Original Article

# Evaluation of the Gastrointestinal Clinical, Endoscopic, and Histological Findings in Patients with Bile Reflux Diseases: A Cross-Sectional Study

**Sabeha Al-Bayati, Ahmed Sahir Alnajjar[1]**

Department of Medicine, College of Medicine, Mustansiriya University, [1]Department of Internal Medicine, Al-Yarmouk Teaching Hospital, Baghdad, Iraq

## Abstract

**Background:** Bile reflux occurs when the bile flows upward from the duodenum to the stomach and esophagus. It occurs when the pyloric sphincter is damaged or fails to work correctly; bile can enter the stomach and then be transported into the esophagus as in gastric reflux. **Objective:** This study aims to evaluate clinical findings and the endoscopic and histological changes caused by bile reflux disease on gastric mucosa. **Patients and Methods:** This is a cross-sectional study carried out at Gastrointestinal Endoscopy Unit in Al-Yarmouk Teaching Hospital in Baghdad during the period from January 2016 to October 2016, upper endoscopy done to 50 patients in the Gastrointestinal Tract Center of Al-Yarmouk Teaching Hospital, in whom there is endoscopic evidence of bile reflux disease and biopsies from gastric mucosa were taken and send for histopathology and *Helicobacter pylori* examination. **Results:** Bile reflux was noted in 19 males (38%) and 31 females (62%). Bile reflux disease was more in age below 50 years (29 patients), more in the female, while after the age of 65 years, the male/female ratio was 1.5/1. The most common symptoms were epigastric pain. The most common endoscopic findings were gastric erythema. The major risk factors were cholecystectomy (8%). Pylori were present in about 24% of the patients. **Conclusion:** Bile reflux disease was more common in young female and cholecystectomy was common risk factor.

**Keywords:** Bile reflux, *Helicobacter pylori*, Oesophago-Gastro-Duodenoscopy

## Introduction

Biliary reflux, bile reflux, or duodenogastric reflux is a condition that occurs when bile flows upward (refluxes) from the duodenum into the stomach and esophagus.[1]

Bile is a digestive fluid made by the liver, stored in the gallbladder, and discharged into the duodenum after food is ingested to aid in the digestion of fat. Normally, the pyloric sphincter prevents bile from entering the stomach. When the pyloric sphincter is damaged or fails to work correctly, bile can enter the stomach and then be transported into the esophagus as in gastric reflux. The presence of small amounts of bile in the stomach is relatively common and usually asymptomatic, but excessive refluxed bile causes irritation and inflammation.[2]

Biliary reflux can be confused with acid reflux, also known as gastroesophageal reflux disease (GERD). While bile reflux involves fluid from the small intestine flowing into the stomach and esophagus, acid reflux is backflow of stomach acid into the esophagus. These conditions are often related, and differentiating between the two can be difficult. The signs and symptoms are similar, and the two conditions may occur at the same time.

Bile is often a suspected cause of reflux when people respond incompletely or not at all too powerful acid-suppressant medications.

Unlike acid reflux, bile reflux usually not completely controlled by changes in diet or lifestyle. Treatment involves medications or in severe cases of surgery.[3]

**Address for correspondence:** Dr. Sabeha Al-Bayati, Department of Medicine, College of Medicine, Mustansiriya University, Baghdad, Iraq.
E-mail: sabehaalbayati@yahoo.com

Access this article online

Quick Response Code:

Website: http://www.mmjonweb.org

DOI: 10.4103/MJ.MJ_5_19



**How to cite this article:** Al-Bayati S, Alnajjar AS. Evaluation of the gastrointestinal clinical, endoscopic, and histological findings in patients with bile reflux diseases: A cross-sectional study. Mustansiriya Med J 2019;18:10-5.

