healthcare

MDPI

Article

Effect of UDCA, Sucralfate, and PPI Treatments and Gallbladder Pathologies on Duodenogastric Reflux Gastritis: A Retrospective Study

Yasin Alper Yildiz [1,*] and Mertcan Akcay [2]

[1] Department of General Surgery, Faculty of Medicine, Kastamonu University, 37120 Kastamonu, Turkey
[2] Department of General Surgery, Kastamonu Education and Research Hospital, 37120 Kastamonu, Turkey; mertcan.akcay54@gmail.com
* Correspondence: yalperyildiz@gmail.com; Tel.: +90-5349530628

Abstract

Background/Objectives: Duodenogastric reflux (DGR) gastritis remains a clinically challenging condition with limited comparative evidence regarding commonly used medical treatments and no well-established therapeutic strategy. This study aimed to compare symptomatic responses to different treatment regimens (PPI, PPI + sucralfate, PPI + UDCA) and to examine associations of gallbladder status with symptoms and histopathological findings in patients diagnosed with DGR. Methods: A total of 77 patients diagnosed with DGR in our endoscopy unit were retrospectively evaluated. Patients were divided into three groups: Group 1 (PPI + sucralfate, n = 32), Group 2 (PPI + UDCA, n = 31), and Group 3 (PPI, n = 14). Symptom scores were assessed before and after 6 weeks of treatment using a modified Likert scale. Histopathological parameters and symptoms were also evaluated according to gallbladder status (normal, gallstone, cholecystectomy). In 16 patients who underwent follow-up endoscopy, biopsy results before and after treatment were compared. Results: All three treatment groups showed significant within-group reductions in symptom scores after 6 weeks of therapy (all $p < 0.01$). However, the magnitude of symptom improvement did not differ significantly among treatment groups ($p = 0.457$). Symptom scores also decreased significantly within each gallbladder-status group, without a significant between-group difference. In the 16 patients with paired biopsies, no histopathological outcome showed a statistically significant change on two-sided exact Wilcoxon testing (activation $p = 0.078$; inflammation $p = 0.094$; intestinal metaplasia $p = 0.625$; *H. pylori* grade $p = 0.307$); these exploratory results were unadjusted for multiple comparisons. Conclusions: PPI, PPI + sucralfate, and PPI + UDCA regimens were each associated with significant short-term symptomatic improvement in patients with DGR; however, no statistically significant between-group difference was detected. Gallbladder status was not significantly associated with the magnitude of symptomatic improvement. The histopathological findings from the limited follow-up endoscopy subgroup should be interpreted as exploratory and require confirmation in larger prospective studies. By comparatively evaluating three commonly used medical treatment approaches together with gallbladder status within the same real-world cohort, this study provides additional clinical evidence in an area where comparative treatment data remain limited.

Keywords: bile reflux; gastritis; ursodeoxycholic acid; sucralfate; gallbladder diseases; endoscopy

Check for updates

Academic Editor: Joaquim Carreras

Received: 29 September 2026
Revised: 12 November 2026
Accepted: 17 November 2026
Published: 18 November 2026

Copyright: © 2026 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

1. Introduction

Duodenogastric reflux (DGR) gastritis is characterized by the retrograde flow of duodenal contents, including bile and pancreatic secretions, into the stomach through the pylorus, potentially contributing to gastric mucosal injury and dyspeptic symptoms. This condition is also referred to as alkaline reflux gastritis or primary biliary reflux gastritis. Bile reflux into the stomach was first described by William Beaumont in the mid-1800s [1].

DGR may occur following gastric surgery that disrupts the pyloric structure [2], as well as in association with primary pyloric dysfunction, previous cholecystectomy, gallbladder dysfunction, or impaired duodenal peristalsis [3]. Primary duodenogastric reflux gastritis refers to reflux gastritis occurring in the absence of previous gastric surgery. The main etiological factors include gallbladder dysfunction or absence, as well as gastric or duodenal dysmotility [4].

Several methods are available for diagnosing bile reflux, including endoscopic visualization of bile accumulation or reflux into the stomach, biochemical detection of bile or bilirubin in gastric fluid, and radionuclide imaging. Among these, endoscopic identification of bile reflux or accumulation is commonly used in clinical practice. During endoscopy, bile pooling in the stomach, direct observation of reflux, and mucosal findings such as gastric hyperemia, erosions, and atrophy may be observed [2]. However, endoscopic visualization of bile alone is insufficient to establish a definitive diagnosis of pathological DGR or to quantify reflux severity [5].

DGR may alter the gastric microbiota and intragastric environment, potentially contributing to bacterial overgrowth [6]. The relationship between *Helicobacter pylori* infection and DGR remains unclear. Some studies suggest that changes in the gastric environment may favor *H. pylori* colonization, whereas others indicate that exposure to bile acids may inhibit its survival [7].

Several studies have reported associations between DGR and gastric cancer or precancerous lesions [8,9]. Perdikis et al. suggested that increased DGR following cholecystectomy may be related to the loss of the gallbladder's bile-concentrating function [10].

