



Surgical referral for cholecystectomy in patients with atypical symptoms



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ABSTRACT

Background: Cholelithiasis referrals often present with concomitant or isolated atypical symptoms such as reflux, bloating, or epigastric pain. We sought to identify the impact of preoperative symptomatology of atypical or dyspepsia-type biliary colic on operative and non-operative clinical outcomes.

Methods: A retrospective review of patients referred for gallstone disease from 2014 to 2018 at a single institution in Los Angeles County was performed.

Results: Of 746 patients evaluated for gallstone disease, 87.4% (n = 652) underwent cholecystectomy – 90.8% (n = 592) had symptom resolution postoperatively whereas 9.2% (n = 60) did not. Over half presented with concomitant atypical and/or dyspepsia symptoms (n = 411). Heartburn/reflux was significantly associated with unresolved symptoms postoperatively (OR 2.1, 1.0–4.4, p = 0.04). Overall, 11.1% (n = 83) of all 746 patients and 20.2% of patients with atypical and/or dyspepsia symptoms improved with medical management of gastritis or *Helicobacter pylori* triple therapy pre/post-operatively.

Conclusion: Atypical biliary colic and/or dyspepsia is associated with unresolved symptoms following cholecystectomy. Such patients may benefit from *H. pylori* testing or PPI trial prior to cholecystectomy.

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Introduction

In the United States, up to 20% of adults have gallstones, and 1–3% eventually become symptomatic, resulting in approximately 500,000–750,000 cholecystectomies performed annually.^{1–3} Amidst the constellation of classic biliary colic symptoms, patients referred for surgical evaluation of gallstone disease often present with concomitant or isolated atypical symptoms such as heartburn, reflux, bloating, epigastric or other non-specific abdominal pain. Untreated gastroesophageal reflux disease (GERD), *Helicobacter pylori* infection, sphincter of Oddi dysfunction, or underlying gastrointestinal disorders often contribute to unnecessary surgical intervention and unresolved symptoms following cholecystectomy. Thus, it is increasingly important to accurately diagnose biliary colic.^{1,2,4}

Classic biliary colic is characterized by paroxysmal, postprandial right upper quadrant abdominal pain with associated nausea and vomiting. This presentation has become a hallmark for identifying gallstone disease.³ However, while it is well known that

biliary colic presents with a wide range of atypical symptoms; it is not uncommon for patients to be worked up for cardiac disease, when in reality they have biliary colic induced chest pain. Because of the wide spectrum of presentation, many patients with the mere radiographic finding of gallstones are reflexively referred to the surgeon, regardless of symptoms.

Clinical decision-making which is heavy-handed in reliance on imaging over that of detailed history and physical exam perpetuates unneeded surgical intervention and contributes to persistent symptoms postoperatively. Up to 40% of patients remain symptomatic after cholecystectomy, which is often due to overlooked underlying etiologies of abdominal pain such as functional dyspepsia, gastritis or reflux.³ However, there is limited understanding of the interplay of atypical biliary colic and/or dyspepsia whether in isolation or concurrent with classic biliary colic symptoms and its implications on ultimate outcomes, whether managed by medical therapy or with surgical intervention. Thus, the aim of our study is to identify the impact of preoperative clinical symptomatology of biliary colic – whether classic, atypical or dyspepsia type – on operative and non-operative clinical outcomes.

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Materials and methods

Institutional Review Board approval was obtained prior to initiation of this study. A retrospective review of all patients referred for surgical evaluation of gallbladder disease to a single clinic at Harbor-UCLA Medical Center between 2014 and 2018 was performed. Patients were referred by primary care physicians, the emergency department, urgent care, and outside community partners for evaluation of elective, outpatient cholecystectomy.

Patients were excluded if they failed to attend their scheduled surgical clinic visit or were lost to follow-up prior to initiation of any diagnostic or therapeutic interventions. Demographics, clinical symptoms, radiographic findings, and outcomes were collected and analyzed. Symptoms were classified into three categories: classic biliary colic, atypical biliary colic, and classic dyspepsia (Table 1).