The increased enterogastric reflux may provide the basis for increased mucosal injury. Alkaline reflux gastritis can appear in two circumstances: gastric resection with ablation of the pylorus and primary biliary reflux due to the failure of the pylorus.[4]

Reflux of bile and other contents of the duodenum, along with gastric acid and *Helicobacter pylori* infection, are the main etiological factors which play roles in the pathophysiological processes leading to gastric mucosal lesions in patients with chronic gastritis, and to some extent, these factors may act synergistically.[5]

### Tests and diagnosis

A description of symptoms is often enough to diagnose a reflux problem. However, distinguishing between acid reflux and bile reflux is difficult and requires further testing. There also likely to have tests to check for damage to the esophagus and stomach, as well as for precancerous changes.

Tests may include:

- Endoscopy – it looks for the esophagus, stomach, and duodenum and may take tissue samples to test for Barrett's esophagus, esophageal cancer, or gastritis
- Ambulatory acid tests – these tests use an acid-measuring probe to identify when, and for how long, acid refluxes into the esophagus
    - In one test, a thin, flexible tube (catheter) with a probe at the end is threaded through the nose into your esophagus
    - In another, (the Bravo test), the probe is attached to the lower portion of the esophagus during endoscopy. Ambulatory acid tests can help to rule out acid reflux but not bile reflux.
- Esophageal impedance – this test measures whether gas or liquids reflux into the esophagus. It is helpful for people who regurgitate substances that are not acidic (such as bile) and cannot be detected by an acid probe. As in a standard probe test, esophageal impedance uses a probe that is placed into the esophagus with a catheter.[6]

### Symptoms

- Epigastric pain aggravated by eating
- Frequent heartburn which is not corrected by treatment for gastric reflux
- Dyspepsia (sensation of pain or discomfort in the upper abdomen may describe as indigestion, gassiness, early satiety, postprandial fullness, gnawing, or burning)
- Vomiting a greenish-yellow fluid (bile).[7]

Severe refractory symptoms may require using either nuclear scanning with $^{99m}$Tc-HIDA to document reflux or an alkaline challenge test, where 0.1 N NaOH is infused into the stomach in an effort to reproduce the patients symptoms.[8]

### Causes

Most damage to the pyloric valve occurs as a complication of gastric surgery.

Other causes of biliary reflux may be:

- Peptic ulcer
- Gallbladder surgery (cholecystectomy).

Significant fractions of cases are idiopathic.

Treatment of bile reflux disease in the intact or operated stomach is challenging and not based on a large number of controlled trials.[9-13] Lifestyle adjustments and medications can be very effective for acid reflux, but bile reflux medications are harder to treat. There is little evidence assessing the effectiveness of bile reflux treatments, in part because of the difficulty of establishing bile reflux as the cause of symptoms. Ursodeoxycholic acid, bile acid sequestrants, and proton-pump inhibitor are the medication used in the treatment of bile reflux disease. Surgery is recommended in patients who failed to respond to medical therapy with severe symptoms.

The aim of the study was to evaluate clinical findings and the endoscopic and histological changes caused by bile reflux disease on gastric mucosa.

## Patients and Methods

This is a cross-sectional study carried out at Gastrointestinal (GI) Endoscopy Unit in Al-Yarmouk Teaching Hospital in Baghdad during the period from January 2016 to October 2016 (after obtaining the acceptance of the ethical committee in the Department of Medicine/Al-Mustansiriya College of Medicine), 50 patients were included (31 females and 19 males), who underwent upper GI endoscopy, and ee endoscopic parameters were evaluated:

1. The presence of bile into the stomach
2. The endoscopic changes
3. The presence of risk factors (gastric and biliary surgery).

All the patients were asked for the acceptance to be involved in this research.

From 150 patients who underwent upper endoscopy, only 50 patients who fulfilled the criteria were selected to be included in this study. In addition, these are the criteria for selection of the patients:

- All patients with symptoms suggesting reflux disease (heartburn and regurgitation), dyspepsia, and epigastric pain
- All patients with endoscopic evidence of bile reflux disease.

Biopsies were taken from the gastric mucosa of the antrum of the stomach and any suspicious lesions as 2–3 biopsies for the patient. All biopsies send for histopathology and *H. pylori* examination.