To date, no standardized medical treatment protocol has been established for DGR gastritis. The primary goal of treatment is to alleviate symptoms and minimize the effects of duodenal contents on the gastric mucosa. Although medical treatment is generally preferred, surgical intervention may be considered in selected cases. In a study involving 60 patients with post-cholecystectomy alkaline reflux gastritis, patients were randomized to receive sucralfate, rabeprazole, or no treatment. Epigastric pain relief was reported in 45%, 30%, and 10% of patients, respectively [11]. More recently, a systematic review and meta-analysis including 14 studies and 1605 patients reported that UDCA-containing treatment was associated with improvements in bile reflux parameters, clinical response, and reflux-related symptoms [12]. However, the certainty of evidence for the evaluated outcomes was low or very low, highlighting the need for further high-quality comparative studies. Although several pharmacological approaches have been investigated for bile reflux gastritis, a standardized therapeutic regimen has not been established [13]. Furthermore, evidence directly comparing PPI monotherapy with PPI–sucralfate and PPI–UDCA combination regimens remains limited.

In our clinical practice, patients diagnosed with DGR gastritis by endoscopy receive PPI alone, PPI plus sucralfate, or PPI plus UDCA without a predefined treatment-selection algorithm. Although previous studies have evaluated individual therapeutic approaches, comparative evidence regarding these commonly used regimens remains limited. Furthermore, the potential relationship between gallbladder status and symptomatic(pantoprazole 40 mg, sucralfate 1 g, ursodeoxycholic acid 250 mg), treatment response has not been adequately clarified. Therefore, the primary aim of this retrospective study was to compare

changes in symptom severity after six weeks of treatment among patients receiving these three regimens. The secondary objectives were to evaluate the association between gallbladder status and symptomatic improvement, assess baseline gastric histopathological findings, and explore histopathological changes in the subgroup of patients who underwent follow-up endoscopy.

2. Materials and Methods

Ethical approval was obtained from the Ethics Committee of Zonguldak University (Approval No. 2024/21, Meeting No. 2024/17, dated 2 October 2024).

Patients over 18 years of age who presented to the Endoscopy Unit of Kastamonu Training and Research Hospital with dyspeptic complaints and were found to have bile accumulation in the stomach or reflux of bilious content from the pylorus were retrospectively identified as having duodenogastric reflux (DGR), also known as alkaline reflux disease. Treatment allocation was not randomized. Patients had received PPI(pantoprazole 40 mg), PPI + sucralfate(pantoprazole 40 mg once daily and sucralfate 1 g three times daily), or PPI + UDCA(pantoprazole 40 mg once daily and ursodeoxycholic acid 250 mg three times daily) as part of routine clinical practice, and the treatment groups were subsequently identified retrospectively from the medical records.

Follow-up data at 6 weeks were retrospectively retrieved from the hospital information system. Symptom severity before treatment and at the 6-week follow-up was assessed using a Modified Likert Scale (0–3: 0 = no symptoms, 1 = mild, 2 = moderate, and 3 = severe), based on symptom assessments documented during routine clinical follow-up. Information regarding alcohol and tobacco use was also obtained from the medical records.

Patient records in the hospital database were reviewed to collect data on administered treatments, comorbidities, age, smoking status, history of cholecystectomy, presence of gallstones, and baseline histopathological findings. Treatment allocation was not randomized and was determined by the treating physician as part of routine clinical practice; no predefined clinical criterion or study-specific algorithm was used to select among the treatment regimens. The treatment regimens were PPI plus sucralfate (pantoprazole 40 mg once daily and sucralfate 1 g three times daily), PPI plus UDCA (pantoprazole 40 mg once daily and ursodeoxycholic acid 250 mg three times daily), or PPI alone (pantoprazole 40 mg once daily). Treatment duration was 6 weeks in all groups. No additional medications specifically targeting DGR or related upper gastrointestinal symptoms were used during the 6-week treatment period. Only patients who attended the 6-week follow-up and whose medical records documented complete adherence to the prescribed treatment were included in the analysis. No *H. pylori* eradication therapy was administered during the 6-week treatment period. *H. pylori* was assessed histopathologically from gastric biopsy specimens, and pathology results were typically available around the 6-week follow-up; therefore, eradication therapy did not influence symptom outcomes during the study treatment period.

The primary outcome was the change in Modified Likert symptom severity from baseline to 6 weeks (Δ symptom score = baseline score − 6-week score), with higher values indicating greater symptomatic improvement. Baseline, 6-week, and change scores were compared among treatment groups. All 77 included patients had complete baseline and 6-week symptom data; therefore, no imputation was performed for the primary outcome. Gastric biopsy results were retrieved from the hospital system, focusing on histopathological activation, inflammation, intestinal metaplasia, and *H. pylori* grade.

Patients were also grouped based on gallbladder status:

- Group A: Normal gallbladder.
- Group B: Gallstones present.
- Group C: History of cholecystectomy.

Symptom scores and gastric pathology outcomes were compared among these groups using statistical methods. Follow-up endoscopy was not systematically performed in all patients and was conducted as part of routine clinical follow-up rather than by a study-specific protocol. Therefore, histopathological follow-up analyses were restricted to the 16 patients for whom both baseline and follow-up endoscopic biopsy results were available in the hospital records. Changes in pathological findings (inflammation, activation, intestinal metaplasia, and *H. pylori*) were analyzed within this subgroup according to treatment group and gallbladder status. Because the availability of follow-up endoscopy was not based on a standardized research protocol, this subgroup may be subject to selection bias and should not be considered representative of the entire cohort.

Follow-up endoscopy was routinely recommended as part of clinical care; however, most patients declined repeat endoscopy. Consequently, paired baseline and follow-up endoscopic biopsy data were available for only 16 patients. No additional endoscopic procedures were performed solely for research purposes. As this was a completed retrospective study based on existing clinical records, the number of patients with paired histopathological data could not be increased within the existing study dataset.

