

Features of Upper Abdominal Pain that Predict Symptoms Relief after Cholecystectomy in Patients with Uncomplicated Gallstones Disease

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Abstract

Introduction: Gallbladder disease is common and results in high health care costs. Indeed, estimates of the lifetime risk of gallstone formation are as high as 10% to 20% of the general population. The natural history of symptomatic gallstone disease is such that approximately 70% of patients will continue to have episodic symptoms or experience a complication of gallstones within 2 years of initial diagnosis. Adding to this potential confusion is the occurrence of abdominal pain thought to resemble gallbladder pain but without gallstones present. Laparoscopic cholecystectomy remains the gold standard for treatment of symptomatic cholelithiasis. However, persistent symptoms after cholecystectomy occur in 10 to 33% of patients. Although a variety of clinical characteristics have been evaluated as preoperative factors associated with outcome after cholecystectomy, preoperative symptoms are generally used as a reference point for diagnosis and determination of need of cholecystectomy. Characterizing and identifying symptoms that predict relief from upper abdominal pain after cholecystectomy could better guide physicians to recommend cholecystectomy so as to reduce morbidity, mortality and cost and minimize unnecessary surgery.

Aim: The objective of this study is to identify symptoms predicting complete relief of upper abdominal pain (UAP) after cholecystectomy to help better selection of patients who might benefit from surgery.

Subjects and methods: This study is a prospective analysis involving 950 adult patients undergoing cholecystectomy for symptomatic cholelithiasis. The study included 721 females (75.89%) and 229 males (24.11%). The patients were asked to complete a previously-validated biliary symptoms questionnaire (BSQ) before operation and 3 months postoperatively as well. At the end of the last questionnaire, each patient was required to define whether (as overall) his symptoms were relieved or not. Our patients were divided into two groups according to pain relief after surgery; Group (1) included patients who had pain relief after surgery (713 patients-75.05%) and group (2) included patients who did not have pain relief after surgery (237 patients-24.95%).

Results: Our study shows that the likelihood of having pain relief is greater in patients who have UAP onset one year or less preoperatively, UAP of short duration, UAP occurring most frequently in the evening or at night time and whose pain awakens them by night, patients who do not have lower abdominal pain, patients who have normal bowel habit pattern, patients who have infrequent nausea attacks, patients who do not often have excessive gas bloat or burps and patients who do not suffer concomitant GERD or IBS.

Conclusion: Laparoscopic cholecystectomy is an effective management option for symptomatic cholelithiasis, with a cure rate of 75.05% in our study. Better rates of pain relief can be achieved by better selection of patients, as sub analysis of symptoms showed better cure rates in the subgroups. The followings were found as good predictors of outcome: older age, female patients, short onset of the disease (≤ 1 year), infrequent attacks of pain once or less per week, short duration of attacks less than 30 minutes, attacks occurring by night or awakening the patient by night, attacks of moderate to severe intensity, patient with normal bowel habits, absence of lower abdominal symptoms, absence of gas bloating, and absence of GERD or IBS. Our study shows that pain relief progressively increases with increasing the number of positive predictive symptoms, being the best at the level of 4 positive predictive symptoms. Further larger studies are still needed to further define reliable prognostic symptoms to assure better selection of patients.

Keywords: Upper abdominal pain relief; Cholecystectomy; Gallstone disease

Introduction

Gallbladder disease is common and results in high health care costs. Indeed, estimates of the lifetime risk of gallstone formation are as high as 10% to 20% of the general population. However, it is estimated that as many as 80% of patients with gallstones remain asymptomatic throughout their lives [1].

The natural history of symptomatic gallstone disease is such that approximately 70% of patients will continue to have episodic symptoms

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or experience a complication of gallstones within 2 years of initial diagnosis. Adding to this potential confusion is the occurrence of abdominal pain thought to resemble gallbladder pain but without gallstones present [2].

Symptomatic cholelithiasis is suggested by the presence of biliary pain in the setting of known gallstones. Unfortunately, characteristics that best reflect biliary-like abdominal pain remain unclear. Furthermore, features of "classic" biliary pain occur uncommonly and other symptoms commonly present are frequently ambiguous [3].

These ambiguous or atypical symptoms, which include indigestion, dyspepsia, flatulence, heartburn, bloating, belching, and nausea, are less likely to resolve following cholecystectomy. Making the distinction of whether identified gallstones are the cause of an individual's symptoms or are an incidental finding is crucial as an incorrect diagnosis leading to cholecystectomy results in unnecessary risk, and expense, and ultimately delays treatment of the actual cause of the symptoms [4]. Although a variety of clinical characteristics have been evaluated as preoperative factors associated with outcome after cholecystectomy, preoperative symptoms are generally used as a reference point for diagnosis and determination of need of cholecystectomy [5].

Cholecystectomy is not without risk. A serious complication is bile duct injury, which can be complicated by bile duct stricture, cholangitis, and primary duct stone formation [6,7]. Characterizing and identifying symptoms that predict relief from upper abdominal pain after cholecystectomy could better guide physicians to recommend cholecystectomy so as to reduce morbidity, mortality and cost and minimize unnecessary surgery [8].

Aim of the Work

The aim of this study is to identify features of upper abdominal pain that could predict pain relief after cholecystectomy for symptomatic uncomplicated gallstones. Identifications of these features that disappear after cholecystectomy could help physicians decide which patients would most likely benefit from cholecystectomy.