The number of symptoms for each of these three categories was calculated for each patient along with the presence of concomitant classic biliary and atypical biliary colic, concomitant classic biliary colic and dyspepsia, or concomitant atypical biliary colic and dyspepsia symptoms. Additional variables collected included results from ultrasound imaging, and if available, cholescintigraphy (HIDA scan), computed tomography (CT scan), and esophagogastroduodenoscopy (EGD) as well as outcomes following therapeutic interventions of proton-pump inhibitor (PPI) trial, histamine H2-receptor blocker trial, or cholecystectomy. If clinically indicated, patients were tested for *H. pylori* with the stool antigen test and response to triple therapy was evaluated. While a discrete algorithm was not applied and individual provider clinical decision making guided management, in general, those patients with isolated classic biliary colic symptoms proceeded to laparoscopic cholecystectomy, whereas those with mixed classic biliary colic and atypical symptoms underwent *H. pylori* testing, and those with mixed classic biliary colic and dyspeptic symptoms received PPI or H2-receptor blocker trials either prior to or in concurrence with surgical intervention. Outcomes were tracked as per documentation of follow-up with the surgeon between 2 and 8 weeks postoperatively depending on the course of individual patient recovery.

Univariate and multivariable analyses were performed to evaluate clinical outcomes with significance set at $p < 0.05$. All data were entered into Microsoft Excel (Microsoft Corporation, Redmond, WA), and all statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC) or Stata Version 12 (Stata Corporation, College Station, TX).

Results

In the five-year study period, a total of 746 patients were evaluated for gallstone disease. The demographic and clinical characteristics of the patient cohort are summarized in Table 2. The median age was 43 years, median BMI was 30, 93.4% (n = 697) were Hispanic, and 85.0% (n = 634) were female.

Among the cohort, 97.2% (n = 725) had classic biliary symptoms,

Table 2
Patient demographics & clinical characteristics (N = 746).

Age (median years)	43 (15–87)
Sex	
Female	634 (85.0%)
Male	112 (15.0%)
Ethnicity	
Hispanic American	697 (93.4%)
African American	13 (1.7%)
South Asian/Asian Pacific Islander	13 (1.7%)
Caucasian	6 (0.8%)
Middle Eastern	2 (0.2%)
Other	15 (2.0%)
BMI (median)	30 (18–59)
Referral origin	
Primary care or outside hospital	253 (33.9%)
Emergency or urgent care	242 (32.4%)
Inpatient referral	6 (0.8%)
Unknown	245 (32.8%)
Referral reason	
Right upper quadrant pain	458 (61.4%)
Epigastric pain	68 (9.1%)
Atypical pain (diffuse, left upper, back)	216 (29.0%)
Atypical symptoms (i.e., nausea, bloating)	4 (0.5%)
Duration of symptoms	
Acute (1–11 months)	280 (37.5%)
Chronic (12 months or greater)	371 (49.7%)

22.1% (n = 165) had atypical biliary symptoms, and 47.6% (n = 355) had dyspepsia symptoms. On initial presentation, 21.3% (n = 159) of patients had concomitant classic biliary and atypical biliary colic, 44.9% (n = 335) concomitant classic biliary colic and dyspepsia, and 14.6% (n = 109) concomitant atypical biliary colic and dyspepsia.

Of 746 patients evaluated for gallstone disease, 87.4% (n = 652) of patients underwent cholecystectomy, of whom, 90.8% (n = 592) had symptom resolution postoperatively whereas 9.2% (n = 60) had unresolved symptoms postoperatively. The distribution of cholecystectomies performed include 55.0% (n = 358) laparoscopic, 42.3% (n = 276) robotic, 1.4% (n = 9) laparoscopic conversion to open, and 1.4% (n = 9) with intraoperative cholangiogram.

Significant individual predictors of unresolved symptoms postoperatively are demonstrated in Fig. 1. Significant predictors of unresolved symptoms postoperatively include preoperative nausea/vomiting (p = 0.03), epigastric pain (p = 0.04), left upper quadrant pain (p = 0.02), heartburn/reflux (p = 0.009), diarrhea (p = 0.0005), constipation (p = 0.04), combined classic and atypical biliary symptoms (p = 0.002), combined classic biliary and dyspepsia symptoms (p = 0.02). This is further reinforced when comparing predictors of resolved versus unresolved symptoms postoperatively in Table 3. In general, patients who presented with concomitant atypical or dyspeptic type symptoms had an increased

Table 1
Presenting symptoms.