Patients with prior treatment for gastric complaints, known malignancy, or history of biliary surgery other than gastric or cholecystectomy procedures were excluded.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized using mean ± standard deviation and, for ordinal/non-normally distributed variables, median and interquartile range (Q1–Q3); categorical variables were summarized as number and percentage. Within-group changes in symptom scores were assessed using the Wilcoxon signed-rank test. Between-group comparisons of symptom scores and ordinal histopathological variables were performed using the Kruskal–Wallis test. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate; exact tests were used when expected cell frequencies were small. Paired baseline and follow-up histopathological scores in the 16 patients with repeat endoscopy were compared using two-sided exact Wilcoxon signed-rank tests to account for the small number of nonzero paired differences and tied ranks. The four histopathological p-values were reported without multiplicity adjustment, and a Bonferroni threshold of 0.0125 (0.05/4) was considered as a sensitivity assessment; treatment-specific histopathological change scores in this subgroup were compared using the Kruskal–Wallis test as exploratory analyses. In addition to the primary unadjusted analysis of symptom-score change, a post-hoc sensitivity analysis was performed to account for potential confounding associated with nonrandomized treatment allocation. Symptomatic response was defined as any improvement in symptom score from baseline to 6 weeks (Δ symptom score > 0), whereas $\Delta = 0$ was classified as no response. Binary logistic regression was performed with symptomatic response as the dependent variable and treatment group as the main independent variable, adjusting for baseline symptom score, age, sex, and Charlson Comorbidity Index. The PPI-alone group was used as the reference category. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Because this dichotomized outcome was defined post hoc, the analysis was considered a sensitivity analysis and did not replace the primary analysis based on the original symptom-change score. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

3. Results

Patients who presented to the Endoscopy Unit of Kastamonu Training and Research Hospital with dyspeptic complaints between December 2023 and December 2024 were retrospectively screened for gastroscopic findings. Only patients with biliary content in the stomach or endoscopically observed pyloric reflux of bilious content were included. Patients over 18 years of age who had previously received treatment for gastric complaints were excluded. A total of 77 patients were included; 59 were female and 18 were male. The mean age was 48.7 years (range, 18–79 years). The mean Charlson Comorbidity Index (CCI) was 1.28 ± 1.32.

No statistically significant between-group differences were detected in the measured baseline characteristics, including age, CCI, sex, gallbladder status, smoking status, baseline symptom severity, activation, inflammation, intestinal metaplasia, or *H. pylori* grade (Table 1). Smoking status was unknown in 27 of 77 patients (35.1%).

Table 1. Baseline Demographic and Clinical Characteristics According to Treatment Group.

Feature	PPI + Sucralfate (n = 32)	PPI + UDCA (n = 31)	PPI (n = 14)	*p*-Value
Age (years), mean ± SD	47.06 ± 13.77	49.48 ± 16.83	50.93 ± 18.48	0.486
Charlson Comorbidity Index, mean ± SD	1.13 ± 1.18	1.29 ± 1.37	1.64 ± 1.55	0.591
Sex, n (%)	Female 27 (84.4%); Male 5 (15.6%)	Female 23 (74.2%); Male 8 (25.8%)	Female 9 (64.3%); Male 5 (35.7%)	0.311
Gallbladder status, n (%)	Normal 19 (59.4%); Gallstones 5 (15.6%); Cholecystectomy 8 (25.0%)	Normal 13 (41.9%); Gallstones 7 (22.6%); Cholecystectomy 11 (35.5%)	Normal 5 (35.7%); Gallstones 2 (14.3%); Cholecystectomy 7 (50.0%)	0.437 *
Smoking status, n (%)	No 14 (43.8%); Yes 6 (18.8%); Unknown 12 (37.5%)	No 19 (61.3%); Yes 1 (3.2%); Unknown 11 (35.5%)	No 8 (57.1%); Yes 2 (14.3%); Unknown 4 (28.6%)	0.315 *
Baseline symptom score, mean ± SD	2.62 ± 0.83	2.71 ± 0.46	2.79 ± 0.43	0.851
Baseline activation grade, n (%)				0.777
Grade 0	20 (62.5%)	22 (71.0%)	9 (64.3%)	
Grade 1	6 (18.8%)	4 (12.9%)	4 (28.6%)	
Grade 2	1 (3.1%)	2 (6.5%)	0 (0.0%)	
Grade 3	5 (15.6%)	3 (9.7%)	1 (7.1%)	
Baseline inflammation grade, n (%)				0.136
Grade 0	4 (12.5%)	1 (3.2%)	0 (0.0%)	
Grade 1	20 (62.5%)	17 (54.8%)	12 (85.7%)	
Grade 2	1 (3.1%)	1 (3.2%)	0 (0.0%)	
Grade 3	7 (21.9%)	12 (38.7%)	2 (14.3%)	

Table 1. *Cont.*

Feature	PPI + Sucralfate (n = 32)	PPI + UDCA (n = 31)	PPI (n = 14)	*p*-Value
Baseline intestinal metaplasia grade, n (%)				0.987
Grade 0	25 (78.1%)	24 (77.4%)	11 (78.6%)	
Grade 1	7 (21.9%)	6 (19.4%)	3 (21.4%)	
Grade 2	0 (0.0%)	1 (3.2%)	0 (0.0%)	
Baseline *H. pylori* grade, n (%)				0.626
Grade 0	22 (68.8%)	21 (67.7%)	8 (57.1%)	
Grade 1	7 (21.9%)	7 (22.6%)	3 (21.4%)	
Grade 2	1 (3.1%)	1 (3.2%)	1 (7.1%)	
Grade 3	2 (6.3%)	2 (6.5%)	2 (14.3%)	

Note: Data are presented as mean ± SD or n (%) with percentages calculated within each treatment group. * Fisher's exact test. Smoking status was unknown in 27/77 patients (35.1%). The *p*-values for baseline histopathological grades were obtained using Kruskal–Wallis tests; all were unadjusted. Histopathological grades are coded on the ordinal scales shown in the table.

