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The Prevalence of Bile Reflux Gastritis Following Cholecystectomy: A Meta-Analysis and Systematic Review

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Abstract

Purpose: We reviewed the most current available evidence on the prevalence of bile reflux gastritis following cholecystectomy.

Methods: The literature search was performed in PubMed, Google Scholar, and the Cochrane Library database.

Results: A total of four studies examining 135 patients were included. The mean age of patients was 54.1 ± 14.53 years. *Helicobacter pylori* infection was diagnosed in 51 (37.7%) patients preoperatively. The meta-analysis result showed a 49% prevalence of bile reflux gastritis following cholecystectomy at 31 ± 46.80 months postoperatively. Reported digestive symptoms included: Bloating, epigastric pain, heartburn, gastroesophageal disease, belching, stomach fullness, and vomiting. Furthermore, gastric endoscopic findings were: Chronic inflammation of gastric mucosa, neutrophil activation, glandular atrophic gastritis, bile stasis, edema, and fovea hyperplasia.

Conclusion: The prevalence of bile reflux gastritis after therapeutic cholecystectomy is high. The presence of gastrointestinal symptoms should prompt the consideration of bile reflux gastritis as a potential etiology.

Keywords: Bile reflux gastritis; Cholecystectomy; Gastritis; Gallbladder; Alkaline reflux

Introduction

Gallstone disease is commonly encountered in clinical practice. The prevalence of this disease is estimated at approximately 10% to 15% in the adult population in the United States (US) and 4.2% to 23% in China [1,2]. Gastrointestinal Symptoms (GIS) such as heartburn, vomiting, and epigastric pain may be indicative of the diagnosis of gallstone disease, however, some patients may be asymptomatic. Removal of the gallbladder (cholecystectomy) has proven to be an effective treatment method for gallstone disease and other biliary-related diseases resulting in the resolution of GIS [3]. Despite the benefit of cholecystectomy, bile reflux remains consistent after this procedure in some patients and is associated with the recurrence of GIS after surgery [4]. The mechanism leading to bile reflux following cholecystectomy is not fully understood.

It is suggested that the loss of storage function of the gallbladder causes impairment in the pattern of bile excretion, and loss of neuro-hormonal responses causing motility changes in the upper gastrointestinal system may lead to duodenogastric reflux and new occurrence of GIS [4,5]. This is significant because duodenogastric reflux causes chronic inflammation of the gastric tissue. Chronic inflammation is recognized as a risk factor for human cancer at various sites. One of the suggested underlying mechanisms involves greater production of carcinogenic reactive oxygen and nitrogen species which may occur due to prolonged activation of inflammatory cells. In the stomach, chronic inflammation caused by *Helicobacter pylori* (H-pylori) infection is a known precursor of gastric cancer [6,7]. The presence of bile acids in the stomach induces inflammation of the stomach's lining known as reactive gastritis. However, whether reactive gastritis is conducive to gastric cancer is not fully elucidated [8]. Several previous studies reported an increased occurrence of duodenogastric reflux after cholecystectomy [5,9]. To date, data on the prevalence of bile reflex gastritis following this surgical procedure is scattered in the literature, yet complaints of GIS remain consistent after cholecystectomy in some patients, and they might be at a higher risk of gastric cancer [8]. To our knowledge, this is the first systematic review and meta-analysis evaluating available evidence on the prevalence of bile reflux gastritis after gallbladder removal surgery.

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Thus, we thought to investigate the English language literature on the prevalence of bile reflux gastritis following cholecystectomy in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

Material and Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocol 2015 statement [10]. All stages of literature search, study selection, data extraction, and quality assessment were performed independently by 2 authors. Any disagreement was resolved by discussion and consensus with a third reviewer (HA). This systematic review and meta-analysis is under the registration process by the Prospective Register of Systematic Reviews (PROSPERO), with registration ID: CRD42024543490, available at https://www.crd.york.ac.uk/PROSPERO/#recordDetails.

