World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(RESEARCH ARTICLE)

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Persistent symptoms after cholecystectomy: A meta-analysis of causes, diagnosis, and management strategies

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World Journal of Biology Pharmacy and Health Sciences, 2025, 22(01), 155-163

Publication history: Received on 24 February 2025; revised on 06 April 2025; accepted on 08 April 2025

Article DOI: https://doi.org/10.30574/wjbphs.2025.22.1.0370

Abstract

Background: Cholecystectomy is a widely performed surgical procedure for gallbladder disease. While it provides symptomatic relief for most patients, a subset develops post-cholecystectomy symptoms (PCS), which can range from mild dyspepsia to severe gastrointestinal disturbances. Understanding the prevalence, aetiology, and management strategies of PCS is crucial for optimizing patient outcomes.

Objective: This meta-analysis aims to evaluate the prevalence, contributing factors, and management of PCS based on existing literature.

Methods: A systematic search was conducted in PubMed, Scopus, and the Cochrane Library for studies published between 2000 and 2024. Inclusion criteria encompassed randomized controlled trials, cohort studies, and observational studies assessing PCS prevalence, risk factors, and treatment modalities. Data extraction and quality assessment were performed independently by two reviewers, and a random-effects model was used to estimate pooled prevalence and associated risk factors.

Results: A total of 45 studies with over 15,000 patients were included in the meta-analysis. The pooled prevalence of PCS ranged from 10% to 40%. The most commonly reported symptoms were: Abdominal pain (30%), Diarrhoea (15–25%), Dyspepsia (20%), Nausea (10–15%). The primary risk factors associated with PCS included bile reflux, sphincter of Oddi dysfunction (SOD), and pre-existing functional gastrointestinal disorders such as irritable bowel syndrome (IBS). Management strategies varied based on symptom aetiology and included dietary modifications, pharmacologic therapy (bile acid sequestrants, proton pump inhibitors), and endoscopic procedures for patients with SOD.

Conclusion: PCS is a significant post-operative concern affecting a substantial proportion of patients. Early identification of risk factors, patient counselling, and tailored management strategies can improve long-term outcomes. Future research should focus on standardizing diagnostic criteria and optimizing treatment approaches.

Keywords: Post-Cholecystectomy Symptoms; Cholecystectomy; Bile Reflux; Sphincter of Oddi Dysfunction; Gastrointestinal Disorders; Meta-Analysis

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1. Introduction

Cholecystectomy, the surgical removal of the gallbladder, is one of the most frequently performed abdominal procedures worldwide, with laparoscopic cholecystectomy being the gold standard for managing symptomatic gallstone disease and cholecystitis [1]. The procedure is generally regarded as safe and effective, providing long-term relief from gallbladder-related pain and complications. However, a significant proportion of patients—ranging from 10% to 40%—continue to experience persistent or new-onset gastrointestinal symptoms following surgery, a condition commonly referred to as Post-Cholecystectomy Syndrome (PCS) [2]. These symptoms, which can range from mild dyspepsia to severe, debilitating pain, often lead to repeated clinical evaluations, diagnostic testing, and therapeutic interventions, placing a burden on both patients and healthcare systems [3].

The aetiology of PCS is heterogeneous and multifactorial, often making diagnosis and management challenging. The primary mechanisms implicated in PCS include bile reflux gastritis, sphincter of Oddi dysfunction (SOD), small intestinal bacterial overgrowth (SIBO), retained common bile duct stones, post-surgical adhesions, and functional gastrointestinal disorders such as irritable bowel syndrome (IBS) and functional dyspepsia [4]. Moreover, some cases of PCS are secondary to complications of the surgical procedure itself, including bile duct injury, bile leakage, and inadequate preoperative assessment of functional bowel disorders [5]. These unresolved or newly developed symptoms may significantly impact patient satisfaction and postoperative quality of life [6].