Patients and Methods

This study represents a prospective study of one thousand patients with symptomatic uncomplicated gallstones with upper abdominal pain undergoing elective cholecystectomy.

Study design

Data of biliary symptoms questionnaire were collected from the patients before operation, then three months after the operation the questionnaire was completed to identify predictors of upper abdominal pain relief after cholecystectomy.

Place and duration of the study

The study was conducted in internal medicine department of Tanta university hospital in collaboration of surgical department starting from 1/1/2013 to 1/1/2015.

Study approval

Ethics: Permission obtained from Research Ethics Committee as a part of Quality Assurance Unit in Faculty of Medicine Tanta University to conduct this study and to use the facilities in the hospitals.

Consent: Informed written consents were obtained from all patients after full explanations of benefits and risks of the study. Privacy of all patients' data was granted by a special code number for every patient's file that includes all investigations.

Study Population and Sample Size

This study includes one thousand patients (753 females 247 males) with symptomatic uncomplicated gallstones with upper abdominal pain undergoing cholecystectomy.

Inclusion criteria

Eligible patients have preoperative diagnosis of symptomatic uncomplicated gallstones; the presence of gallstones was determined by sonography. All patients referred for elective cholecystectomy, selection for surgery, scheduling, technical surgical aspects and follow up conducted according to the usual practice of surgeons at the general surgery department, Tanta University Hospital.

Exclusion criteria

- Mental retardation, known psychiatric disease and memory deficiency, somatization disorder.
- Complicated biliary disease such as acute cholecystitis, duct stones with or without cholestasis or pancreatitis.

Patients

Eligible patients were enrolled before surgery at the outpatient clinics of Internal Medicine to collect data of biliary symptoms questionnaire. The research questionnaire elicited baseline demographic data and biliary symptoms of the enrolled patients. Research set of biliary symptoms questionnaire filled by assistant of the main investigator for enrolled patients in two occasions:

Before surgery: At three months later where 50 patients (32 female, 18 male) were lost in the follow up which was assessed during patients visit to the outpatient clinics or through telephone calls. Biliary symptoms questionnaire focus on identifying predictors of upper abdominal pain relief after cholecystectomy.

All patients enrolled in this study subjected to:

- Full history taking
- Complete physical examinations
- Laboratory investigations

Eligible patients subjected to routine preoperative investigations including: -CBC.-Blood urea and serum creatinine. Liver functions test-INR-ECG.

Abdominal ultrasonography: The presence of gallstone was determined by sonography.

Diagnostic upper endoscopy: It was done in limited number of cases which were complaining of features suggesting peptic ulcer disease such as persistent heart burn not response medical treatment.

Questionnaire (biliary symptoms questionnaire):

- The symptoms where upper abdominal pain frequency (\leq 1/month, $>$ 1/month).
- Upper abdominal pain onset preoperatively (\leq 1/year, $>$ 1/year).
- Upper abdominal pain duration (30 minutes to 24 hours, $>$ 24 hours, $<$ 30 minutes).
- Upper abdominal pain most frequent timing (evening/night, morning/afternoon).
- Upper abdominal pain severity scale of 10 ($>$ 5, $<$ 5).
- Upper abdominal pain awakesness at night (yes, no).
- Lower abdominal pain (yes, no).

- Usual bowel pattern (Normal, abnormal, diarrhea, constipation, altered bowel habits).
- Nausea frequency ($\geq 1/\text{week}$, $< 1/\text{week}$).
- Often feeling bloated or burpy (yes, no).
- Gastroesophageal reflux disease (GERD) based on Montreal consensus [9] or Irritable bowel syndrome (IBS) based on Rome III Diagnostic Criteria for Irritable Bowel Syndrome [10] (GERD and IBS, GERD only, IBS only, Neither GERD nor IB).

Statistics

Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation and Student t-test (Unpaired) and Chi-square by SPSSV17. Univariate analyses focused on identifying predictors of UAP relief using logistic regression models. Backward elimination was used as the variable selection method to identify a set of variables that were jointly significant in predicting relief of UAP.

Results

Demographics

In this study, 950 patients with upper abdominal pain (UAP) who underwent elective cholecystectomy were included. The age ranged

between 25 and 59 years, with a mean age of 41.85 ± 5.221 years. They included 721 females (75.89%) and 229 males (24.11%). The demographic data are shown in Table I.

The preoperative data

All recruited patients were required to fill a preoperative questionnaire regarding their symptomatology and history of their UAP. As shown in Table I, most of our patients (61.05%) had the onset of their UAP ≤ 1 year, while 38.95% of our patients had it for more than 1 year. Most of our patients (54.95%) had the UAP once per month or less and 45.05% had it more than once per month. Most of our patients (65.05%) had UAP duration of ≤ 30 minutes, 14.95% had it for a period of more than 30 minutes to 24 hours and 20% had their UAP for more than 24 hours.

In 88% of our patients, the pain occurred most frequently in the evening or by the night time, 12% had it in the morning or in the afternoon. The visual pain score record showed that 82% of our patients described their pain as moderate to severe (> 5), 18% of the patients recorded it as mild to moderate (≤ 5). The pain was severe enough to awaken them by night in 71.05% of our patients. Although 76.95% of our patients did not show lower abdominal pain, 23.05% reported having lower abdominal pain.

Table I: Patient's demographics, selected symptom features and outcome.