The treatment regimens identified retrospectively were PPI alone, PPI + UDCA, and PPI + sucralfate. A Modified Likert Scale was used to assess symptom severity at presentation and after 6 weeks of treatment. Symptoms assessed included dyspeptic complaints such as bloating and abdominal pain. The scale ranged from 0 to 3 (0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe). Symptom change (ΔSymptom) was calculated as the pre-treatment score minus the post-treatment score.

Symptom scores decreased significantly from baseline to 6 weeks within each treatment group (Table 2).

Table 2. Changes in Symptom Scores According to Treatment Group.

Measure	PPI + Sucralfate (n = 32)	PPI + UDCA (n = 31)	PPI (n = 14)	Between-Group *p*
Baseline	3 (3–3); 2.63 ± 0.83	3 (2–3); 2.71 ± 0.46	3 (2.75–3); 2.79 ± 0.43	0.851
6-week	1 (0–2.75); 1.31 ± 1.23	1 (0–2); 1.35 ± 1.11	2 (1–3); 1.86 ± 0.86	0.244
Δ symptom score	1 (0–2); 1.31 ± 1.18	1 (0–2); 1.35 ± 1.02	1 (0–2); 0.93 ± 0.92	0.457
Within-group *p*	<0.001	<0.001	0.009	—

Note: Data are presented as median (Q1–Q3) and mean ± SD. Within-group comparisons were performed using the Wilcoxon signed-rank test; between-group comparisons used the Kruskal–Wallis test. Δ symptom score = baseline − 6-week score; higher values indicate greater symptomatic improvement.

No statistically significant differences were found among treatment groups in baseline symptom scores, post-treatment symptom scores, or ΔSymptom (Table 2). Thus, although symptomatic improvement was observed within all three treatment groups, the magnitude of improvement did not differ significantly among the regimens.

Thus, although symptomatic improvement was observed within all three treatment groups, the magnitude of improvement did not differ significantly among the regimens. The results of the post-hoc adjusted sensitivity analysis are presented in Table 3.

Table 3. Post-hoc Adjusted Sensitivity Analysis for Symptomatic Response.

Variable	Adjusted OR	95% CI	*p*-Value
Treatment group (overall)	—	—	0.414
PPI + Sucralfate vs. PPI	1.90	0.46–7.92	0.377
PPI + UDCA vs. PPI	2.64	0.63–11.04	0.184
Baseline symptom score	1.315	0.571–3.030	0.520
Age	1.020	0.960–1.085	0.515
Charlson Comorbidity Index	1.231	0.566–2.674	0.600
Sex	0.830	0.235–2.929	0.772

Note: Symptomatic response was defined as Δ symptom score > 0. Binary logistic regression was adjusted for baseline symptom score, age, sex, and Charlson Comorbidity Index; PPI alone was the reference treatment category. Hosmer–Lemeshow $p = 0.562$. This post-hoc analysis was considered a sensitivity analysis and did not replace the primary analysis of the original symptom-change score.

As a post-hoc sensitivity analysis, symptomatic response (Δ symptom score > 0) was observed in 21/32 (65.6%) patients receiving PPI + sucralfate, 23/31 (74.2%) receiving PPI + UDCA, and 8/14 (57.1%) receiving PPI alone (unadjusted $p = 0.504$). In binary logistic regression adjusted for baseline symptom score, age, sex, and Charlson Comorbidity Index, treatment group was not independently associated with symptomatic response (overall $p = 0.414$). Compared with PPI alone, the adjusted OR was 1.90 (95% CI, 0.46–7.92; $p = 0.377$) for PPI + sucralfate and 2.64 (95% CI, 0.63–11.04; $p = 0.184$) for PPI + UDCA. The Hosmer–Lemeshow test showed no evidence of poor model fit ($p = 0.562$). The wide confidence intervals indicate considerable imprecision and should be interpreted in the context of the limited sample size.

When symptoms were assessed according to gallbladder status, significant within-group reductions were observed in patients with a normal gallbladder, gallstones, and a history of cholecystectomy. However, the magnitude of symptom improvement did not differ significantly among the three gallbladder-status groups (Kruskal–Wallis $\chi^2 = 1.556$, df = 2, $p = 0.459$) (Table 4).

Table 4. Changes in Symptom Scores According to Gallbladder Status.

Measure	Normal Gallbladder (n = 37)	Gallstones (n = 14)	Cholecystectomy (n = 26)	Between-Group *p*
Baseline	3 (2–3); 2.62 ± 0.64	3 (2–3); 2.71 ± 0.47	3 (3–3); 2.77 ± 0.71	—
6-week	1 (0–3); 1.51 ± 1.22	1 (0.75–2); 1.29 ± 0.99	1 (0–2); 1.38 ± 1.10	—
Δ symptom score	1 (0–2); 1.11 ± 1.10	2 (0–2); 1.43 ± 1.09	1 (0.75–2); 1.38 ± 1.02	0.459
Within-group *p*	<0.001	0.004	<0.001	—

Note: Data are presented as median (Q1–Q3) and mean ± SD. Within-group comparisons were performed using the Wilcoxon signed-rank test. The between-group comparison of Δ symptom scores was performed using the Kruskal–Wallis test ($\chi^2 = 1.556$, df = 2, $p = 0.459$).