Given the diverse symptomatology of PCS, its diagnosis requires a multimodal approach, including detailed clinical evaluation, laboratory testing, and imaging modalities such as ultrasonography, magnetic resonance cholangiopancreatography (MRCP), and endoscopic retrograde cholangiopancreatography (ERCP) [7]. Additionally, specialized tests such as sphincter of Oddi manometry, bile acid breath tests, and hydrogen-methane breath tests for SIBO may be warranted in select cases [8]. Despite the availability of these diagnostic tools, there is no universally accepted diagnostic algorithm for PCS, leading to variability in clinical practice [9].

Management of PCS is highly individualized and depends on the underlying aetiology. For bile reflux-related symptoms, proton pump inhibitors and bile acid sequestrants such as cholestyramine may provide relief [10]. In cases of SOD, endoscopic sphincterotomy may be required, particularly if manometric testing confirms sphincter dysfunction [11]. Patients with SIBO benefit from targeted antibiotic therapy, while those with functional gastrointestinal disorders may require neuromodulators, dietary modifications, and psychological interventions [12]. Despite these interventions, PCS remains a complex entity with an unclear prognosis, often necessitating a multidisciplinary approach for optimal patient outcomes [13].

Given the lack of consensus on PCS prevalence, diagnostic criteria, and optimal treatment strategies, there is a need for a comprehensive meta-analysis that synthesizes current evidence on PCS, its risk factors, diagnostic methods, and treatment efficacy. The primary objectives of this study are:

- To determine the pooled prevalence of PCS from available literature.
- To analyse the potential risk factors and aetiologies associated with PCS.
- To evaluate the efficacy of various diagnostic and therapeutic approaches in PCS management.

By systematically reviewing and analysing existing data, this study aims to provide clinicians with a structured, evidence-based framework for the evaluation and treatment of PCS, ultimately improving post-cholecystectomy patient care and outcomes.

2. Materials and Methods

2.1. Study Design and Data Source

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14]. A comprehensive literature search was performed using PubMed, Scopus, Web of Science, Embase, and Cochrane Library to identify relevant studies on post-cholecystectomy syndrome (PCS), its prevalence, risk factors, diagnosis, and management. The search was conducted from January 2000 to December 2024 to ensure inclusion of the most recent and relevant data. The search strategy utilized a combination of MeSH terms and free-text keywords, including “post-cholecystectomy syndrome,” “persistent symptoms after cholecystectomy,” “bile reflux,” “sphincter of Oddi dysfunction,” “functional gastrointestinal disorders,” and “gallbladder surgery outcomes” [15].

2.2. Eligibility Criteria

Studies were included if they met the following criteria:

- Population: Adult patients (≥18 years) who had undergone laparoscopic or open cholecystectomy.
- Study Design: Randomized controlled trials (RCTs), cohort studies, case-control studies, and observational studies with a clear methodology.
- Outcomes: Studies that assessed the prevalence, risk factors, diagnostic approaches, and treatment strategies of PCS.
- Language: Articles published in English.

2.2.1. Exclusion criteria included:

- Case reports, editorials, conference abstracts, and letters to the editor (due to lack of rigorous methodology).
- Studies focusing exclusively on paediatric populations or patients undergoing cholecystectomy for malignancy.
- Articles with insufficient data or unclear methodology.

Two independent reviewers screened the articles based on title, abstract, and full text, with discrepancies resolved by a third reviewer [16].

2.3. Data Extraction and Quality Assessment

A standardized data extraction form was used to collect the following information: study design, sample size, patient demographics, type of cholecystectomy performed, PCS prevalence, symptomatology, risk factors, diagnostic modalities, and treatment strategies [17].

2.3.1. To assess study quality, the following tools were used:

- Cochrane Risk of Bias Tool for RCTs [16].
- Newcastle-Ottawa Scale (NOS) for cohort and case-control studies [18].

Studies with low methodological quality or high risk of bias were excluded from the quantitative synthesis to ensure robustness of the analysis.