Literature search

A systematic search was performed using an electronic search in PubMed, Google Scholar, and the Cochrane Library. The appropriate key terms and free text field search were performed for "bile reflux", "bile reflux gastritis", "gastritis", "alkaline gastritis", "duodenogastric reflux", "biliary gastritis", "cholecystectomy", "gallbladder removal". The search included all study designs, with further studies not captured by the search identified *via* bibliographic cross-referencing. Titles and abstracts were screened independently for full-text review by two investigators.

Inclusion criteria

The included studies were limited to adult (18 years) patients diagnosed with bile reflux gastritis and with a history of cholecystectomy surgery. Prospective and retrospective observational studies, randomized clinical trials, and non-comparative clinical studies were included. The data ranges from 2000 and the last search was performed in July 2024.

Exclusion criteria

Only studies published in English were included in this systematic review and meta-analysis. Abstracts, conference articles, opinion pieces, editorial letters, single case reports, reviews, and meta-analyses were excluded from the final review. Nonhuman studies and those without appropriate data published related to this study's primary and secondary outcomes were also excluded.

Data Extraction

Data on the included studies (author's name, year of publication, sample size, study design, age, reported symptoms, histopathological findings, follow-up time, and the results of each study were recorded). To ensure accuracy, the data extraction process was independently performed by two investigators and was reviewed by the senior investigator.

Statistical analysis

Data analysis was performed using the Stata/SE 18.0 software version. The main measure of the effect was prevalence (ratio of cases to the total population). Cochrane's test (Q-test) showing significant heterogeneity in the meta-analysis and (I^2) showing the amount of heterogeneity, ranging from 0% to 100% were used to assess the heterogeneity among studies. Random-effects meta-analysis was performed to estimate the main index, which was the pooled prevalence at the 95% confidence interval. Forest plots were used to show the pooled prevalence of bile reflux gastritis at 31 Standard Deviation (SD) 46.80 months following surgery on average. Small study publication bias effects were assessed using funnel plot visual inspection and Egger's test. Averages of quantitative variables were reported according to studies and were each weighted by sample size (N).

Results

The initial literature search retrieved a total of 483 studies from the database. After screening the study's titles and abstracts, 33 studies qualified for further analysis. Twenty-three studies were duplicates, and 3 studies were in languages other than English, therefore removed. Four studies met the final inclusion criteria. The included studies in this review were case series Figure 1.

Descriptive characteristics

A total of 135 patients were included in this systematic review and meta-analysis. The mean age of the patients was 54.1 ± 14.53 years. Furthermore, 51 (37.7%) patients were diagnosed with *H. pylori* infection preoperatively. The basic characteristics of the patients included in this study are shown in Table 1.

Digestive symptoms

All patients included in this study underwent cholecystectomy due to gallbladder stones and biliary diseases requiring the removal of the gallbladder. Reported digestive symptoms included: Bloating, epigastric pain, heartburn, Gastroesophageal Disease (GERD), belching, stomach fullness, and vomiting Table 1.

Outcome

The pooled estimation of meta-analysis of prevalence from the four studies reported a prevalence of 49%; *i.e.*, suggesting that 49 out of every 100 cholecystectomy surgeries experience bile reflux gastritis at 31 ± 46.80 months following surgery on average. The heterogeneity index is I^2=55.11% (Figure 2). Bile reflux gastritis was assessed using gastric biopsies and endoscopy in all studies. Gastric histopathological findings were: Chronic inflammation of gastric mucosa, Neutrophil activation, Glandular atrophic gastritis, bile stasis, edema, and fovea