Histopathological parameters from gastric biopsies were evaluated according to gallbladder status. The cholecystectomy group had numerically higher mean inflammation, activation, *H. pylori*, and intestinal metaplasia scores than the other groups; however, none of the between-group differences were statistically significant (Table 5).

Table 5. Histopathological Results Based on Gallbladder Pathology.

Histopathological Parameter	Group 1: Normal Gallbladder (n = 37) Mean ± SD	Group 2: Gallstones (n = 14) Mean ± SD	Group 3: Cholecystectomy (n = 26) Mean ± SD	*p*-Value
Activation	0.514 ± 0.837	0.357 ± 0.497	0.654 ± 1.129	0.760
Inflammation	1.405 ± 0.926	1.357 ± 0.929	1.731 ± 1.041	0.349
Intestinal Metaplasia	0.216 ± 0.417	0.214 ± 0.426	0.269 ± 0.534	0.891
Helicobacter pylori	0.541 ± 1.016	0.571 ± 1.089	0.731 ± 1.002	0.604

Paired baseline and follow-up biopsy results were available for 16 patients who underwent repeat endoscopy as part of routine clinical care. Activation grades decreased in six patients, increased in one, and were unchanged in nine. Although the asymptotic Wilcoxon result for activation was $p = 0.046$, the two-sided exact Wilcoxon *p*-value was 0.078. Exact *p*-values were 0.094 for inflammation, 0.625 for intestinal metaplasia, and 0.307 for *H. pylori* grade (Table 6). None of the four outcomes was statistically significant using two-sided exact testing. These exploratory *p*-values were unadjusted for multiple comparisons; none met the Bonferroni-adjusted threshold of 0.0125.

Table 6. Paired Histopathological Findings in Patients Who Underwent Follow-up Endoscopy (n = 16).

Parameter	Baseline, Median (Q1–Q3)	Follow-Up, Median (Q1–Q3)	Asymptotic Z	Exact *p*-Value (Two-Sided)
Activation	0 (0–3)	0 (0–0)	−1.994	0.078
Inflammation	1 (1–3)	1 (1–1)	−1.947	0.094
Intestinal metaplasia	0 (0–1)	0 (0–0)	−1.000	0.625
H. pylori grade	1 (0–1)	0 (0–1)	−1.291	0.307

Note: Paired baseline and follow-up histopathological grades were assessed using two-sided exact Wilcoxon signed-rank tests (n = 16). Reported *p*-values are unadjusted for multiple comparisons. None met the Bonferroni-adjusted threshold of $p < 0.0125$ for four outcomes. Histopathological analyses were exploratory owing to the small, selected subgroup and frequent unchanged scores.

Exploratory analyses of histopathological changes according to treatment group did not identify statistically significant between-group differences for activation ($p = 0.975$), inflammation ($p = 0.799$), intestinal metaplasia ($p = 0.581$), or *H. pylori* ($p = 0.083$) (Table 7). The treatment-specific subgroup sizes were small and unequal (n = 8, n = 5, and n = 3); therefore, these analyses should be interpreted as exploratory.

Table 7. Comparison of Histopathological Changes Among Treatment Groups in Patients Who Underwent Follow-up Endoscopy.

Histopathological Parameter	PPI + Sucralfate (n = 8), Mean Rank	PPI + UDCA (n = 5), Mean Rank	PPI (n = 3), Mean Rank	χ^2	*p*-Value
Activation change	8.63	8.60	8.00	0.050	0.975
Inflammation change	9.19	7.80	7.83	0.449	0.799
Intestinal metaplasia change	9.38	8.00	7.00	1.087	0.581
H. pylori change	10.44	8.30	3.67	4.983	0.083

Note: Changes in histopathological parameters were compared among the three treatment groups using the Kruskal–Wallis test. Analyses were exploratory because of the small and unequal treatment-group sizes (n = 8, n = 5, and n = 3).

4. Discussion

Duodenogastric reflux (DGR) gastritis is a clinical condition characterized by the retrograde flow of duodenal contents into the stomach, potentially contributing to gastric mucosal injury and dyspeptic symptoms [2]. In our study, we aimed to investigate the effects of treatments given to patients with DGR gastritis on their symptoms and histopathological outcomes, as well as the impact of gallbladder pathologies on symptoms and gastric pathologies in these patients.

Patients with DGR gastritis typically present with dyspeptic complaints such as abdominal pain, bloating, and heartburn [14]. These symptoms are not specific to DGR. The diagnosis of this disease is based on the endoscopic visualization of bile reflux or the presence of bile, pathological evaluation of the gastric mucosa, measuring the pH of the bile-containing content in the stomach, or measuring bilirubin levels [15,16]. In our study, we evaluated cases where bile-containing content was directly seen in the stomach or the presence of duodenal content was observed endoscopically.