All patients were instructed to fast overnight, endoscopy was performed on the following day, patients were examined using PENTAX gastroscopy EPK/I5000, local anesthesia was

used in the procedure, they received three puffs of lidocaine 10% spray to the mouth and oropharynx, and the endoscopic tube was lubricated with 2% lidocaine jelly and intravenous diazepam and remifentanil. Biopsies were taken from the antrum of the stomach and any suspicious lesions as 2–3 biopsies for the patient. In addition, kept in formalin 10%, send for histological assessment in the hospital, and read by the same histopathologist at the Laboratory of Al-Yarmouk Teaching Hospital.

Chi-square test used to evaluate differences according to different parameters, $P < 0.05$ considered statistically significant.

## Results

Fifty patients (31 female and 19 male) were included in this study with male/female ratio of 1/1.6, and the range of their age was between 16 and 88 years. In addition, the mean age of the patients with bile reflux disease was 46.3 years.

Bile reflux was noted in 19 males (38%) and 31 females (62%), as shown in Table 1.

This study showed that bile reflux disease was more in age below 50 years (29 patients), 17 cases were female and 12 were male. After the age of 65 years, the male/female ratio become 1.5/1 (six males and four females), and this was statistically not significant.

### The patients were classified according to their symptoms

According to their symptoms, the patients were classified: epigastric pain, dyspepsia, heartburn, and vomiting (some patients had >1 symptom). The most common symptoms were epigastric pain (46%) unresponsive to antacids and aggravated by eating, as shown in Table 2.

Endoscopically, all the patients have bile in the stomach, 25 patients (50%) had gastric erythema (gastritis), 13 (26%) with duodenitis, 9 (18%) with gastric erosions, 9 (18%) with ulcer (4 duodenal, 3 transpyloric, and 2 gastric ulcers), 5 (10%) with thickening of gastric mucosa, and 4 (8%) with gastric atrophy (some patients had more than one endoscopic findings), as shown in Table 3.

The most frequent risk factors for bile reflux disease were cholecystectomy that was observed in four patients (8%). Moreover, one case observed with gastrojejunostomy, as shown in Table 4.

Multiple biopsies were taken from gastric antrum of the patients which revealed 24 patients (48%) with chronic inflammation, 16 patients (32%) with acute inflammation, 12 patients (24%) with *H. pylori*, and 10 patients (20%) were normal, as shown in Table 5. Table 6 demonstrate the distribution of histological findings and risk factors according to age. Table 7 showed the distribution of clinical and endoscopic finding according to age. The distribution of clinical and endoscopic findings according to gender are presented in Table 8. Finally, the distribution of histological findings and risk factors according to gender can be seen in Table 9.

**Table 1: Distribution of the patients with bile reflux according to age and gender**

| | *n* (%) |
|---|---|
| Age (years) | |
| <50 *n* (%) | 29 (58.0) |
| ≥50 *n* (%) | 21 (42.0) |
| Mean's (range) | 46.3±19.9 (16-88) |
| Gender *n* (%) | |
| Male | 19 (38.0) |
| Female | 31 (62.0) |

**Table 2: Distribution according to their symptoms**

| Clinical findings | *n* (%) |
|---|---|
| Heartburn | 14 (28.0) |
| Epigastric pain | 23 (46.0) |
| Dyspepsia | 15 (30.0) |
| Vomiting | 12 (24.0) |

**Table 3: Distribution of patients according to their endoscopic findings**

| Endoscopic findings | *n* (%) |
|---|---|
| Gastric erythema | 25 (50.0) |
| Duodenitis | 13 (26.0) |
| Ulcer | |
| Transpyloric ulcer | 3 (6.0) |
| Gastric ulcer | 2 (4.0) |
| Duodenal ulcer | 4 (8.0) |
| Gastric erosions | 9 (18.0) |
| Other findings (nodularity) | 2 (4.0) |
| Thickening of gastric fold | 5 (10.0) |
| Gastric atrophy | 4 (8.0) |