Classic biliary colic	Atypical symptoms	Classic dyspepsia
Right upper quadrant pain	Flatulence	Epigastric abdominal pain
Postprandial pain	Diarrhea	Left upper quadrant abdominal pain
Pain radiating to the back	Constipation	Heartburn
Nausea	Unintentional weight loss	Reflux
Vomiting	Chest pain	Regurgitation
	Chronic cough	Early satiety
	Lower abdominal pain	Bloating
		Belching

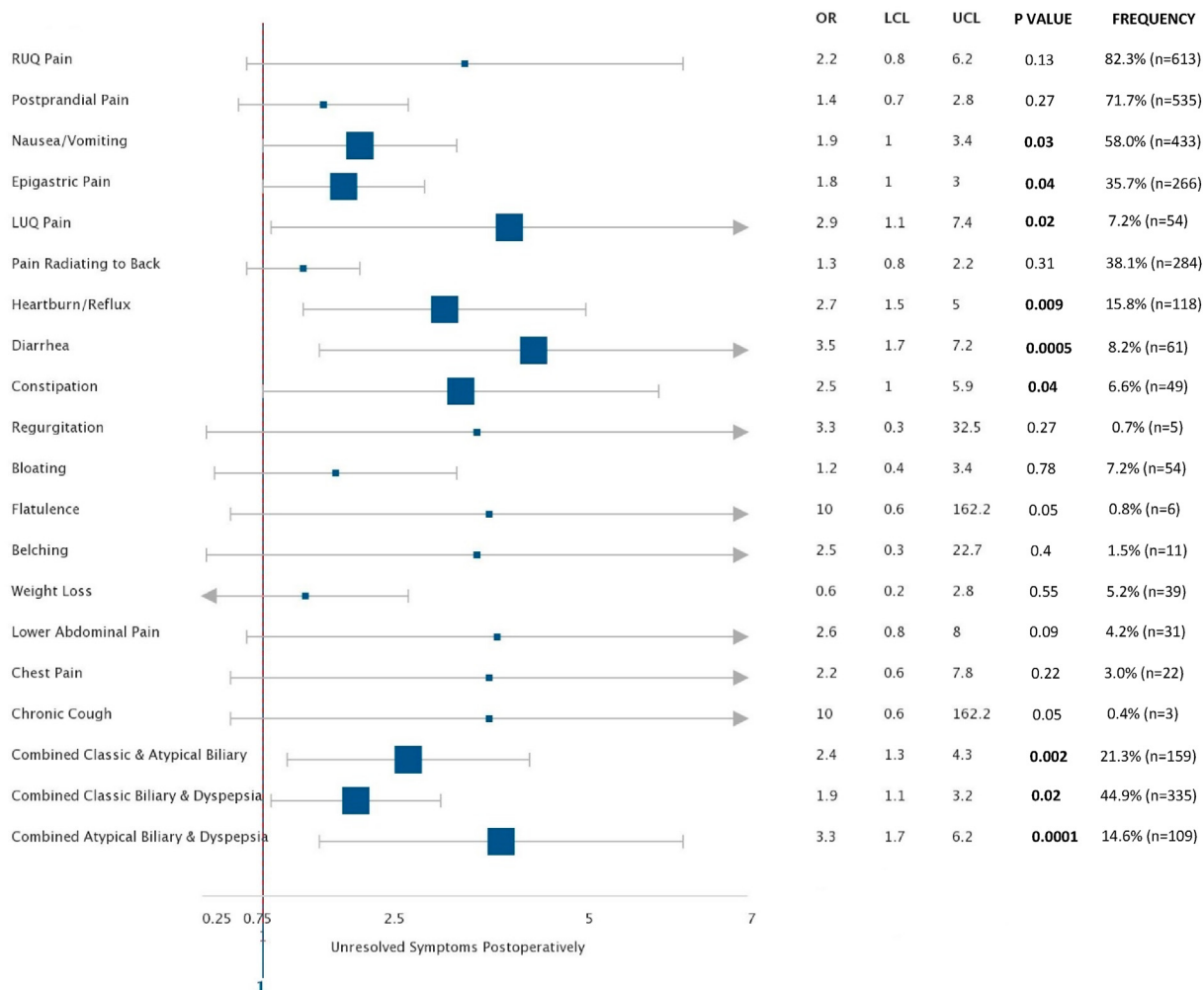


Fig. 1. Unresolved symptoms following cholecystectomy (odds ratio plot).

