30.4) | 0.447 |
| Gastric ulcer (n,%) | 1 (%3.3) | 5 (%31.3) | 6 (%13.0) | 0.007 |
| Duodenal ulcer (n,%) | 2 (%6.7) | 6 (%37.5) | 8 (%17.4) | 0.009 |
| Bulbitis (n,%) | 1 (%3.3) | 8 (%50.0) | 9 (%19.6) | <0.001 |
| Hiatal hernia (n,%) | 2 (%6.7) | 2 (%12.5) | 4 (%8.7) | 0.504 |
| LES disfunction (n,%) | 5 (%16.7) | 1 (%6.3) | 6 (%13.0) | 0.318 |
| Alkalen reflux gastritis (n,%) | 1 (%3.3) | 1 (%6.3) | 2 (%4.3) | 0.644 |
| Barret metaplasia (n,%) | 0 (%0) | 6 (%37.5) | 6 (%13.0) | <0.001 |
| Atrophic gastritis (n,%) | 0 (%0) | 0 (%0) | 0 (%0) | - |
| Celiac disease (n,%) | 0 (%0) | 0 (%0) | 0 (%0) | - |
| HP (n,%) | 16 (%53.3) | 11 (%68.8) | 27 (%58.7) | 0.312 |

LES: Less Eosophageal Sphincter, HP: Helicobacter Pylori

rate was significantly higher than the Non-COPD group. In addition, the rate of barret metaplasia secondary to reflux was found to be significantly higher in the COPD group.

It is known that tend to increase the other mucosal pathologies as well as increase reflux esophagitis in COPD patients (18). Islam et al. studied the prevalence of peptic ulcer in 64 COPD patients. As a result, they reported that the prevalence of peptic ulcer in COPD was 14.06% and this rate was well above the normal population (8). Kikuchi et al. found that the frequency of GER and peptic ulcer in COPD patients was higher than in the population. They associate with smoking, treatments and hypoxia (19).When the relationship between COPD and gastrointestinal mucosa ulcers is analyzed, it can be said that the drugs used, severity of the disease and smoking have an active role. Likewise, it has been shown in animal experiments on rats that hypoxia causes damage to the gastric and intestinal mucosa (20). Similarly, the presence of COPD in humans causes ulcers in the gastric and intestinal mucosa due to its hypoxic effect alone. In a study conducted with a healthy group, it was reported that hypercapnia affects body pH as well as increases gastric fluid acidity (21). In a study in which the frequency of peptic ulcers was examined in patients with obstructive sleep apnea syndrome (OSAS) and the presence of HP was similar between the groups, both gastric ulcer and duodenal ulcer were significantly more common in the OSAS patient group compared to the healthy control group (22). This indicates the negative effect of hypoxia on the gastrointestinal tract mucosa regardless of the underlying disease. Similarly, in our study, we found both gastric ulcer and duodenal ulcer at a higher rate in the COPD patients group. In addition, it is known that there is an interaction between COPD disease and peptic ulcer. Yarkin et al. hasshown that; COPD patients with peptic ulcer were hospitalized for a significantly longer time (23). In this context, it can be said that there is a significant relationship between disease severity and peptic ulcer. Likewise, in our study, we found significantly higher incidence of gastritis and peptic ulcer in the severe COPD group with lower FEV1 values.

While hypoxia and secondary harmful oxygen radicals cause mucosal erosions, ulcers and bleeding, it is known that gastric and intestinal mucosal irritation due to smoking and steroid use is associated with mucosal damage (8,9,12,15). Studies have reported that peptic ulcers are seen twice as often in smokers compared to non-smokers (24). In addition, smoking and intensive steroid therapy in patients with a diagnosis of COPD who develop peptic ulcer perforation have been reported as effective factors in the development of peptic ulcer (25-27).

Our study has strengths and weaknesses. The small number of our patients and the retrospective design are the weaknesses of our study. Performing endoscopic and histopathological examinations in all patients included in the study, accepting the diagnosis of COPD according to the GOLD criteria, in addition to the comparison between COPD patients and the healthy population, the comparison between treatment-controlled and uncontrolled COPD patients according to FEV1 values, which is an important

criterion for treatment, are the strengths of our study.

In conclusion, it was observed that reflux esophagitis and barret metaplasia were associated with more mucosal damage such as inflammation and ulcer in COPD patients. The reason for this is thought to be secondary to gastrointestinal irritation in COPD patients, due to chronic hypoxia and hypoxia-induced mucosal ischemia and harmful oxygen radicals. In addition, the drugs used in the treatment of COPD and smoking are more, so the GIS mucosa is negatively affected. Therefore, it is important to determine the current situation by performing upper GIS endoscopy in COPD patients with dyspeptic complaints and to treat HP infection and pathological endoscopic findings.

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