**Table 4: Risk factors in patients with bile reflux disease**

| Risk factors | *n* (%) |
|---|---|
| Risk factor surgery | |
| Cholecystectomy | 4 (8.0) |
| Gastrojejunostomy | 1 (2.0) |
| No | 45 (90.0) |

**Table 5: Histological findings in bile reflux disease**

| Histological findings | *n* (%) |
|---|---|
| Acute or chronic inflammation | |
| Acute | 16 (32.0) |
| Chronic | 24 (48.0) |
| No | 10 (20.0) |
| The presence of *H. pylori* | |
| *H. pylori* | 12 (24) |

*H. pylori: Helicobacter pylori*

**Table 6: Distribution of histological findings and risk factors according to age**

| | Age <50 years, *n* (%) | ≥50 years, *n* (%) | *P** |
|---|---|---|---|
| Risk factor surgery | | | |
| Cholecystectomy | 2 (6.9) | 2 (9.5) | 0.660 |
| Gastrojejunostomy | 1 (3.4) | - | |
| No | 26 (89.7) | 19 (90.5) | |
| Histological finding | | | |
| Acute or chronic inflammation | | | |
| Acute | 12 (41.4) | 4 (19) | 0.185 |
| Chronic | 10 (34.5) | 14 (66.7) | |
| No | 7 (24.1) | 3 (14.3) | |
| *H. pylori* | | | |
| Yes | 4 (13.8) | 8 (38.1) | 0.243 |
| No | 25 (86.2) | 13 (61.9) | |

*Significant difference between proportions using Pearson Chi-square test at 0.05 level. *H. pylori: Helicobacter pylori*

**Table 7: Distribution of clinical and endoscopic finding according to age**

| | Age <50 years, *n* (%) | ≥50 years, *n* (%) | *P** |
|---|---|---|---|
| Clinical findings | | | |
| Heartburn | | | |
| Yes | 9 (31.0) | 5 (23.8) | 0.574 |
| No | 20 (69.0) | 16 (76.2) | |
| Epigastric pain | | | |
| Yes | 16 (55.2) | 7 (33.3) | 0.126 |
| No | 13 (44.8) | 14 (66.7) | |
| Dyspepsia | | | |
| Yes | 7 (24.1) | 8 (38.1) | 0.288 |
| No | 22 (75.9) | 13 (61.9) | |
| Vomiting | | | |
| Yes | 7 (24.1) | 5 (23.8) | 0.979 |
| No | 22 (75.9) | 16 (76.2) | |
| Endoscopic findings | | | |
| Gastric erythema | | | |
| Yes | 14 (48.3) | 11 (52.4) | 0.774 |
| No | 15 (51.7) | 10 (47.6) | |
| Duodenitis | | | |
| Yes | 6 (20.7) | 7 (33.3) | 0.314 |
| No | 23 (79.3) | 14 (66.7) | |
| Ulcer | | | |
| T-PU | 1 (3.4) | 2 (9.5) | 0.734 |
| GU | 1 (3.4) | 1 (4.8) | |
| DU | 3 (10.3) | 1 (4.8) | |
| No | 24 (82.8) | 17 (81.0) | |
| Gastric erosion | | | |
| Yes | 6 (20.7) | 3 (14.3) | 0.561 |
| No | 23 (79.3) | 18 (85.7) | |
| Other findings (nodularity) | | | |
| Yes | 1 (3.4) | 1 (4.8) | 0.815 |
| No | 28 (96.6) | 20 (95.2) | |
| Thickening of gastric fold | | | |
| Yes | 3 (10.3) | 2 (9.5) | 0.924 |
| No | 26 (89.7) | 19 (90.5) | |
| Gastric atrophy | | | |
| Yes | 1 (3.4) | 3 (14.3) | 0.163 |
| No | 28 (96.6) | 18 (85.7) | |

*Significant difference between proportions using Pearson Chi-square test at 0.05 level. T-PU: Transpyloric ulcer, GU: Gastric ulcer, DU: Duodenal ulcer

## Discussion

This study showed that bile reflux disease is more common in female, while in another studies done in Romania and China, they found that male patients were more.[4,14]

Regarding the age, our study showed that most of the patients were below 50 years old like the Chinese study, whereas the Romanian study showed that the majority were above 50 years old.[4,14]

Regarding the endoscopic findings in our study and the Romanian study, the most common findings were erythema of the gastric mucosa as 50% in our study versus 64% in Romanian study.