odds ratio of having persistent pain after surgery; however, patients who were referred with no classic biliary complaints at all were at highest risk OR 3.3 (1.7–6.2, $p = 0.0001$) (Table 3).

In particular, preoperative atypical biliary colic was significantly associated with persistent heartburn/reflux, the most common unresolved symptom postoperatively on both univariate (OR = 2.5, 1.2–5.2, $p = 0.02$) and multivariable analysis (OR 2.1, 1.0–4.4, $p = 0.04$). Among these patients with unresolved dyspeptic symptoms following cholecystectomy ($n = 60$), 38.3% ($n = 23$) experienced symptom resolution with medical therapy – either PPI, H2 blocker, or *H. pylori* triple therapy. Of the remaining 37 patients who did not respond to surgical or medical therapy, an overwhelming majority had symptoms of persistent dyspepsia – epigastric pain, heartburn, and reflux – and were referred back to their PCP or GI for further medical workup.

With regard to preoperative index of suspicion, 26% of patients ($n = 193$) were suspected of having symptoms of gastritis rather than biliary colic, and were tested preoperatively for *H. pylori*. Of these, 39% ($n = 76$) were found to be *H. pylori* positive preoperatively. Fifty-eight percent of the *H. pylori* positive patients ($n = 44$, 5.9% of total cohort) experienced partial or complete symptom resolution with triple therapy, and 35.5% ($n = 27$, 3.6% of total cohort) avoided unnecessary surgical intervention, never requiring a cholecystectomy on subsequent follow-up of at least one year.

Overall, 11.1% ($n = 83$) of all 746 patients and 20.2% of all patients with atypical and/or dyspepsia symptoms ($n = 411$) improved with medical management of gastritis or *H. pylori* triple therapy administered either pre- or post-operatively. Of 94 patients managed non-operatively with medical therapy, 63.8% ($n = 60$) experienced symptom resolution. The remaining patients were not offered surgery and referred back to their PCP for continued workup.

Of the 553 patients who were offered cholecystectomy upfront, 8% ($n = 44$) had unresolved pain symptoms postoperatively, of whom 45% ($n = 20$) were *H. pylori* positive and 60% ($n = 12$) of those treated had symptom resolution after *H. pylori* triple therapy. When compared to those that were tested preoperatively, the odds ratio for *H. pylori* infection postoperatively was 2.2 (95% CI 1.1–4.5, $p = 0.02$).

Discussion

Whether or not to offer cholecystectomy to patients with gallstones and atypical symptoms has always been the general surgeon’s dilemma. The presence of atypical or dyspepsia type symptoms especially heartburn/reflux in the preoperative setting is associated with unresolved symptoms post-cholecystectomy. While a majority of patients present with classic biliary colic

Table 3
Odd Ratio of Cholecystectomy, Resolved vs. Unresolved Symptoms Postoperatively.