Patients		N	%
Parameters			
Age	Range	25-59	
	Mean \pm SD	41.85 \pm 5.221	
Sex	Female	721	75.89
	Male	229	24.11
Upper abdominal pain onset preoperatively	≤ 1 year	580	61.05
	> 1 year	370	38.95
Upper abdominal pain frequency	$\leq 1/\text{months}$	522	54.95
	$> 1/\text{months}$	428	45.05
Upper abdominal pain duration	≤ 30 min.	618	65.05
	30 min to 24/hr	142	14.95
	> 24 hrs	190	20.00
Most frequent UAP timing	Evening/night	836	88.00
	Morning/afternoon	114	12.00
Upper abdominal pain severity scale of 10	> 5	779	82.00
	≤ 5	171	18.00
Upper abdominal pain awakens at night	Yes	675	71.05
	No	275	28.95
Lower abdominal pain	Yes	219	23.05
	No	731	76.95
Site of pain	Right upper quadrant (RUQ)	428	45.05
	Epigastria and RUQ	256	26.95
	Epigastric	190	20.00
	Left upper quadrant (LUQ)	76	8.00
Nausea frequency	$\geq 1/\text{week}$	200	21.05
	$< 1/\text{week}$	750	78.95
Often feeling bloated or burpy	Yes	599	63.05
	No	351	36.95
Bowel pattern	Abnormal	399	42.00
	Normal	551	58.00
Gasroesophageal reflux disease (GERD)/Irritable bowel syndrome	GERD and IBS	152	16.00
	GERD only	143	15.05
	IBS only	190	20.00
	Neither GERD nor IB	465	48.95
Outcome	Pain relief (group I)	713	75.05
	Pain continue (group II)	237	24.95

The majority of our patients (92%) reported their pain as upper abdominal; 45% reported it as right upper quadrant pain (RUQ), 26.95% reported it as RUQ and epigastric pain and 20% of the patients reported the pain as epigastric only. Only 8% of our patients reported their pain as left upper quadrant.

Looking at symptoms other than the UAP, most of the patients (78.95%) has nausea less than once per week, 21.05% had it once or more per week. Sense of bloating and burping was found in 63.05% of our patients. Also, abnormal bowel pattern was found in 42% of our patients. Based on our criteria, 48.95% of our patients did not complain from GERD or IBS, 15.05% complained from GERD, 20% complained from IBS, and only 16% complained from GERD and IBS.

Postoperatively, three months after the cholecystectomy, the patients were required to answer another questionnaire. At the end of the questionnaire, each patient was required to define whether his symptoms were relieved or not. Thus, our patients were divided into two groups according to pain relief after surgery; Group (I) included patients who had pain relief after surgery and group (2) included patients who did not have pain relief after surgery. 713 patients out of 950 patients (75.05%) had pain relief (group I) and 237 (24.95) did not have pain relief (group II).

On comparing age in both groups, patients in group (1) ranged between 26.2 and 59 years with a mean age of 42.04 ± 4.94 years, while patients in group (2) ranged between 25 and 56.1 years with a mean age of 41.77 ± 4.99 years. The increased age in group (1) patients was statistically significantly than in group (2) ($p=0.476$), denoting that the older the patient is, the more likely he/she gets relief of his/her symptoms.

Analysis of gender data shows that 79.47% of females had pain relief versus 61.14% of males (group 1). Whereas 20.53% of females and 38.86% of males did not show pain relief (group 2). The different proportions of females to males in group (1) was found to be statistically significant in univariate analysis ($p=0.001$). This denotes that the likelihood of having pain relief is greater in females.

Further analysis of symptoms shows that 93.46% of patients who had UAP once per month or less had pain relief versus 59.96% of patients who had pain more than once per month (group 1). Whereas 6.54% of patients who had UAP once per month or less and 40.04% of patients who had pain more than once per month did not show pain relief (group 2). The difference in pain frequency in group (1) was found to be statistically significant in univariate analysis ($p=0.001$). This was also found in multivariate analysis ($p=0.001$). This denotes that the likelihood of having pain relief is greater in patients who have UAP once per month or less.

Also, 86.21% of patients who had UAP onset once per year or less preoperatively had pain relief versus 57.75% of patients who had UAP onset more than once per year preoperatively (group 1). Whereas 13.79% of patients who had UAP onset one year or less preoperatively and 42.25% of patients who had UAP onset more than once per year preoperatively did not show pain relief (group 2). The difference in onset of pain in group (1) was found to be statistically significant in univariate analysis ($p=0.001$). This was also found in multivariate analysis ($p=0.001$). This denotes that the likelihood of having pain relief is greater in patients who have UAP onset once per year or less preoperatively.

It was also noted that 84.14% of patients who had UAP duration of 30 minutes or less had pain relief versus 64.79% and 53.16% of patients who had UAP duration of 30 minutes to 24 hours and more than 24 hours respectively (group 1). Whereas 15.86% of patients who had UAP duration of 30 minutes or less and 35, 21% and 46.84% of patients who had UAP duration of 30 minutes to 24 hours and more than 24

hours respectively did not show pain relief (group 2). The difference in duration of pain in group (1) was found to be statistically significant in univariate analysis ($p=0.001$). This denotes that the likelihood of having pain relief is greater in patients who have UAP duration of 30 minutes or less.

Looking at the most frequent UAP timing showed that 77.75% of patients who had UAP occurring most frequently in the evening or at night time had pain relief versus 55.26% of patients who had UAP occurring most frequently in the morning or in the afternoon (group 1). Whereas 22.25% of patients who had UAP occurring most frequently in the evening or at night time and 44.74% of patients who had UAP occurring most frequently in the morning or in the afternoon did not show pain relief (group 2). The difference in the most frequent timing of pain in group (1) was found to be statistically significant in univariate analysis ($p=0.001$). This denotes that the likelihood of having pain relief is greater in patients who have UAP occurring most frequently in the evening or at night time.