Duodenitis was seen in 26% of our patients which was not found in the previous already mentioned studies.

Gastric erosion is present in 18% in our study versus 5% in the Romanian study. Furthermore, thickening of gastric folds and gastric atrophy were present in our study and in the Romanian study.

Regarding the histological findings in our study, the chronic inflammation was the most common in 48%, while it is 84% in the Romanian study.

Not all the patients with bile reflux disease had inflammation, as 20% were histologically normal.

The presence of *H. pylori* on histopathology examination was present in 24% in our study, while it was 16% in the Romanian study and 36% in the Chinese study.

The major risk factor for bile reflux disease was cholecystectomy and it is predominant in female, and it was the main risk for female in the Romanian study.

The most common symptoms were epigastric pain (48%), heartburn, dyspepsia, and vomiting.

Reflux of bile, along with gastric acid and *H. pylori* infection, is the main factors that lead to gastric mucosal lesions in patients with chronic gastritis.[15]

Healthy individuals have anatomical and functional barriers that restrict increased intestinal reflux. The pylorus and the physiologically correct angle between the duodenum and the stomach are the main anatomical factors, which could be defected in these patients.[16]

The endoscopic lesions found are not specific for the bile reflux disease, and they could be found in any other circumstances. Therefore, the presence of bile reflux at the examination may be caused by retching during the endoscopy, and it is not necessary to be correlated with the permanent presence of bile into the stomach. Furthermore, gastric erythema may be induced by several elements, especially *H. pylori* infection.

**Table 8: Distribution of clinical and endoscopic findings according to gender**

| | Male, *n* (%) | Female, *n* (%) | *P** |
|---|---|---|---|
| Clinical findings | | | |
| Heartburn | | | |
| Yes | 8 (42.1) | 6 (19.4) | 0.082 |
| No | 11 (57.9) | 25 (80.6) | |
| Epigastric pain | | | |
| Yes | 9 (47.4) | 14 (45.2) | 0.879 |
| No | 10 (52.6) | 17 (54.8) | |
| Dyspepsia | | | |
| Yes | 5 (26.3) | 10 (32.3) | 0.656 |
| No | 14 (73.7) | 21 (67.7) | |
| Vomiting | | | |
| Yes | 5 (26.3) | 7 (22.6) | 0.764 |
| No | 14 (73.7) | 24 (77.4) | |
| Endoscopic findings | | | |
| Gastric erythema | | | |
| Yes | 11 (57.9) | 14 (45.2) | 0.382 |
| No | 8 (42.1) | 17 (54.8) | |
| Duodenitis | | | |
| Yes | 7 (36.8) | 6 (19.4) | 0.171 |
| No | 12 (63.2) | 25 (80.6) | |
| Ulcer | | | |
| T-PU | 3 (15.8) | - | 0.135 |
| GU | 1 (5.3) | 1 (3.2) | |
| DU | 1 (5.3) | 3 (9.7) | |
| No | 14 (73.7) | 27 (87.1) | |
| Gastric erosion | | | |
| Yes | 4 (21.1) | 5 (16.1) | 0.660 |
| No | 15 (78.9) | 26 (83.9) | |
| Other findings (nodularity) | | | |
| Yes | - | 2 (6.5) | 0.258 |
| No | 19 (100.0) | 29 (93.5) | |
| Thickening of gastric fold | | | |
| Yes | 4 (21.1) | 1 (3.2) | 0.053 |
| No | 15 (78.9) | 30 (96.8) | |
| Gastric atrophy | | | |
| Yes | - | 4 (12.9) | 0.103 |
| No | 19 (100.0) | 27 (87.1) | |