Symptoms on presentation	Frequency	Cholecystectomy Performed (n = 652)	Postoperative Symptom Resolution (n = 617)	Postoperative Unresolved Symptoms (n = 60)
RUQ pain	82.3% (n = 614)	7.1 (4.4–11.2, p < 0.0001)	0.6 (0.2–2.1, p = 0.43)	2.2 (0.8–6.2, p = 0.13)
Postprandial pain	71.7% (n = 535)	2.3 (1.5–3.6, p = 0.0002)	0.7 (0.3–1.6, p = 0.41)	1.4 (0.7–2.8, p = 0.27)
Nausea/vomiting	58.0% (n = 433)	2.2 (1.4–3.3, p = 0.0005)	0.5 (0.2–1.1, p = 0.09)	1.9 (1.0–3.4, p = 0.03)
Epigastric pain	35.7% (n = 266)	0.4 (0.3–0.6, p < 0.0001)	0.6 (0.3–1.3, p = 0.2)	1.8 (1.0–3.0, p = 0.04)
LUQ pain	7.2% (n = 54)	0.1 (0.07–0.2, p < 0.0001)	0.2 (0.1–0.7, p = 0.003)	2.9 (1.1–7.4, p = 0.02)
Pain radiating to back	38.1% (n = 284)	1.4 (0.9–2.2, p = 0.19)	0.6 (0.3–1.2, p = 0.12)	1.3 (0.8–2.2, p = 0.31)
Heartburn/reflux	15.8% (n = 118)	0.4 (0.3–0.7, p = 0.0008)	0.3 (0.1–0.6, p = 0.0004)	2.7 (1.5–5.0, p = 0.009)
Regurgitation	0.7% (n = 5)	0.6 (0.06–5.2, p = 0.62)	NA	3.3 (0.3–32.5, p = 0.27)
Bloating	7.2% (n = 54)	0.3 (0.2–0.6, p < 0.0001)	1.0 (0.2–4.4, p = 0.98)	1.2 (0.4–3.4, p = 0.78)
Flatulence	0.8% (n = 6)	0.1 (0.01–0.4, p < 0.0001)	0.1 (0.003–0.9, p = 0.005)	10.0 (0.6–162.2, p = 0.05)
Belching	1.5% (n = 11)	0.1 (0.03–0.4, p < 0.0001)	0.2 (0.02–2.0, p = 0.15)	2.5 (0.3–22.7, p = 0.4)
Early satiety	1.7% (n = 13)	0.8 (0.2–3.6, p = 0.76)	NA	NA
Diarrhea	8.2% (n = 61)	0.4 (0.2–0.8, p = 0.01)	0.4 (0.2–1.2, p = 0.1)	3.5 (1.7–7.2, p = 0.0005)
Constipation	6.6% (n = 49)	0.4 (0.2–0.8, p = 0.009)	0.6 (0.2–2.1, p = 0.45)	2.5 (1.0–5.9, p = 0.04)
Weight loss	5.2% (n = 39)	0.6 (0.3–1.5, p = 0.30)	1.8 (0.2–13.6, p = 0.56)	0.6 (0.2–2.8, p = 0.55)
Lower abdominal pain	4.2% (n = 31)	0.2 (0.1–0.5, p < 0.0001)	0.3 (0.1–1.1, p = 0.05)	2.6 (0.8–8.0, p = 0.09)
Chest pain	3.0% (n = 22)	0.5 (0.2–1.3, p = 0.15)	0.4 (0.1–1.9, p = 0.24)	2.2 (0.6–7.8, p = 0.22)
Chronic cough	0.4% (n = 3)	0.3 (0.03–3.2, p = 0.28)	NA	10.0 (0.6–162.2, p = 0.05)
Combined classic & atypical biliary symptoms	21.3% (n = 159)	0.4 (0.2–0.6, p < 0.0001)	0.6 (0.3–1.2, p = 0.12)	2.4 (1.3–4.3, p = 0.002)
Combined classic biliary & dyspepsia symptoms	44.9% (n = 335)	0.4 (0.3–0.7, p = 0.0002)	0.4 (0.2–0.8, p = 0.01)	1.9 (1.1–3.2, p = 0.02)
Combined atypical biliary & dyspepsia symptoms	14.6% (n = 109)	0.2 (0.1–0.4, p < 0.0001)	0.3 (0.2–0.8, p = 0.007)	3.3 (1.7–6.2, p = 0.0001)

symptomatology of right upper quadrant abdominal pain elicited post-prandially with associated intolerance of oral intake, the presence of atypical symptoms or dyspepsia should alert a clinician to other potential underlying etiologies which may be addressed non-operatively. Accurately identifying the etiology of clinical symptomatology preoperatively is essential to guide informed surgical decision making. In a study of 47 junior physicians, only 21% accurately diagnosed biliary colic.⁵ Dyspepsia was most commonly misdiagnosed in 40% of cases and incorrectly attributed to as a symptom of biliary colic in 14% of cases.⁵ Similar to dyspepsia, clinically distinguishing atypical symptoms as attributable to biliary colic versus isolated or concurrent *H. pylori* infection is also essential.

