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Original Article

Surgery Section

Symptomatic Gallstone Disease and Associated Upper Gastrointestinal Pathologies- A Prospective Cohort Study

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ABSTRACT

Introduction: Gallstones Disease (GSD) is one of the common medical problems leading to surgical intervention. The gold standard treatment for cholelithiasis is cholecystectomy. Co-existence of concurrent Upper Gastrointestinal (UGI) problems in GSD patients have attributed to the Post-cholecystectomy Syndrome (PCS). PCS consists of a group of abdominal symptoms, that recur and/or persist after cholecystectomy. The associated upper Gastrointestinal (GI) pathologies are identified by UGI endoscopy. *Helicobacter pylori* (*H.pylori*) infection has been implicated in many GI and extra-GI diseases. This aspect of identifying associated pathologies in symptomatic gallstone disease and identifying *H.pylori* infection using gene-sequencing method has not been studied in Indian population.

Aim: To study the associated UGI pathology detected by preoperative UGI endoscopy in symptomatic GSD and to compare the outcome based on the trend of PCS overtime.

Materials and Methods: The present prospective cohort study conducted in the Department of Surgery at Mahatma Gandhi Medical College and Research Insititute, Puducherry, India. The duration of the study was 18 months, from January 2019 to July 2020. The individuals over 18 years of age, who were symptomatic and ultrasonographically proven to have cholelithiasis formed the study group. The sample size was calculated to be N=50 (reduced to N=30 due to Coronavirus Disease-2019 (COVID-19) pandemic). Patients underwent UGI endoscopy prior to surgery, to assess for associated pathology including *H.pylori*. They were followed at regular intervals postoperatively and assessed based on questionnaire for the occurrence of PCS. The quantitative and qualitative variables were summarised as frequency, percentage and Pearson's Chi-square test and Fisher's-exact test, respectively. The sensitivity and specificity of *H.pylori* positivity by Histopathological Evaluation (HPE) in biopsy samples was compared to Polymerase Chain Reaction (PCR) as the gold standard. The significance level was set at p-value <0.05. The trend of the symptoms was also studied overtime.

Results: The mean age of the study population was 39.4±11.93 years. UGI abnormalities were present in 89.7% of the study group. *H.pylori* was identified in eight patients by histopathology examination while PCR detected 16 patients to have *H.pylori*. Sixteen out of 30 patients (53.3%) had PCS. It was also noted that, early PCS numbers tend to reduce over time, but the overall and late PCS numbers tend to increase over time. Although, a statistical analysis could not be performed, a graph was drawn to study the symptoms over the study period allowing observation of vital relation to gallstone disease. UGI pathology and *H.pylori* infection had a significant association with overall PCS with p-value=0.022 and 0.026, respectively.

Conclusion: The present study recommends the use of preoperative UGI endoscopy in symptomatic GSD. The identification of *H.pylori* by PCR using population-based gene-sequences has a role in treatment of gallstone disease. The trend shows difference in behaviour of PCS overtime.

Keywords: Cholecystectomy, Cholelithiasis, Gene sequence, *Helicobactor pylori* infection

INTRODUCTION

Individual with GSD electively present with typical biliary colic pain or atypical symptoms such as abdominal discomfort, dyspepsia, nausea, belching, heartburn, food intolerance, flatulence, vomiting, and loss of appetite [1-3]. These atypical symptoms have also been shown to be caused by associated GI pathology [4,5]. A proportion of patients, who undergo cholecystectomy may complain of persisting or recurring symptoms. These are known *as* PCS. These are usually categorised as early (1-30 days) and late (from 31st day to 180th day) depending on the time of onset of symptoms in the postoperative period [6,7]. Associated UGI pathology has been blamed as one of the reasons for PCS. The use of preoperative Upper-Gastrointestinal Endoscopy (UGIE) has been shown to play a vital role in identifying concurrent UGI pathology [8-10]. In addition to the UGI pathology identified by UGIE, *H.pylori* has also been implicated in this symptomatology [11-13]. Several methods have been described for identification of *H.pylori*, among which PCR is considered the gold standard [14-16]. The present study was aimed to look at the incidence of associated UGI pathology in patients with GSD and associate the incidence of PCS with UGI pathology and *H.pylori* infection as detected by PCR.

MATERIALS AND METHODS

The present prospective cohort study conducted in the Department of Surgery at Mahatma Gandhi Medical College and Research Insititute, Puducherry, India. The duration of the study was 18 months, from January 2019 to July 2020. The study was carried out after obtaining Institute Ethics Committee clearance (02/2019/41). Informed consent was taken from all the patients.

Sample size calculation: The sample size was calculated using the formula:

$$\frac{n \geq Z^2 1-\alpha/2 \times p\ (1-p)}{d^2}$$

and the reference values Alpha-0.05, estimated population (p)-0.08 and estimated error (d)-0.07. This required a study size of 50. However, due to COVID-19 pandemic, the sample was reduced to 30.