*Significant difference between proportions using Pearson Chi-square test at 0.05 level. T-PU: Transpyloric ulcer, GU: Gastric ulcer, DU: Duodenal ulcer

Therefore, in most cases, bile reflux disease is nonerosive chronic superficial gastritis, and there are other circumstances associated with erosions.[17,18]

The exact mechanisms, by which bile as well as other refluxing contents of the duodenum cause gastric mucosal damage are still unclear.[17] It indicated that interaction of bile acid, a component of bile, with M3 muscarinic receptor subtype expressed in chief cells may contribute to mucosal damage, manifested as active inflammation, intestinal metaplasia, glandular atrophy and focal hyperplasia, and other pathophysiological consequences of bile reflux.[15,19,20]

Diagnosis of bile reflux can be challenging because many patients with bile in their stomach have no symptoms, so a combination

**Table 9: Distribution of histological findings and risk factors according to gender**

| | Male, *n* (%) | Female, *n* (%) | *P** |
|---|---|---|---|
| Risk factor surgery | | | |
| Cholecystectomy | - | 4 (12.9) | 0.799 |
| Gastrojejunostomy | 1 (5.3) | - | |
| No | 18 (94.7) | 27 (87.1) | |
| Histological findings | | | |
| Acute or chronic inflammation | | | |
| Acute | 5 (26.3) | 11 (35.4) | 0.938 |
| Chronic | 10 (52.6) | 14 (45.2) | |
| No | 4 (21.1) | 6 (19.4) | |
| *H. pylori* | | | |
| Yes | 5 (26.3) | 7 (22.6) | 0.332 |
| No | 14 (73.7) | 24 (77.4) | |

*Significant difference between proportions using Pearson Chi-square test at 0.05 level

of clinical, endoscopic, and histological findings are required, and there are no universally agreed upon criteria for diagnosis.[21]

A bile reflux index has been suggested based on the histology (the presence of intestinal metaplasia and tissue edema and the absence of *H. pylori* and chronic inflammation), using this method patients with GERD were found to have a more prevalence of bile reflux gastropathy than controls.[22]

A more direct approach has been to use a gastric probe to assess the bilirubin level in the stomach, but this is a test of reflux and not gastropathy.[23]

There is no similar study in our country or near countries.

## Conclusion

1. The majority of cases with bile reflux disease were females below 50 years of age
2. The cholecystectomy was the main risk factor for bile reflux disease
3. The erythema of the gastric mucosa was the main endoscopic changes for bile reflux disease.

### Recommendations

1. To do multiple studies on bile reflux disease with a larger number of patients
2. To do a study on patients with bile reflux disease before and after treatment.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