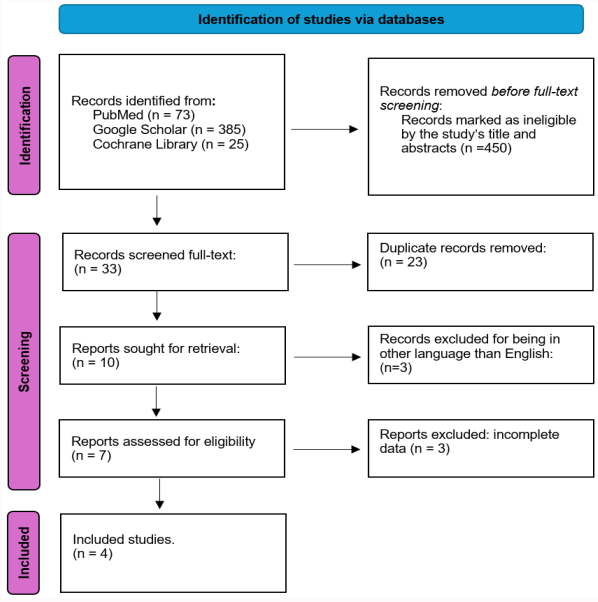

Figure 1: PRISMA flowchart of literature search and data extraction and selection (*n* represents the number of articles included).

Table 1: Basic characteristics of included studies.

Author	N	Age (years)	Study design	*H. pylori* (n)	Reposted gastrointestinal symptoms
Kuran et al. [12]	20	55.9	Prospective	10	-
Apea et al. [11]	31	74	Prospective	23	Bloating, epigastric pain, heart burn, belching, fullness
Mercan et al. [5]	50	43	Prospective cohort	14	-
Othman et al. [9]	34	43.53	Retrospective cohort	4	Epigastric pain, heart burn, vomiting, GERD

GERD: Gastroesophageal Reflux Disease; *H. pylori*: *Helicobacter pylori* infection; N: Total Number of Patients in each study; (n): number of patients diagnosed with *Helicobacter pylori* infection

Table 2: Quantitative data, diagnostic time and histopathological findings reported in included studies.

Author	N	Gastritis (n)	Time of gastritis diagnosis after surgery (months)	Screening	Gastric histopathological characteristics
Kuran et al. [12]	20	12	85	Biopsy	-
Apea et al. [11]	31	18	6	Biopsy, endoscopy	-
Mercan et al. [5]	50	15	2	Biopsy	Chronic inflammation, Neutrophil activation, Glandular atrophic gastritis
Othman et al. [9]	34	18	-	Biopsy, endoscopy	Chronic inflammation, chronic atrophic gastritis, bile stasis, edema, fovea hyperplasia

N: Total Number of Patients in each study; (n): number of patients diagnosed with bile reflux gastritis

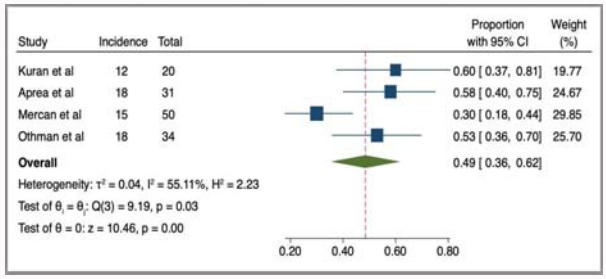

Figure 2: Forest plot showing the prevalence of bile reflux gastritis after cholecystectomy.

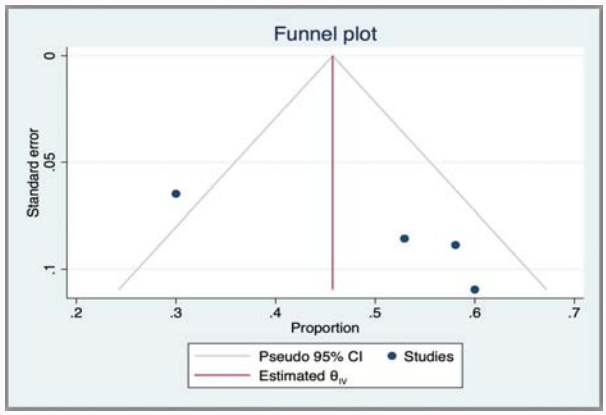

Figure 3: Bias publication assessment in the funnel plot.

hyperplasia Table 2.