This becomes especially important in an era where a growing body of literature demonstrates surgeons may be over-performing cholecystectomies with the advent and convenience of laparoscopic approaches.^{3,6} A lower threshold for performing laparoscopic surgery has driven increased cholecystectomy rates.⁶

This phenomenon has given rise to the concept of “ineffective cholecystectomies” whereby patients remain persistently symptomatic postoperatively. A systematic review and meta-analysis by Latenstein et al. demonstrated that concomitant cholelithiasis and functional gastrointestinal disorders predicted ineffective cholecystectomies with lack of symptom resolution.³ In a study of 1714 symptomatic patients who underwent cholecystectomy, females with longer, more frequent preoperative upper abdominal pain are more likely to experience continued post-cholecystectomy upper abdominal pain.⁶

Identifying predictors of ineffective cholecystectomies prior to the cholecystectomy is important. One in five of all our patients with atypical or dyspeptic symptoms on referral had symptom improvement with medical management of gastritis or *H. pylori* triple therapy administered either pre- or post-operatively. The cumulative

success of non-operative management of patient symptoms with medical therapy was over 64%, and over a third of patients with *H. pylori* avoided cholecystectomy given resolution of symptoms following triple therapy. This is particularly relevant given our Hispanic predominant patient population has a higher incidence of *H. pylori* at nearly 40% - four times higher than that of Caucasians.^{7,8}

Hispanics have the greatest prevalence of *H. pylori* associated dyspepsia and gastritis symptoms and are among the few ethnic groups with higher rates of *H. pylori* seropositivity when compared to Caucasians.^{7,9} Interestingly, each successive generation of Hispanics has a decreased risk of *H. pylori* infection.⁷ Despite controlling for BMI, smoking status, and family history of cancer, Hispanics still have higher rates of *H. pylori* seropositivity.^{8,9} With the projected rise in Hispanics currently comprising 17.1% of the general US population to 31% by 2060, it becomes even more important that consideration be given to *H. pylori* as a potential underlying etiology of biliary complaints that don't neatly fit into the box of classic biliary colic.^{8,9}

Our retrospective study design is limited by data from a single institution in which the patient cohort is overwhelmingly comprised of middle-aged, overweight and obese, Hispanic females. As an urban, academic county hospital in Los Angeles, we primarily serve a socioeconomically disadvantaged, racially- and ethnically-diverse population. The Hispanic predominance of our patient population brings with it a higher prevalence of *H. pylori* and thus likely contributes to a greater incidence of dyspepsia and atypical symptoms among surgical referrals. This also limits applicability to institutions with a majority Caucasian population where *H. pylori* incidence usually averages under 10%.^{7,8} In Los Angeles, *H. pylori* is not just more common among Hispanics, but also among lower socioeconomic status groups.^{10,11} Limitations in follow-up include potential for patients to seek care at other neighboring institutions. Also, as an academic, teaching institution,

variabilities in any particular trainee's elicitation of medical history elements and thoroughness of documentation including negative review of systems are likely to exist. Likewise, there is potential for variation in management among different attending surgeons. With exception of a few cases of readmission for pain, there were no major surgical complications given the elective nature and high volume of cholecystectomies performed.

Conclusions

In a cross-sectional analysis of a county, Hispanic pre-dominant population, concomitant atypical biliary colic and/or dyspepsia on presentation is associated with unresolved, persistent symptoms following cholecystectomy. Such patients may benefit from *H. pylori* testing and PPI trial prior to cholecystectomy. A more thorough approach to the early identification and management of atypical symptoms can have significant implications to optimize patient outcomes and reduce unnecessary surgical intervention by ruling out other underlying medical entities such as gastritis, reflux, *H. pylori* infection, or biliary dyskinesia. Accurate diagnosis with thorough elicitation of history and management with appropriate medical therapy among patients referred to surgery for presumptive biliary disease avoids unnecessary surgery along with its associated risks and costs.

Declaration of competing interest

All authors do not have any financial or personal conflicts of interest to disclose.

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