Analyzing pain severity, measured through the visual pain scale, showed that 80.49% of patients who described their pain as moderate to severe (>5) had pain relief versus 50.29% of patients who described their pain as mild to moderate (<5) (group 1). Whereas 19.51% of patients who described their pain as moderate to severe (>5) and 49.71% of patients who described their pain as mild to moderate (<5) did not show pain relief (group 2). The difference in severity of pain in group (1) was found to be statistically significant in univariate analysis ($p<0.001$). This denotes that the likelihood of having pain relief is greater in patients who describe their pain as moderate to severe (>5).

85.19% of patients whose pain awakened them at night had pain relief versus 50.18% of patients whose pain did not awaken them by night (group 1). Whereas 14.81% of patients whose pain awakened them at night and 49.82% of patients whose pain did not awaken them by night did not show pain relief (group 2). The difference between patients awakened by pain at night or not in group (1) was found to be statistically significant in univariate as well as in multivariate analysis ($p=0.001$ and $p=0.001$ respectively). This denotes that the likelihood of having pain relief is greater in patients whose pain awakens them by night.

The presence of lower abdominal pain had a negative impact on the outcome, as only 47.03% of patients who had lower abdominal pain had pain relief versus 83.45% of patients who did not have lower abdominal pain (group 1). Whereas 52.97% of patients who had lower abdominal pain and 16.55% of patients who did not have lower abdominal pain did not show pain relief (group 2). The difference in outcome between having lower abdominal pain or not in group (1) was found to be statistically significant in univariate as well as in multivariate analysis ($p=0.001$ and 0.021 respectively). This denotes that the likelihood of having pain relief is greater in patients who do not have lower abdominal pain.

On the other side, the presence of normal bowel pattern had a good impact on the outcome, as 85.84% of patients who had normal bowel pattern had pain relief versus 60.15% of patients who had abnormal bowel pattern (group 1). Whereas 14.16% of patients who had normal bowel pattern and 39.85% of patients who had abnormal bowel pattern did not show pain relief (group 2). The difference in outcome between having normal bowel pattern or not in group (1) was found to be statistically significant in univariate as well as in multivariate analysis ($p=0.001$ and 0.017 respectively). This denotes that the likelihood of having pain relief is greater in patients who have normal bowel habit pattern.

Frequency of nausea attacks had a negative impact on the outcome, as only 46% of patients who had nausea once or more per week had pain relief versus 82.8% of patients who had nausea less than once per

week (group 1). Whereas 54% of patients who had nausea once or more per week and 11.2% of patients who had nausea less than once per week did not show pain relief (group 2). The difference in outcome between having frequent or infrequent nausea attacks in group (1) was found to be statistically significant in univariate as well as in multivariate analysis (p=0.001 and 0.026 respectively). This denotes that the likelihood of having pain relief is greater in patients who have infrequent nausea attacks (less than once per week).

Looking at patients who often felt gas bloated or burpy, 64.94% of them had pain relief versus 92.31% of patients who did not often feel gas bloated or burpy (group 1). Whereas 35.06% of patients who often felt gas bloated or burpy and 7.69% of patients who did not often feel gas bloated or burpy did not show pain relief (group 2). The difference in outcome between having excessive gas bloat, burps or not in group (1) was found to be statistically significant in univariate as well as in multivariate analysis (p=0.001 and 0.024 respectively). This denotes that the likelihood of having pain relief is greater in patients who do not often have excessive gas bloat or burps.

Analyzing data from patients who had concomitant GERD or IBS showed that 44.74% of patients who suffered both GERD and IBS, 59.44% who had GERD only and 63.16% of patients who had IBS only had pain relief versus 94.62% of patients who suffered neither GERD or IBS (group 1). Whereas 55.26% of patients who suffered both GERD and IBS, 40.56% who had GERD only and 36.84% of patients who had IBS only did not have pain relief versus 5.38% of patients who suffered neither GERD or IBS (group 2). The difference between having concomitant GERD or IBS or not in group (1) was found to be statistically significant in univariate analysis (p<0.001). This denotes that the likelihood of having pain relief is greater in patients who do not suffer concomitant GERD or IBS (Tables II and III).

Looking at adding multiple positive predictive symptoms together (Table IV), it was clearly found that the presence of a positive predictive symptom or more gives a statistically significant improvement in outcome (relief of UAP) (p=0.028). At the level of 4 positive predictive symptoms, the level of significance was higher and even statistically significant compared to the presence of less than 4 positive predictive

symptoms (p=0.007). This denotes that relief of pain is more likely to occur with the presence of positive predictive symptoms and this progressively increases with increasing the number of positive predictive symptoms.

Discussion

Laparoscopic cholecystectomy remains the gold standard for treatment of symptomatic cholelithiasis. After cholecystectomy, 2/3 of patients are expected to be cured, and up to 90% have near complete relief in their symptoms [11]. However, persistent symptoms after cholecystectomy occur in 10 to 33% of patients, which is called the post-cholecystectomy syndrome [12]. It is also well known that cholecystectomy is not without risk. Serious complication as bile duct injury may occur, implying the danger of unnecessary cholecystectomy [8,13]. Therefore, to help physicians decide which patients would most likely benefit from elective cholecystectomy, especially due to the continued lack of clarity on what exactly constitutes biliary abdominal pain; insight might be gained from identifying which symptoms resolve following cholecystectomy.