Publication bias

The assessment for potential publication bias was initially performed using the funnel plot for studies symmetry and was not easy to assess given there were few studies included in this review. Whereas the result of Egger's test suggested no statistically significant evidence of publication bias (t=2.96, P=>0.097) Figure 3.

Discussion

Bile reflux gastritis (reactive gastritis) is a condition that is characterized by the backflow of duodenogastric fluid (bile acids, pancreatic and duodenal juices) into the stomach and esophagus leading to GIS such as epigastric pain, heartburn, vomiting, and GERD. Common gastric mucosal alterations that may be observed include chronic inflammation, erythema, the presence of bile in the stomach, erosion, gastric atrophy, intestinal metaplasia, and foveolar hyperplasia [4,5]. The cause leading to bile reflux in the stomach is multifactorial. Based on our findings and those of previous studies suggest that cholecystectomy seems to increase the risks for bile reflux gastritis, given that a significantly higher prevalence of bile reflux gastritis is diagnosed following surgery [11,12] (Figure 2).

Cholecystectomy can be a treatment method for patients with certain biliary disorders (gallstone disease). This procedure consists of the removal of the gallbladder, which might result in adverse effects to a certain degree due to the loss of the gallbladder storage function after surgery that may result in the release of the bile directly into the duodenum [3], moreover, cholecystectomy is associated with dysfunctional sphincter of Oddi after surgery, thus increasing the risk of bile reflux in the stomach [13]. The adverse effect of bile content on the gastric mucosa is mediated through inflammatory stimulation [4]. It is suggested that bile acids and lysolecithin are the major elements that damage the protective barriers of the gastric mucosa by dissolving phospholipids and cholesterol, which induces hydrogen ions in gastric juice to diffuse into gastric mucosa and increase the permeability of gastric epithelial cells [14-17], explaining the presence of histopathological changes of the gastric mucosa assessed in some patients included in this review. However, it is worth pointing out that several other factors might have contributed to the occurrence of gastritis diagnosed in these patients.

H. pylori infection is a known risk factor causing inflammatory changes to the gastric mucosa and a precursor of gastric cancer. This infection was prevalent in some patients included in this review (37.7%) Table 2, suggesting that the presence of gastric mucosal changes found in these patients could partly be due to the synergistic effect of the pre-existence of *H. pylori* infection. Based on available evidence, the impact of *H. pylori* infection on gastric mucosa in patients with bile reflux following cholecystectomy remains controversial [5], it was suggested that bile reflux following cholecystectomy may attenuate the colonization of *H. pylori* infection [18-21]. Conversely, a few other studies showed a higher colonization rate of this infection in patients with bile reflux after cholecystectomy [22,23]. Thus, solely from our findings, we could not determine whether the colonization

of *H. pylori* infection found in patients included in this review was impacted by the presence of bile reflux gastritis, whether this infection intensified the degree of bile reflux gastritis was difficult to determine. More studies with better designs are needed to better understand this possible association.

Diabetes mellitus was previously shown to be a risk factor for bile reflux gastritis [9]. This disorder is characterized by chronic hyperglycemia that may cause vagus nerve damage, resulting in delayed gastric emptying without mechanical obstruction (diabetic gastroparesis), increasing the risk for reflux of duodenal content in the stomach [24,25]. Moreover, obesity was also reported to be a risk factor for bile reflux gastritis [9]. This disease has been shown to play a role in the pathophysiological mechanisms of various diseases. How obesity would contribute to the occurrence of bile reflux gastritis is not clear, therefore more studies are needed.

GIS such as bloating, epigastric pain, heartburn, belching, fullness, vomiting, and GERD were the most common symptoms reported by patients included in this study. however, the presence of GIS was not proportional to the diagnosis of bile reflux gastritis as some patients were asymptomatic but with bile reflux gastritis, which can make the diagnosis challenging for physicians in the clinical setting. To date, there is no golden standard for diagnosing bile reflux gastritis [26].