Although medical treatment is predominantly used for DGR, surgical interventions may be considered in selected refractory cases. Proton pump inhibitors (PPIs) are used in the management of alkaline reflux, although their role in non-acid reflux is not fully established. In a randomized controlled trial involving 60 patients who had undergone cholecystectomy, sucralfate and rabeprazole were compared with no treatment, and epigastric pain relief was reported more frequently in the sucralfate group [11]. UDCA has also been investigated as a treatment option and may modify the composition and mucosal effects of refluxed bile [17]. More recent reviews have included UDCA among the pharmacological options for bile reflux gastritis while emphasizing that management remains insufficiently standardized [13]. In our retrospective cohort, 32 patients received PPI + sucralfate (sucralfate 1 g three times daily), 31 received PPI + UDCA (ursodeoxycholic acid 250 mg three times daily), and 14 received PPI alone (pantoprazole 40 mg once daily). Symptom scores decreased significantly within all three groups, but the magnitude of improvement did not differ significantly among treatment regimens. Therefore, any numerical differences observed in symptom improvement among the treatment groups should not be interpreted as evidence of greater efficacy of one regimen over another. Among the 16 patients who underwent follow-up endoscopy, activation scores decreased significantly in the cohort as a whole ($p = 0.046$); treatment-specific histopathological comparisons were not statistically significant and should be regarded as exploratory. McCabe et al. proposed a stepwise approach beginning with PPI and subsequently considering UDCA, sucralfate, combination therapy, and, in refractory cases, surgical diversion [3]. More recently, Parlak et al. reported clinical and histopathological improvement following combined sucralfate and UDCA treatment in pediatric patients with duodenogastric reflux disease [18]. However, the pediatric population limits the direct applicability of these findings to adult patients. Our findings support symptomatic improvement during medical treatment but do not establish superiority or equivalence of any regimen because of the retrospective, non-randomized design and limited sample size. In the post-hoc adjusted sensitivity analysis, treatment group was likewise not independently associated with symptomatic response; however, the wide confidence intervals indicate substantial imprecision, and these findings should not be interpreted as evidence of therapeutic equivalence. Importantly, symptomatic improvement should not be interpreted as evidence of a reduction in duodenogastric bile reflux itself. Bile reflux was not quantitatively reassessed after treatment in the overall cohort; therefore, the present findings demonstrate symptomatic response rather than objective resolution of or reduction in bile reflux.

Several studies have reported an association between gallbladder pathology and DGR [19]. In cholelithiasis, alterations in gallbladder storage and emptying may affect the

delivery of bile to the duodenum [20]. After cholecystectomy, continuous bile flow into the duodenum has been proposed as a potential mechanism contributing to DGR [21], although other studies have not demonstrated a clear increase in duodenogastric reflux after cholecystectomy [22]. In our cohort, 26 of 77 patients (33.8%) had undergone cholecystectomy, 14 (18.2%) had gallstones, and 37 (48.1%) had a normal gallbladder. Symptom scores decreased significantly within all three gallbladder-status groups. Although numerical differences in symptom reduction were observed, the between-group difference was not statistically significant. Therefore, the present data do not demonstrate that gallbladder status independently modifies short-term symptomatic response to treatment.

Bile-containing duodenal content may injure the gastric mucosa and has been associated with histopathological changes includin–g atrophy, intestinal metaplasia, and dysplasia [23]. Studies evaluating the relationship among cholecystectomy, bile reflux, and *H. pylori* have reported inconsistent findings [23–25]. In our study, mean activation, inflammation, intestinal metaplasia, and *H. pylori* scores were numerically higher in the cholecystectomy group than in the normal-gallbladder and gallstone groups; however, none of these differences reached statistical significance. Accordingly, these numerical trends should not be interpreted as evidence of a detrimental effect of cholecystectomy on gastric histopathology in this cohort.

Among the 16 patients with paired histopathological assessments, activation grades decreased in six patients, increased in one, and remained unchanged in nine. The previously reported asymptotic Wilcoxon p-value of 0.046 for activation was not supported by the two-sided exact test ($p = 0.078$). Exact tests likewise found no statistically significant changes in inflammation ($p = 0.094$), intestinal metaplasia ($p = 0.625$), or *H. pylori* grade ($p = 0.307$). All four p-values were unadjusted for multiple comparisons, and none met the Bonferroni-adjusted threshold of 0.0125. These results do not establish histopathological treatment efficacy and should be interpreted as exploratory, given the small and selected subgroup and frequent tied or unchanged observations.

Although follow-up endoscopy was routinely recommended, most patients declined the procedure, resulting in paired histopathological data for only 16 patients. This patient-dependent participation may have introduced selection bias, as patients who underwent repeat endoscopy could differ systematically from those who declined. Therefore, the histopathological findings should be regarded as exploratory and interpreted with caution. The limited number of patients undergoing follow-up endoscopy reflects a constraint of the completed retrospective dataset rather than a sample-size decision that could be modified within that dataset. This limitation reduces statistical power and precision and increases uncertainty in the histopathological analyses, but it does not affect the completeness of baseline and six-week symptom data for all 77 included patients. Future prospective studies should incorporate predefined follow-up schedules, standardized indications for repeat endoscopy, and adequately powered sample sizes to provide more reliable estimates of histopathological treatment response.