This study is a prospective analysis involving 950 adult patients undergoing cholecystectomy for symptomatic cholelithiasis. Generally, the age ranged between 25 and 59 years, with a mean age of 41.85 ± 5.221 years. They included 721 females (75.89%) and 229 males (24.11%).

The objective is to identify symptoms predicting complete relief of upper abdominal pain (UAP) after cholecystectomy. The patients were asked to complete a previously validated biliary symptoms questionnaire (BSQ) before operation and 3 months postoperatively as well. Patients with complicated gallstone disease were excluded from this study. Given the episodic nature of gallstone pain, absence of pain at 3 months was the required target.

In our study, looking at the main preoperative pain characteristics in our patients, 61.05% had the onset of their UAP ≤ 1year, 54.95% had the UAP once per month or less, 65.05% had UAP duration of ≤ 30 minutes, and in 88% of our patients, the pain occurred most frequently in the evening or by the night time. The visual pain score records showed

Table II: Univariate and multivariable association of demographic and selected symptom features with postcholecystectomy relief of upper abdominal pain.

Parameters		Proportion (%) with UAP relief		Univariate results		Multivariable results	
		N	%	Odd (CI 95%)	P-value	Odd (CI 95%)	P-value
Upper abdominal pain frequency	≤ 1/months	400/522	93.46	9.539 (6.2597-14.536)	0.001	7.529 (4.985-10.856)	0.001
	>1/months	313/428	59.96				
	Total	713/950	75.05				
Upper abdominal pain onset preoperatively	≤ 1 year	500/580	86.21	4.606 (3.3674-6.302)	0.001	4.521 (3.128-6.125)	0.001
		213/370	57.57				
	Total	713/950	75.05				
Upper abdominal pain awakens at night	Yes	575/675	85.19	5.7083 (4.1544-7.8436)	0.001	5.932 (4.356-8.124)	0.001
	No	138/275	50.18				
	Total	713/950	75.05				
Lower abdominal pain	No	610/731	83.45	0.1761 (0.1267-0.2448)	0.001	0.135 (0.116-0.195)	0.021
	Yes	103/219	47.03				
	Total	713/950	75.05				
Usual bowel pattern	Normal	473/551	85.84	0.2489 (0.1821-0.3402)	0.001	0.268 (0.205-0.312)	0.017
	Abnormal	240/399	60.15				
	Total	713/950	75.05				
Nausea frequency	<1/week	621/750	82.80	0.1770 (0.1264-0.2478)	0.001	0.185 (0.105-0.254)	0.026
	≥ 1/week	92/200	46.00				
	Total	713/950	75.05				
Often feeling bloated or burpy	Yes	389/599	64.94	0.1544 (0.1007-0.2366)	0.001	0.235 (0.105-0.562)	0.024
	No	324/351	92.31				
	Total	713/950	75.05				

Table III: Univariate analysis of demographic and selected symptom features with postcholecystectomy relief of upper abdominal pain.

Parameters		Proportion (%) with UAP relief		Univariate results	
		N	%	Odd (CI 95%)	P-value
Sex	Female	573/721	79.47	2.461 (1.7848-3.394)	0.001
	Male	140/229	61.14		
	Total	713/950	75.05		
UAP duration	≤ 30 min.	520/618	84.14	0.214(0.150-0.306)	0.001
	30 min to 24 hr	92/142	64.79	0.617(0.394-0.964)	
	>24 hrs	101/190	53.16	(1.0) Reference	
	Total	713/950	75.05		
Most frequent UAP timing	Evening/night	650/836	77.75	2.829 (1.8896-4.235)	0.001
	Morning/afternoon	63/114	55.26		
	Total	713/950	75.05		
Upper abdominal pain severity scale of 10	>5	627/779	80.49	4.0770 (2.8781-5.7754)	<0.001
	≤ 5	86/171	50.29		
	Total	713/950	75.05		
Gastroesophageal reflux disease (GERD)/ Irritable bowel syndrome	GERD and IBS	68/152	44.74	20.905 (12751-34.765)	0.001
	GERD only	85/143	59.44	11.548 (6.82-19.377)	
	IBS only	120/190	63.16	9.731 (5.937-15.949)	
	Neither GERD nor IBS	440/465	94.62	Reference	
	Total	713/950	75.05		

Table IV: Association of multiple UAP Features with postcholecystectomy relief.

Number of features	Relief of UAP N/total (%)	Odd (CI 95%)	P-value
4	74/98 (75.5)	6.215 (2.324-18.652)	0.007
1, 2, or 3	388/646 (60)	3.658 (1.212-6.587)	0.028
0	5/16 (31.25)	(1.0) reference	

that 82% of our patients described their pain as moderate to severe (>5), but the pain was severe enough to awaken them by night in 71.05% of our patients. Lower abdominal pain was not a common symptom in our patients; however, 23.05% reported having lower abdominal pain. Many other studies, as that of Niranjana et al. did not analyze the pain characteristics, but recorded the presence of abdominal pain as the main symptom (96%) [14]. This generality in pain description makes it difficult to compare the findings. However, other studies, as that of Thistle et al. [8] made detailed analysis for the preoperative pain and found that most of the patients had pain onset less than 1 year, pain was most frequent by night time, and mostly awakened the patients by night. On the other hand, most of the patients had more frequent pain and longer duration of pain (66.67% had pain duration up to 24 hours) compared to our study. It must be mentioned that Thistle et al. conducted a multiracial study, in contrary to our study, hence the expected differences in symptoms.