Endoscopy and tissue biopsies were the major screening techniques for the diagnosis of bile reflux gastritis in patients included in this study Table 2. The endoscopy method is widely used to inspect the digestive tract as it can directly visualize the current stomach status for the presence of bile stains, edema, and erythema as seen in a few patients in this review. Whereas, given the lack of specificity of the endoscopy, the tissue biopsy is preferable for histologic features of the gastric mucosa. Gastric fluid aspiration was also used in some studies; but this technique can be problematic due to the periodicity of pathological reflux leading to a decreased detection rate [26].

The cause-effect relationship between the presence of bile reflux gastritis and the occurrence of gastric cancer is still a subject of debate. A more recent meta-analysis of 8 studies reported that cholecystectomy was associated with an 11% higher risk of gastric cancer. The authors suggested that the risk for cancer was significantly elevated in the Asian population, suggesting that racial differences may play a role in the occurrence of gastric cancer after cholecystectomy [27]. The report from the Swedish National Inpatient Register of 252,672 patients showed that cholecystectomy increased the likelihood of gastric cancer and that the risk of cancer occurrence was less likely over time [8]. Several studies suggested that the risk of gastric cancer is diminished more than 10 years after surgery, nonetheless the detection bias should not be ruled out due to frequent check-ups which may occur within the 10 years following cholecystectomy [8,28]. Corroboratively, some authors suggested that the recurrence of stones in the bile duct after cholecystectomy is rather associated with gastric cancer, but with a limited understanding.

Therefore, the use of bile duct stone therapy after gallbladder removal seems to be reasonable for reducing the potential risk of developing gastric cancer [29,30]. A systematic review by Choi et al. found that long-term use of ursodeoxycholic acid prophylaxis for gallstone formation may reduce the risk of gastric cancer after cholecystectomy [31]. Currently, there is no consensus on the course of treatment for bile reflux gastritis. Therefore, different therapies have been proposed [26]. Ursodeoxycholic Acid (UDCA) treatment has proven to be effective in the management of bile reflux gastritis as this medication plays a role in both protecting gastric mucosa and reducing reflux. UDCA antagonizes the cytotoxicity of hydrophobic bile acids, inhibits apoptosis, and clears free radicals to improve antioxidant ability. Additionally, this medication can also promote the excretion of endogenous bile acids, reduce bile viscosity, and accelerate bile flow [32]. Various other therapies such as hydrotalcite, Proton Pump Inhibitors (PPIs), and prokinetic agents have been accepted for the treatment of bile reflux gastritis [33,34]. Based on certain reports, the efficacy of a single medication use for bile reflux gastritis is poor with a higher rate of recurrence of this condition. Thus, the combination of medications (polytherapy) may need to be favoured to achieve the desired efficacy [34]. Given the limited data on the treatment of bile reflux gastritis and the results of this study, we could not determine which specific medication, or the dosage of the medication to be used in the management of bile reflux gastritis, more studies would be needed before any recommendation.

Although this study was the first to report the most current prevalence of bile reflux gastritis following cholecystectomy, it had a few limitations: First, few studies with a small sample size were included in this review, which might have impacted the between studies heterogeneity thus the overall result. Second, the reported outcomes were retrieved from poorly designed studies that might have interfered with the overall result of this review hence limiting our understanding of the prevalence of bile reflux gastritis after cholecystectomy.

Conclusion

The prevalence of bile reflux gastritis after therapeutic cholecystectomy is high. Moreover, *Helicobacter pylori* infection, Diabetes mellitus, and obesity may contribute to the occurrence of this condition after surgery. The presence of gastrointestinal symptoms such as epigastric pain, heartburn, nausea, vomiting, and gastroesophageal reflux disease after cholecystectomy should prompt the consideration of bile reflux gastritis as a potential etiology. Given the limitations of this study, the results should be interpreted with care. More studies are needed to understand the prevalence of bile reflux gastritis following cholecystectomy fully.

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