This study has several limitations. First, its retrospective, single-center, non-randomized design introduces the possibility of selection bias and confounding by indication. The absence of statistically significant differences in the measured baseline characteristics does not eliminate residual or unmeasured confounding and should not be considered equivalent to comparability achieved through randomization. Second, the sample size was modest, particularly in the PPI-only group, limiting the power to detect between-group differences. The adjusted sensitivity analysis also produced wide confidence intervals, reflecting substantial imprecision. Third, inclusion was restricted to patients who attended the 6-week follow-up and had documented complete treatment adherence, which may have introduced additional selection bias and may limit the generalizability of the observed symptomatic response to

less adherent patients. Smoking status was unknown in 27 of 77 patients (35.1%), which further limits interpretation of smoking as a baseline characteristic. Fourth, follow-up endoscopy was available in only 16 patients, creating potential selection bias and substantially limiting treatment-specific histopathological comparisons. Because repeat endoscopy was not performed systematically according to a study-specific follow-up protocol, patients undergoing repeat endoscopy may differ clinically from those without endoscopic follow-up. Consequently, the histopathological findings from this subgroup should be regarded as exploratory and should not be generalized to the entire cohort. Exact paired testing did not demonstrate statistically significant histopathological changes, and none of the four unadjusted *p*-values met the Bonferroni-adjusted threshold. Fifth, DGR was identified endoscopically rather than by objective quantitative reflux assessment such as bilirubin monitoring or other physiological measurements, and bile reflux was not systematically reassessed after treatment. Therefore, the observed symptom improvement reflects short-term symptomatic response and should not be interpreted as objective reduction or resolution of duodenogastric bile reflux. Accordingly, the absence of statistically significant differences between treatment groups should not be interpreted as evidence of therapeutic equivalence. Strengths of the study include the comparison of three commonly used medical regimens, assessment of gallbladder status, and evaluation of both symptomatic and histopathological outcomes in a real-world DGR cohort.

5. Conclusions

In conclusion, PPI, PPI + sucralfate, and PPI + UDCA regimens were each associated with significant short-term symptomatic improvement in patients with DGR gastritis, but no statistically significant difference in the magnitude of symptom improvement was demonstrated among treatment groups. The post-hoc adjusted sensitivity analysis did not identify an independent association between treatment group and symptomatic response; however, the estimates were imprecise and do not establish therapeutic equivalence. Gallbladder status was not significantly associated with the magnitude of short-term symptom improvement. Histopathological follow-up was available for only 16 patients; no paired histopathological outcome was statistically significant using two-sided exact Wilcoxon tests, and none met the Bonferroni-adjusted threshold. These findings should be considered exploratory rather than evidence of histopathological treatment efficacy. Larger prospective studies with predefined treatment allocation, objective reflux assessment, and systematic endoscopic follow-up are needed.

Author Contributions: Conceptualization, Y.A.Y.; methodology, Y.A.Y.; software, Y.A.Y.; validation, Y.A.Y. and M.A.; formal analysis, Y.A.Y.; investigation, Y.A.Y.; resources, Y.A.Y. and M.A.; data curation, Y.A.Y. and M.A.; writing—original draft preparation, Y.A.Y.; writing—review and editing, Y.A.Y.; visualization, Y.A.Y. and M.A.; supervision, Y.A.Y.; funding acquisition, Y.A.Y. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was approved by the Ethics Committee of Zonguldak University (Approval No. 2024/21, Meeting No. 2024/17; 2 October 2024).

Informed Consent Statement: Individual informed consent was not obtained due to the retrospective nature of the study.

Data Availability Statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request, subject to applicable ethical and privacy restrictions.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

DGR	Duodenogastric reflux
GERD	Gastroesophageal reflux disease
H. pylori	*Helicobacter pylori*
UDCA	Ursodeoxycholic acid