## References

1. Cheifetz A. Oxford American Handbook of Gastroenterology and Hepatology. Oxford: Oxford University Press; 2011.

2. Cheli R, Giacosa A, Molinari F. Chronic gastritis and duodenogastric reflux. Scand J Gastroenterol Suppl 1981;67:125-7.
3. Gastroesophageal Reflux (GER) and Gastroesophageal Reflux Disease (GERD). National Digestive Diseases Information Clearinghouse; 2014.
4. Vere CC, Cazacu S, Comănescu V, Mogoantă L, Rogoveanu I, Ciurea T. Endoscopical and histological features in bile reflux gastritis. Rom J Morphol Embryol 2005;46:269-74.
5. Chen SL, Mo JZ, Cao ZJ, Chen XY, Xiao SD. Effects of bile reflux on gastric mucosal lesions in patients with dyspepsia or chronic gastritis. World J Gastroenterol 2005;11:2834-7.
6. Sleisenger MH, Feldman M, Friedman LS, Brandt LJ. Sleisenger and Fordtran's gastrointestinal and liver disease: Pathophysiology, diagnosis, management (9th ed.). Philadelphia, PA: Saunders/Elsevier; 2010.
7. Katz PO. Gastroesophageal reflux disease symptoms on antisecretory therapy: Acid, non-acid, or no GERD. Rev Gastroenterol Disord 2006;6:136-45.
8. Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo, J. Harrison's principles of internal medicine (19th ed.). New York: McGraw Hill Education. 2015. p. 1927.
9. Chen H, Li X, Ge Z, Gao Y, Chen X, Cui Y. Rabeprazole combined with hydrotalcite is effective for patients with bile reflux gastritis after cholecystectomy. Can J Gastroenterol 2010;24:197-201.
10. Stefaniwsky AB, Tint GS, Speck J, Shefer S, Salen G. Ursodeoxycholic acid treatment of bile reflux gastritis. Gastroenterology 1985;89:1000-4.
11. Buch KL, Weinstein WM, Hill TA, Elashoff JD, Reedy TJ, Ippoliti AF, *et al.* Sucralfate therapy in patients with symptoms of alkaline reflux gastritis. A randomized, double-blind study. Am J Med 1985;79:49-54.
12. Nicolai JJ, Speelman P, Tytgat GN, van der Stadt J. Comparison of the combination of cholestyramine/alginates with placebo in the treatment of postgastrectomy biliary reflux gastritis. Eur J Clin Pharmacol 1981;21:189-94.
13. Santarelli L, Gabrielli M, Candelli M, Cremonini F, Nista EC, Cammarota G, *et al.* Post-cholecystectomy alkaline reactive gastritis: A randomized trial comparing sucralfate versus rabeprazole or no treatment. Eur J Gastroenterol Hepatol 2003;15:975-9.
14. Zullo A, Rinaldi V, Hassan C, Lauria V, Attili AF. Gastric pathology in cholecystectomy patients: Role of *Helicobacter pylori* and bile reflux. J Clin Gastroenterol 1998;27:335-8.
15. Chen SL, Mo JZ, Chen XY, Xiao SD. The influence of bile reflux, gastric acid and *Helicobacter pylori* infection on gastric mucosal injury: Severity and localization. Weichang Bingxue 2002;7:280-5.
16. Kuran S, Parlak E, Aydog G, Kacar S, Sasmaz N, Ozden A, *et al.* Bile reflux index after therapeutic biliary procedures. BMC Gastroenterol 2008;8:4.
17. Stein HJ, Smyrk TC, DeMeester TR, Rouse J, Hinder RA. Clinical value of endoscopy and histology in the diagnosis of duodenogastric reflux disease. Surgery 1992;112:796-803.
18. Geboes K, Rutgeerts P, Broeckaert L, Vantrappen G, Desmet V. Histologic appearances of endoscopic gastric mucosal biopsies 10–20 years after partial gastrectomy. Ann Surg 1980;192:179-82.
19. Raufman JP, Cheng K, Zimniak P. Activation of muscarinic receptor signaling by bile acids: Physiological and medical implications. Dig Dis Sci 2003;48:1431-44.
20. Johannesson KA, Hammar E, Staël von Holstein C. Mucosal changes in the gastric remnant: Long-term effects of bile reflux diversion and *Helicobacter pylori* infection. Eur J Gastroenterol Hepatol 2003;15:35-40.
21. Sleisenger MH, Feldman M, Friedman LS, Brandt LJ. Sleisenger and Fordtran's gastrointestinal and liver disease: Pathophysiology, diagnosis, management (10th ed.). Philadelphia , PA: Saunders/Elsevier; 2016.
22. Nakos A, Zezos P, Liratzopoulos N, Efraimidou E, Manolas K, Moschos J, *et al.* The significance of histological evidence of bile reflux gastropathy in patients with gastro-esophageal reflux disease. Med Sci Monit 2009;15:CR313-8.
23. Fein M, Freys SM, Sailer M, Maroske J, Tigges H, Fuchs KH. Gastric bilirubin monitoring to assess duodenogastric reflux. Dig Dis Sci 2002;47:2769-74.