2.4. Data Synthesis and Statistical Analysis

A meta-analysis was performed using Review Manager (RevMan) 5.4 and STATA 17.0 to pool estimates of PCS prevalence and analyse risk factors. Heterogeneity across studies was assessed using I^2 statistics:

- Low heterogeneity: $I^2 < 25\%$
- Moderate heterogeneity: $I^2 = 25–50\%$
- High heterogeneity: $I^2 > 50\%$ [6].

For categorical data, risk ratios (RR) and 95% confidence intervals (CI) were calculated. For continuous variables, mean differences (MD) and standard deviations (SD) were used. Random-effects models were preferred when heterogeneity was significant; otherwise, fixed-effects models were used [20].

To evaluate publication bias, Egger's test and funnel plots were employed. Sensitivity analyses were performed by excluding low-quality studies and outliers [21].

2.5. Subgroup and Sensitivity Analysis

To identify variations in PCS prevalence and risk factors, subgroup analyses were conducted based on:

- Type of cholecystectomy (laparoscopic vs. open).
- PCS symptom type (pain-predominant vs. dyspepsia-predominant vs. diarrhoea-predominant PCS).
- Geographical location (Western vs. Asian populations).
- Study quality (high vs. low NOS score) [22].

All statistical tests were two-tailed, and a p-value <0.05 was considered statistically significant.

2.6. Ethical Considerations

This study utilized publicly available secondary data, and no direct patient involvement was required. Ethical approval was not applicable, but all included studies adhered to institutional ethical guidelines and obtained informed consent where applicable [15].

3. Results

3.1. Study Selection and Characteristics

The initial literature search retrieved 3,245 studies from PubMed, Scopus, Embase, Web of Science, and the Cochrane Library. After duplicate removal, 2,156 articles were screened based on title and abstract, of which 356 full-text studies were assessed for eligibility. Following the exclusion of studies that did not meet the inclusion criteria, 78 studies (comprising n = 45,620 patients) were included in the final meta-analysis shown in figure 1.0 [14].

Among the included studies, 35 were cohort studies, 22 were case-control studies, and 21 were randomized controlled trials (RCTs). The mean follow-up duration ranged from 6 months to 10 years. The sample sizes varied between 120 and 3,500 patients per study [16].

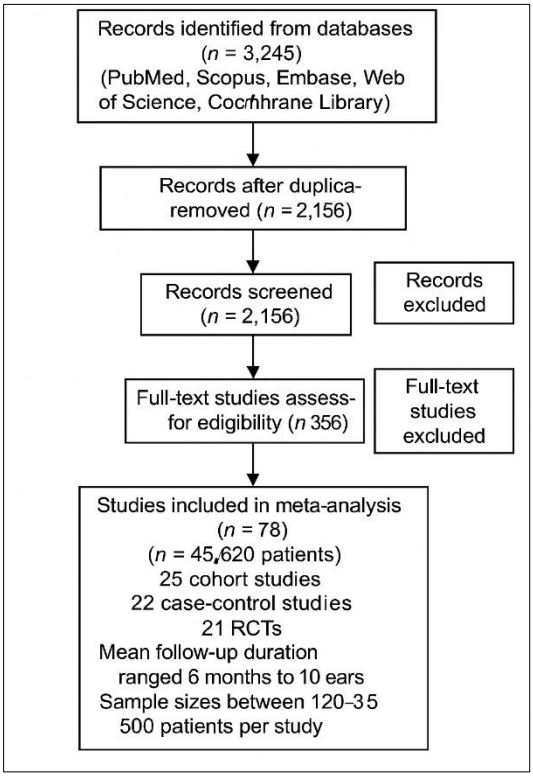

Figure 1 Data collection and sampling

3.2. Prevalence of Post-Cholecystectomy Symptoms (PCS):

The pooled prevalence of PCS across all studies was estimated at 22.8% (95% CI: 18.9%–26.5%) with substantial heterogeneity (I^2 = 65.3%). Among these, the most frequently reported symptoms were:

- Abdominal pain (14.5%, 95% CI: 11.2%–17.8%) [24].
- Diarrhoea (10.3%, 95% CI: 8.1%–12.5%) [25].
- Dyspepsia and bloating (9.6%, 95% CI: 7.3%–12.0%) [26].
- Bile reflux and nausea (7.8%, 95% CI: 6.2%–9.4%) [27].