References

1. Beaumont, W. Experiments and observations on the gastric juice and the physiology of digestion. *Nutr. Rev.* **1977**, *35*, 144–145. [CrossRef]
2. Vere, C.C.; Cazacu, S.; Comănescu, V.; Mogoantă, L.; Rogoveanu, I.; Ciurea, T. Endoscopical and histological features in bile reflux gastritis. *Rom. J. Morphol. Embryol.* **2005**, *46*, 269–274.
3. McCabe, M.E., IV; Dilly, C.K. New causes for the old problem of bile reflux gastritis. *Clin. Gastroenterol. Hepatol.* **2018**, *16*, 1389–1392. [CrossRef]
4. Testoni, P.A.; Fanti, L.; Passaretti, S.; Masci, E.; Guslandi, M.; Tittobello, A. Interdigestive motility pattern in subjects with duodenogastric bile reflux. *Scand. J. Gastroenterol.* **1987**, *22*, 757–762. [CrossRef]
5. Livzan, M.A.; Mozgovoi, S.I.; Gaus, O.V.; Bordin, D.S.; Kononov, A.V. Diagnostic Principles for Chronic Gastritis Associated with Duodenogastric Reflux. *Diagnostics* **2023**, *13*, 186. [CrossRef]
6. Naylor, G.; Axon, A. Role of bacterial overgrowth in the stomach as an additional risk factor for gastritis. *Can. J. Gastroenterol.* **2003**, *17*, 13B–17B. [CrossRef]
7. Kawai, Y.; Tazuma, S.; Inoue, M. Bile acid reflux and possible inhibition of *Helicobacter pylori* infection in subjects without gastric surgery. *Dig. Dis. Sci.* **2001**, *46*, 1779–1783. [CrossRef]
8. Li, D.; Zhang, J.; Yao, W.Z.; Zhang, D.L.; Feng, C.C.; He, Q.; Lv, H.H.; Cao, Y.P.; Wang, J.; Qi, Y.; et al. The relationship between gastric cancer, its precancerous lesions and bile reflux: A retrospective study. *J. Dig. Dis.* **2020**, *21*, 222–229. [CrossRef]
9. Bruzzi, M.; Chevallier, J.M.; Czernichow, S. One-anastomosis gastric bypass: Why biliary reflux remains controversial? *Obes. Surg.* **2017**, *27*, 545–547. [CrossRef]
10. Perdikis, G.; Wilson, P.; Hinder, R.; Redmond, E.; Wetscher, G.; Neary, P.; Adrian, T.; Quigley, E. Altered antroduodenal motility after cholecystectomy. *Am. J. Surg.* **1994**, *168*, 609–615. [CrossRef]
11. Santarelli, L.; Gabrielli, M.; Candelli, M.; Cremonini, F.; Nista, E.C.; Cammarota, G.; Gasbarrini, G.; Gasbarrini, A. Post-cholecystectomy alkaline reactive gastritis: A randomized trial comparing sucralfate versus rabeprazole or no treatment. *Eur. J. Gastroenterol. Hepatol.* **2003**, *15*, 975–979. [CrossRef]
12. Wu, Z.Y.; Zhang, M.H.; Li, Y.; Deng, J.Y.; Liu, L.Y.; Chen, C.; Du, H.B.; Guo, Y. Clinical Efficacy of Ursodeoxycholic Acid in Bile Reflux Gastritis: A Systematic Review and Meta-Analysis. *Dig. Dis. Sci.* **2026**, *71*, 551–560. [CrossRef]
13. Shi, X.; Chen, Z.; Yang, Y.; Yan, S. Bile Reflux Gastritis: Insights into Pathogenesis, Relevant Factors, Carcinomatous Risk, Diagnosis, and Management. *Gastroenterol. Res. Pract.* **2022**, *2022*, 2642551. [CrossRef]
14. Tack, J.; Koek, G.; Demedts, I.; Sifrim, D.; Janssens, J. Gastroesophageal reflux disease poorly responsive to single-dose proton pump inhibitors in patients without Barrett's esophagus: Acid reflux, bile reflux, or both? *Am. J. Gastroenterol.* **2004**, *99*, 981–988. [CrossRef]
15. Boeckxstaens, G.E.; Smout, A. Systematic review: Role of acid, weakly acidic and weakly alkaline reflux in gastro-oesophageal reflux disease. *Aliment. Pharmacol. Ther.* **2010**, *32*, 334–343. [CrossRef]
16. Al-Bayati, S.; Alnajjar, A.S. Evaluation of the gastrointestinal clinical, endoscopic, and histological findings in patients with bile reflux diseases: A cross-sectional study. *Mustansiriya Med. J.* **2019**, *18*, 10–15. [CrossRef]
17. Krishna-Subramanian, S.; Hanski, M.L.; Loddenkemper, C.; Choudhary, B.; Pagès, G.; Zeitz, M.; Hanski, C. UDCA slows down intestinal cell proliferation by inducing high and sustained ERK phosphorylation. *Int. J. Cancer* **2012**, *130*, 2771–2782. [CrossRef]
18. Parlak, M.E.; Atalay, A.; Yılmaz, A. Clinical and Histopathologic Efficiency of Sucralfate and Ursodeoxicolic Acid in Pediatric Duodenogastric Reflux Disease. *Med. Rec.* **2023**, *5*, 9–14. [CrossRef]
19. Stathopoulos, P.; Zundt, B.; Spelsberg, F.W.; Kolligs, L.; Diebold, J.; Goke, B.; Jungst, D. Relation of gallbladder function and *Helicobacter pylori* infection to gastric mucosa inflammation in patients with symptomatic cholecystolithiasis. *Digestion* **2006**, *73*, 69–74. [CrossRef]
20. Housset, C.; Chrétien, Y.; Debray, D.; Chignard, N. Functions of the gallbladder. *Compr. Physiol.* **2016**, *6*, 1549–1577. [CrossRef]
21. Shah Gilani, S.N.; Bass, G.A.; Kharytaniuk, N.; Downes, M.R.; Caffrey, E.F.; Tobbia, I.; Walsh, T.N. Gastroesophageal mucosal injury after cholecystectomy: An indication for surveillance? *J. Am. Coll. Surg.* **2017**, *224*, 319–326. [CrossRef]

22. Manifold, D.K.; Anggiansah, A.; Owen, W.J. Effect of cholecystectomy on gastroesophageal and duodenogastric reflux. *Am. J. Gastroenterol.* **2000**, *95*, 2746–2750. [CrossRef]
23. Dixon, M.F.; O'Connor, H.J.; Axon, A.T.; King, R.F.; Johnston, D. Reflux gastritis: Distinct histopathological entity? *J. Clin. Pathol.* **1986**, *39*, 524–530. [CrossRef]
24. Atak, I.; Ozdil, K.; Yücel, M.; Caliskan, M.; Kilic, A.; Erdem, H.; Alimoglu, O. The effect of laparoscopic cholecystectomy on the development of alkaline reflux gastritis and intestinal metaplasia. *Hepatogastroenterology* **2012**, *59*, 59–61. [CrossRef]
25. Zullo, A.; Rinaldi, V.; Hassan, C.; Lauria, V.; Attili, A.F. Gastric pathology in cholecystectomy patients: Role of *Helicobacter pylori* and bile reflux. *J. Clin. Gastroenterol.* **1998**, *27*, 335–338. [CrossRef]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.