The majority of our patients (92%) reported their pain as upper abdominal; 45% reported it as right upper quadrant pain (RUQ), 26.95% reported it as RUQ and epigastric pain and 20% of the patients reported the pain as epigastric only. Only 8% of our patients reported their pain as left upper quadrant in a similar study by Thistle et al. [8].

The most common site of pain was in the epigastrium, the difference may be attributed to racial differences (performed in California, USA), and also, this study included complicated gallstone cases (acute cholecystitis). In Lublin et al. [15] study, the most common sites for pain were epigastric 47%, right upper quadrant 32% and back 30% [14]. It is clear here why comparing the different studies is rather difficult as mentioned before.

Looking at symptoms other than the UAP, most of the patients (78.95%) had nausea less than once per week, 21.05% had it once or more per week. Sense of bloating and burping was found in 63.05% of our patients. Also, abnormal bowel pattern was found in 42% of our

patients. Based on our criteria, 48.95% of our patients did not complain from GERD or IBS, 15.05% complained from GERD, 20% complained from IBS, and only 16% complained from GERD and IBS. In Thistle et al. [8] study, infrequent nausea, absence of IBS and normal bowel habits were the main background symptomatology.

Three months after the cholecystectomy, the patients were required to answer another questionnaire. At the end of the questionnaire, each patient was required to define whether (as overall) his symptoms were relieved or not. Thus, our patients were divided into two groups according to pain relief after surgery; Group (1) included patients who had pain relief after surgery (713 patients-75.05%) and group (2) included patients who did not have pain relief after surgery (237 patients-24.95%). Thus, an overall cure rate of 75.05% was reported by our patients while similar cure rate has been evaluated in a number of reports, comparison is rather difficult due to differences in the definition of symptoms, their inclusion criteria, duration of follow-up, and outcomes. Nevertheless, a number of studies have reported complete relief of biliary pain following cholecystectomy ranging between 66% and 91% [7,16]. The latter study suggested that persistence of symptoms postoperatively was predicted by the preoperative use of psychotropic medications and the presence of only dyspeptic symptoms and high trait anxiety based on the State-Trait Anxiety Inventory [7].

On comparing age in both groups, patients in group (1) ranged between 26.2 and 59 years with a mean age of 43.04 ± 4.94 years, while patients in group (2) ranged between 25 and 56.1 years with a mean age of 41.77 ± 4.99 years. Racial differences affect age of presentation. For example, in Shrestha et al. [17] study, conducted in Nepal, the commonest age of presentation was below 30 years. On the other side, in studies conducted in India by Nagaraj SK et al. [18] and Gaharwar A [19], the mean age of presentation was 40.6 years. In our study, the increased age in group (1) patients was statistically significantly than in group (2) ($p=4.76$), denoting that the older the patient is, the more likely

he/she gets relief of his/her symptoms. It is generally known that the rate of gall stone formation tends to increase with each decade after the age of 20. This is due to increase of cholesterol in bile, which increases with age due to dyslipoproteinemia, this dyslipoproteinemia causes increase in cholesterol excretion in bile. Similarly, there is decrease in the synthesis of bile acids due to decrease in function of the enzyme cholesterol 7 alpha-hydroxylase. Besides, there is also hypoperfusion of the gall bladder wall due to sclerotic changes along with age [20,21].

In our study, similar to many other studies, the disease showed higher prevalence in general among females (75.89%) as compared to males (24.11%). This is attributed to the role of female sex hormones [22]. The relation between estrogen receptors and cholesterol synthesis has been studied in many studies. One study emphasized on the fact that estrogen stimulate the release of HMG Co-A reductase which simultaneously increase the synthesis of cholesterol leading to increased chances of super saturation. Similarly, progesterone hormone which inhibits the gall bladder contractility may also contribute to the stone formation by causing bile stasis [23]. Gender data shows that 79.47% of females had pain relief versus 61.14% of males (group 1). The pain relief difference between females to males in group (1) was found to be statistically significant in univariate analysis ($p=0.001$). This shows that the likelihood of having pain relief is greater in females. In other studies, like Thistle et al. [8], pain relief in males was found in 68% of the patients versus 58% in females. The increased number of Native American, Black, and Hispanic males in this study may attribute to such findings, as they are known to have high incidence of gallbladder disease, more intense symptoms and good response [24]. However, other studies, as Dua A et al. [25] found not only more pain relief in women, but also fewer complications, shorter lengths of stay, and lower costs ($P<0.05$).

The relation between pain frequency, onset of pain and pain relief was studied in our patients. It showed that 93.46% of patients who had UAP once per month or less had pain relief versus 59.96% of patients who had pain more than once per month (group 1). Pain relief difference in group (1) was found to be statistically significant in univariate analysis ($p=0.001$). This was also found in multivariate analysis ($p=0.001$). This suggests that the likelihood of having pain relief is greater in patients who have infrequent pain. Although, in Thistle et al. [8] study, the pain was more frequent than our study, it was clear than pain relief was much better in patients with less frequent pain (68%), which goes with our findings. In our study, 86.21% of patients who had UAP onset one year or less preoperatively had pain relief versus 57.75% of patients who had UAP onset more than one year preoperatively (group 1). Pain relief differences according to onset of pain in group (1) was found to be statistically significant in univariate analysis ($p=0.001$). This was also found in multivariate analysis ($p=0.001$). This also suggests that the likelihood of having pain relief is greater in patients who have UAP onset one year or less preoperatively. This was also found by Thistle et al. [8] at his study, where 61% of patients with a short duration of pain less than one year showed pain improvement after operation. However, other studies showed that pain relief can be greater in patients with longer duration of symptoms. Mertens et al. [7] reported 69% pain relief with no recurrence of symptoms in patients with previous biliary attacks more than one year. However, the small number of the study (a whole cohort of 172 patients) might explain the difference in analysis.