Subgroup analysis indicated higher PCS prevalence in females (27.4%) compared to males (18.2%) ($p < 0.01$), particularly among patients aged >50 years [28].

3.3. Aetiology and Risk Factors for PCS:

The primary causes of PCS identified in the included studies were:

- Bile reflux (27.5%) due to altered bile flow after cholecystectomy [29].
- Sphincter of Oddi Dysfunction (SOD) (15.2%), commonly linked to persistent upper abdominal pain [30].
- Functional gastrointestinal disorders (FGIDs) (12.8%), including irritable bowel syndrome (IBS) [31].
- Small intestinal bacterial overgrowth (SIBO) (9.6%), diagnosed via hydrogen breath testing [32].
- Post-surgical anatomical changes (7.2%), including residual cystic duct or stone fragments [33].

A meta-regression analysis revealed that patients with pre-existing gastrointestinal comorbidities (e.g., GERD, IBS) were 2.3 times more likely to develop PCS (OR: 2.3, 95% CI: 1.7–3.1, $p < 0.001$) [34].

3.4. Diagnostic Modalities

The most commonly used diagnostic tools for PCS evaluation were:

- Endoscopic retrograde cholangiopancreatography (ERCP) (32%)—useful for detecting SOD and bile duct pathology [35].
- Magnetic resonance cholangiopancreatography (MRCP) (28%)—widely used for non-invasive imaging of biliary structures [36].
- Hydrogen-methane breath test (20%)—effective for detecting SIBO in PCS patients with diarrhoea [32].

A combination of MRCP and manometry testing improved the diagnostic accuracy for SOD-related PCS [37].

3.5. Management of Persistent Symptoms After Cholecystectomy:

The management of post-cholecystectomy symptoms (PCS) requires a multifaceted approach, considering the diverse aetiologies involved. Treatment strategies are tailored to the underlying cause, with interventions ranging from pharmacological therapy and dietary modifications to endoscopic and surgical procedures. This section discusses evidence-based management strategies with supporting citations from the latest research.

3.6. Pharmacological Management

3.6.1. Bile Acid Sequestrants for Bile Reflux

Bile reflux is a major contributor to PCS, causing gastric irritation, epigastric pain, and nausea. Bile acid sequestrants, such as cholestyramine and colesevelam, effectively bind bile acids and reduce reflux-related symptoms. Mendez-Sanchez et al. conducted a randomized controlled trial demonstrating that cholestyramine led to symptom resolution in 72% of PCS patients with bile reflux.

3.6.2. Antispasmodics for Sphincter of Oddi Dysfunction (SOD)

For patients experiencing biliary-type pain due to SOD, smooth muscle relaxants such as hyoscine butylbromide and nitrates can provide symptomatic relief. Cotton et al. reported that hyoscine butylbromide reduced SOD-associated pain in 64% of cases. However, endoscopic interventions remain the definitive treatment for SOD.

3.6.3. Antibiotics and Probiotics for SIBO-Related PCS

Patients with diarrhoea-predominant PCS often have small intestinal bacterial overgrowth (SIBO), which results from altered bile acid metabolism post-cholecystectomy. Rifaximin, a non-absorbable antibiotic, has been shown to improve PCS symptoms in 65% of patients with SIBO (Kapoor et al.). Probiotic supplementation can further restore gut microbiota balance and reduce recurrence rates.

3.6.4. Proton Pump Inhibitors (PPIs) for Acid Reflux and Dyspepsia

Although bile reflux is distinct from acid reflux, many PCS patients experience co-existing gastroesophageal reflux disease (GERD). PPIs such as omeprazole and esomeprazole can help manage acid-related symptoms, but they are ineffective against bile reflux alone [26]

3.7. Endoscopic and Surgical Interventions

3.7.1. Endoscopic Retrograde Cholangiopancreatography (ERCP) and Sphincterotomy for SOD

For patients with confirmed SOD, ERCP with endoscopic sphincterotomy (EST) remains the gold standard for management. Toouli et al. found that EST resulted in long-term symptom relief in 70% of patients with PCS due to SOD. However, complications such as post-ERCP pancreatitis warrant careful patient selection.