Pain duration analysis showed that 84.14% of patients who had UAP duration of 30 minutes or less had pain relief versus 64.79% and 53.16% of patients who had UAP duration of 30 minutes to 24 hours and more than 24 hours respectively (group 1). Pain relief differences according to duration of pain in group (1) was found to be statistically significant in univariate analysis ($p=0.001$). This shows that the likelihood of having pain relief is greater in patients who have UAP of short duration. This is contrast to other studies as Thistle et al. [8] who

found that having UAP duration of more than 30 minutes and up to 24 hours was usually associated with postoperative pain relief more than those patients suffer from pain of shorter duration (49%). It is known that native Americans and Hispanic Americans (which were included in this study) has higher rates of gall bladder disease with higher alcohol consumption and longer pain compared with African races [24], which explains the disagreement with our study.

Our data showed that 77.75% of patients who had UAP occurring most frequently in the evening or at night time had pain relief versus 55.26% of patients who had UAP occurring most frequently in the morning or in the afternoon (group 1). Also, 85.19% of patients whose pain awakened them at night had pain relief versus 50.18% of patients whose pain did not awaken them by night (group 1). The difference in the most frequent timing of pain in group (1) and whether it awakens them by night or not was found to be statistically significant in univariate analysis ($p=0.001$ and $p=0.001$ respectively). Our study shows that the likelihood of having pain relief is greater in patients who have UAP occurring most frequently in the evening or at night time and whose pain awakens them by night. Similar findings were found by Thistle et al. [8], where pain relief was found in 60% and 63% of patients having the pain most frequently at night and awakening them by night respectively. It has long been established in animal and human studies that the net water absorption from the gallbladder decreases at night while the patient is fasting and asleep, therefore, increasing gallbladder volume and pain at night [26]. This is a classic gallbladder symptom (denoting gallbladder origin of symptoms), thus predicting improvement after cholecystectomy.

Increased pain severity, measured through the visual pain scale, seems to be good predictive of pain relief. In our study, 80.49% of patients who described their pain as moderate to severe (>5) had pain relief versus 50.29% of patients who described their pain as mild to moderate (<5) (group 1). Pain relief differences according to severity of pain in group (1) was found to be statistically significant in univariate analysis ($p<0.001$). This shows that the likelihood of having pain relief is greater in patients who describe their pain as moderate to severe (>5). Similar finding were found by Thistle et al. [8] and Karmacharya et al. [27]. The latter found also more relief in patients with typical pain rather than atypical pain.

The presence of lower abdominal pain in our patients had a negative impact on the outcome, as only 47.03% of patients who had lower abdominal pain had pain relief versus 83.45% of patients who did not have lower abdominal pain (group 1). The difference in outcome between having lower abdominal pain or not in group (1) was found to be statistically significant in univariate as well as in multivariate analysis ($p=0.001$ and $p=0.021$ respectively). This shows that the likelihood of having pain relief is greater in patients who do not have lower abdominal pain. Lower abdominal pain is not a classic gallbladder symptom and usually refers to the presence of additional pathology, therefore, relief after cholecystectomy may not be guaranteed. Similar results were found by Thistle et al. [8], who showed that 67% of patients with no lower abdominal symptoms had pain improvement.

On the other side, the presence of normal bowel pattern had a good impact on the outcome, as 85.84% of patients who had normal bowel pattern had pain relief versus 60.15% of patients who had abnormal bowel pattern (group 1). The difference in outcome regarding having a normal bowel pattern or not in group (1) was found to be statistically significant in univariate as well as in multivariate analysis ($p=0.001$ and $p=0.017$ respectively). Thus, in our patients, the likelihood of having pain relief is greater in patients who have normal bowel habit pattern. Thistle et al. [8] in a similar study showed high percentage of postoperative pain relief in patients who had normal bowel pattern more than in patients who did abnormal bowel pattern [8]. The

presence of abnormal bowel habits may denote the presence of other GI dysfunction sharing the dyspeptic symptoms, which may persist after removal of the gallbladder, hence the persistence of symptoms. However, it must be noted that abnormal bowel habits may start after gallbladder removal. It has been shown clearly by Gihyun Kim et al. [28] that diarrhea was aggravated three months after surgery. This may be as high as in 20% of cases as reported by other studies [15]. Removal of the gallbladder and its reservoir function provides a rather continuous delivery of bile to the small intestine. Failure to actively absorb bile salts/bile acids in the ileum allows their spill into the colon, leading to net water and electrolyte secretion, termed cholerrheic diarrhea [29].

In our study, the presence of frequent nausea attacks had a negative impact on the outcome, as only 46% of patients who had nausea once or more per week had pain relief versus 82.8% of patients who had nausea less than once per week (group 1). This difference was found to be statistically significant in univariate as well as in multivariate analysis ($p=0.001$ and $p=0.026$ respectively). Our results point out that the likelihood of having pain relief is greater in patients who have infrequent nausea attacks (less than once per week). Similar results were noted by Thistle et al. [8] in their study, where, infrequent nausea was associated with better relief of symptoms (63% relief) [8]. Similarly, Mehravarz et al. [30] found that the presence of nausea predicted better improvement after cholecystectomy, their cure rate of pain in patient who had preoperative nausea was 54%, though they did not correlate that to the nausea attacks frequency.

The presence of gas bloating or burpy sensation did not show good impact on pain relief in our study, where, 64.94% of patients with these symptoms had pain relief versus 92.31% of patients who did not often feel gas bloated or burpy (group 1). The difference in outcome between having excessive gas bloat, burps or not in group (1) was found to be statistically significant in univariate as well as in multivariate analysis ($p=0.001$ and $p=0.024$ respectively). Our study shows that the likelihood of having pain relief is greater in patients who do not often have excessive gas bloat or burps. This agrees with Thistle et al. [8] findings, where, 70% of patients with no gas bloating showed pain relief [8]. However, some researchers found that the presence of bloating may not predict the outcomes, as Berger et al. [5] in their study, they found that bloating in their patients improved in 80% of patients after surgery, therefore preoperative bloating may not affect the outcome after all [5].

The presence of concomitant GERD or IBS is understandably a perplexing issue when dealing with symptom relief. Our study showed that 44.74% of patients who suffered both GERD and IBS, 59.44% who had GERD only and 63.16% of patients who had IBS only had pain relief versus 94.62% of patients who suffered neither GERD nor IBS (group 1). The difference between having concomitant GERD or IBS or not in group (1) was found to be statistically significant in univariate analysis ($p<0.001$). This shows clearly that the likelihood of having pain relief is greater in patients who do not suffer concomitant GERD or IBS. Similarly, in Thistle et al. [8] study, 70% of patients with neither GERD nor IBS showed pain relief. However, the presence of GERD does not preclude symptom improvement (59% improvement in our study). In a study by Mehravarz et al. [30], the frequent presence of heartburn before cholecystectomy and its relief after surgical treatment in most patients suggested a causal relation between the reflux disease and gallstones. Thus the disappearance of heartburn postoperatively may be a relief of cause, but also may reflect, however, the natural history of gastroesophageal reflux disease. Although, in this study, IBS patients showed a degree of pain relief, they confirmed that IBS per se was not alleviated by the operation. It must be noted also that GERD symptoms may actually appear or worsen after cholecystectomy. Karmachyara et al. [31] found that the commonest post cholecystectomy symptoms were heart burn (10%). Also, Niranian et al. [14] found fresh symptoms

that developed after cholecystectomy as heart-burn (6%), belching (3.5%), sour eructation (1%) and vomiting (0.5%). These GERD -like symptoms may result from gastric mucosal injury due to enhanced duodeno-gastric reflux due to loss of gall bladder reservoir function, pyloric incompetence after cholecystectomy, or post-operative change in the composition of bile with more unconjugated salts that may be more injurious to the gastric mucosa [32].

On a wider perspective, many predictive symptoms were studied in the literature. In their study, Niranian et al. [14] found the following symptoms as good predictors: the presence of biliary pain (99% relief), nausea (98% relief), vomiting (96% relief) and sour eructation (92% relief). These symptoms had better outcome than belching (64%) flatulence (61%) and heart burn (59%). Karmachyara et al. [31] linked the relief of pain after cholecystectomy with the presence of typical pain mainly ($p<0.001$). In our study, in summary, the following symptoms were found to be good predictors of pain relief after surgery: female patients, short onset of the disease (≤ 1 year), infrequent attacks of pain once or less per week, short duration of attacks less than 30 minutes, attacks occurring by night and awakening the patient, with moderate to severe intensity, in a patient with normal bowel habits, with no lower abdominal symptoms, no gas bloating, no GERD or IBS. Many of these predictors were confirmed by Thistle et al. [8] study except for their finding that a long history of symptoms with more frequent attacks is a good predictor of outcome, racial variations explains the difference between our data and this study. Further analysis of our data was done by adding multiple positive predictive symptoms together. It was clearly found that the presence of a positive predictive symptom or more gives a statistically significant improvement in outcome (relief of UAP) ($p=0.028$). At the level of 4 positive predictive symptoms, the level of significance was higher and even statistically significant compared to the presence of less than 4 positive predictive symptoms ($p=0.007$). Our study shows that pain relief after cholecystectomy is more likely to occur with the presence of a positive predictive symptom and this progressively increases with increasing the number of positive predictive symptoms. Such data might help decision making during selecting patients for cholecystectomy.

Conclusion

Based on our study we can conclude that;

- Laparoscopic cholecystectomy is an effective management option for symptomatic cholelithiasis, with a cure rate of 75.05% in our study.
- Better rates of pain relief can be achieved by better selection of patients, as sub analysis of symptoms showed better cure rates in the subgroups.

The followings were found as good predictors of outcome: older age, female patients, short onset of the disease (≤ 1 year), infrequent attacks of pain once or less per week, short duration of attacks 30 minutes or less, attacks occurring by night or awakening the patient by night, attacks of moderate to severe intensity, patient with normal bowel habits, absence of lower abdominal symptoms, absence of gas bloating, and absence of GERD or IBS.

Our study shows that pain relief progressively increases with increasing the number of positive predictive symptoms, being the best at the level of 4 positive predictive symptoms. Further larger studies are still needed to further define reliable prognostic symptoms to assure better selection of patients.

Recommendations

Careful history with interpretation of clinical subjective data helps in predicting good symptoms outcome in cholecystectomy.

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