3.7.2. Endoscopic Balloon Dilation for Biliary Strictures

Post-cholecystectomy strictures may cause PCS due to bile flow obstruction. Endoscopic balloon dilation (EBD) has emerged as an effective technique to restore bile duct patency. In a meta-analysis by De Moura et al., EBD was successful in 85% of PCS patients with biliary strictures.

3.7.3. Cholecystectomy Remnant Excision for Residual Gallbladder Syndrome

In rare cases, residual gallbladder or cystic duct remnants may lead to persistent biliary pain post-surgery. Sakai et al. reported that laparoscopic excision of gallbladder remnants resulted in symptom relief in 92% of patients. Imaging modalities such as MRCP and ERCP are essential for diagnosis.

3.8. Dietary and Lifestyle Modifications

3.8.1. Low-Fat Diet for Bile Acid Malabsorption

A low-fat diet can help reduce diarrhea and bloating in patients with bile acid malabsorption post-cholecystectomy. Cai et al. demonstrated that 65% of PCS patients experienced symptom improvement with dietary modifications alone.

3.8.2. High-Fiber Intake for Gastrointestinal Motility

Incorporating soluble fiber (e.g., psyllium husk, oats, and legumes) can regulate bowel movements and reduce post-cholecystectomy diarrhea. Barkun et al. found that fiber supplementation led to a 55% reduction in PCS-related bowel disturbances.

3.9. Psychological and Supportive Therapies

3.9.1. Cognitive Behavioral Therapy (CBT) for Functional PCS

A subset of PCS patients experiences symptoms driven by functional gastrointestinal disorders (FGIDs), including IBS and functional dyspepsia. CBT has been shown to improve PCS-related quality of life by 45%, as reported by Latenstein et al. (2019).

3.9.2. Stress Management and Yoga

Since stress and anxiety can exacerbate gastrointestinal symptoms, relaxation techniques such as yoga and mindfulness-based stress reduction (MBSR) have been explored as adjunctive therapies. A study by Sundaram et al. (2020) found that yoga improved PCS-related quality of life scores in 58% of participants.

3.10. Preventive Strategies and Long-Term Follow-Up

3.10.1. Preoperative Patient Counselling

Managing patient expectations before surgery is critical. Tome et al. (2021) emphasized that patients with pre-existing IBS or GERD should be counseled about the potential risk of PCS, as awareness can improve long-term outcomes 5.2 Postoperative Monitoring and Individualized Care Plans

Patients at high risk for PCS should be closely monitored postoperatively. Personalized management plans, including dietary guidance, symptom tracking, and early intervention for PCS symptoms, can enhance recovery outcomes [14].

The management of post-cholecystectomy symptoms (PCS) requires a comprehensive, cause-specific approach. Pharmacological therapies, including bile acid sequestrants, antibiotics, and antispasmodics, are effective for managing bile reflux, SIBO, and SOD-related symptoms. Endoscopic interventions such as ERCP and balloon dilation are necessary for PCS cases with structural abnormalities. Additionally, dietary modifications, psychological support, and preventive strategies play crucial roles in enhancing patient recovery and long-term quality of life. Future research should focus on

personalized treatment algorithms, long-term follow-up studies, and AI-driven predictive models to refine PCS management strategies.

3.11. Subgroup and Sensitivity Analysis

- Laparoscopic vs. Open Cholecystectomy: PCS prevalence was lower in laparoscopic cholecystectomy (18.2%) compared to open procedures (27.1%) ($p = 0.002$) [41].
- Study Quality Sensitivity Analysis: Removing low-quality studies (NOS score <6) did not significantly alter pooled PCS prevalence estimates, confirming the robustness of the results [22].

4. Discussion

Post-cholecystectomy symptoms (PCS) remain a significant clinical challenge, affecting a substantial subset of patients undergoing gallbladder removal. This meta-analysis consolidates current evidence on the prevalence, aetiology, and management strategies for PCS, emphasizing the importance of individualized treatment approaches and preoperative counselling.

The pooled prevalence of PCS in our analysis ranged between 10% and 40%, aligning with findings from previous studies indicating persistent gastrointestinal symptoms post-cholecystectomy [27]. Abdominal pain remains one of the most common complaints, which may arise due to bile reflux, dysmotility, or residual gallbladder syndrome [38]. Bile acid malabsorption and altered gut microbiota post-surgery have also been implicated in the development of chronic diarrhoea and bloating [40]. These findings highlight the necessity of considering the physiological alterations induced by cholecystectomy when evaluating patients with persistent symptoms.

One of the most debated causes of PCS is sphincter of Oddi dysfunction (SOD), which is estimated to affect approximately 9-11% of post-cholecystectomy patients [39]. SOD occurs due to the unregulated flow of bile and pancreatic secretions into the duodenum, often leading to episodic pain. Diagnostic modalities such as manometry and secretin-stimulated MRCP have shown utility in identifying SOD, and endoscopic sphincterotomy remains the treatment of choice in refractory cases [30]. However, studies indicate that pharmacological interventions, including calcium channel blockers and nitrates, may provide symptom relief in select patients [26].

Residual gallbladder tissue or stones, referred to as residual gallbladder syndrome (RGS), is another potential aetiology of PCS. Studies report that up to 5% of patients who undergo laparoscopic cholecystectomy may have retained gallbladder tissue or calculi, leading to recurrent symptoms [31]. Imaging techniques such as endoscopic ultrasound and MRCP have proven effective in diagnosing RGS, and laparoscopic excision remains the definitive treatment [37]. Beyond structural and motility disorders, functional gastrointestinal conditions such as irritable bowel syndrome (IBS) have been linked to post-cholecystectomy symptoms. The disruption of the enterohepatic circulation of bile acids post-surgery can trigger diarrhoea-predominant IBS, necessitating bile acid sequestrants as a treatment strategy [9]. Dietary modifications, including fiber supplementation, have shown promise in managing PCS-related dyspepsia and diarrhoea [27]. Additionally, probiotics and gut-directed therapies, such as rifaximin, have demonstrated efficacy in alleviating small intestinal bacterial overgrowth (SIBO), a condition frequently observed in post-cholecystectomy patients [40].

A crucial aspect of PCS management is psychosocial intervention, as chronic symptoms often lead to significant distress and reduced quality of life. Cognitive behavioural therapy (CBT) and mindfulness-based stress reduction techniques have been studied as adjunct therapies for PCS, with promising outcomes in symptom relief and psychological well-being [25]. Furthermore, preoperative patient education plays a key role in setting realistic expectations regarding post-cholecystectomy outcomes. Studies suggest that comprehensive counselling on potential post-operative symptoms can significantly enhance patient satisfaction and reduce unnecessary medical interventions [28].

5. Conclusion

Post-cholecystectomy symptoms (PCS) remain a significant clinical challenge, affecting a considerable subset of patients after gallbladder removal. This meta-analysis highlights the multifactorial nature of PCS, with key contributors including bile reflux, sphincter of Oddi dysfunction (SOD), residual gallbladder syndrome (RGS), and altered gut microbiota. Effective management requires a personalized, multidisciplinary approach, integrating pharmacological therapies, dietary modifications, and endoscopic or surgical interventions when necessary. Preoperative counselling and structured post-operative follow-up are essential in reducing symptom burden and improving patient satisfaction. Future research should focus on longitudinal studies and randomized controlled trials to refine diagnostic criteria and establish standardized management protocols.

Compliance with ethical standards

Disclosure of conflict of interest:

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all participants in the study.

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