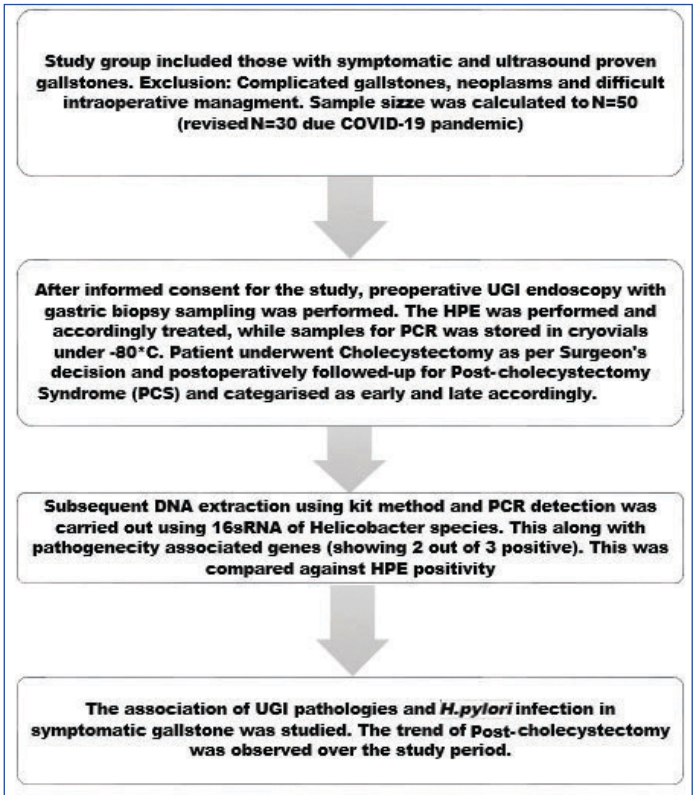
Inclusion criteria: Individuals over 18 years of age, who were planned for elective cholecystectomy for symptomatic and ultrasound proven GSD were included in the study.

Exclusion criteria: Patients, who did not undergo surgery, those found to have complicated GSD and those lost to follow-up were excluded from the study.

Study Procedure

The evaluation included basic demographic details, detailed history and physical examination. The patients were categorised into typical group, i.e., those with "biliary colic", while the atypical group presented with abdominal discomfort, belching, early satiety, fullness, nausea or vomiting, regurgitation, bloating, and retrosternal burning sensation [2,3,17,18]. They were evaluated with baseline investigations and UGIE was performed for identification of concurrent pathologies after informed consent. During UGIE, four biopsy samples (two from the antrum and two from the body of the stomach) were taken as recommended [19]. Two of the samples, one each from body and antrum, were transported in 20% formaldehyde for HPE and the two other samples were preserved in cryovials with 1.8 mL normal saline in the freezer under -80°C for subsequent Deoxyribonucleic Acid (DNA) extraction and PCR evaluation. All patients with positive UGI findings, that included both visual detection and histopathological findings were offered appropriate treatment. *H.pylori* eradication was provided to individual detected preoperatively by HPE. Laparoscopic cholecystectomy was performed and patients were interviewed at regular intervals for symptoms of PCS.

The stored biopsy samples in cryovials were processed using QIAamp DNA ®extraction kit (Qiagen India Pvt., Ltd., Delhi) for whole-genome extraction. The *H.pylori* primers were obtained from Integrated DNA Technologies (IDT)-The Custom Biology Company, Hyderabad and were chosen from previous studies related to the Indian population [16]. *Helicobacter* genus was identified using 16s Ribonucleic Acid (RNA), followed by the genes of Pathogenicity Associated Island (PAI) of *H.pylori*, namely Cytosine-Adenine-Guanine A (CAG A), Vacuolating cytotoxin A s1 allele (vacA s1) subunit and ure C [20-22]. Those biopsy samples positive for the presence of 16s RNA plus any two of the three pathogenetic genes were considered positive for *H.pylori* [14,20]. Methodology has been explained in [Table/Fig-1].



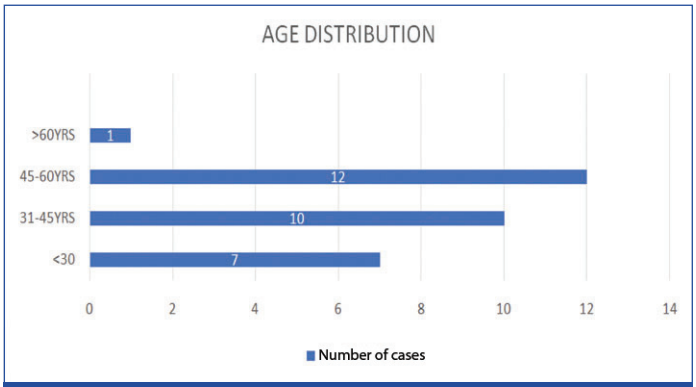
[Table/Fig-1]: Flowchart for methodology.

STATISTICAL ANALYSIS

All data collected were analysed using Statistical Package for Social Sciences (SPSS) version 16.0 (IBM SPSS, US) software. The quantitative variables namely age, gender, number of associated UGI pathologies detected by scopy and HPE were summarised as frequencies and percentage. The tests used, namely histopathological staining and conventional PCR, were compared in terms of sensitivity and specificity for the present study population. To study the statistical association between early, late and overall PCS groups with UGI pathologies and *H.pylori* positivity, Pearson's Chi-square test and Fischer's-exact test was applied. The significance level was set at p-value <0.05. The trend of the symptoms was also studied over the time.

RESULTS

The majority of the study population was between the age group 45-60 years (40%) followed by 31-45 years (30%). The mean age of the study population was 39.4±11.93 years as shown in [Table/Fig-2].



[Table/Fig-2]: Age-wise distribution of subjects.

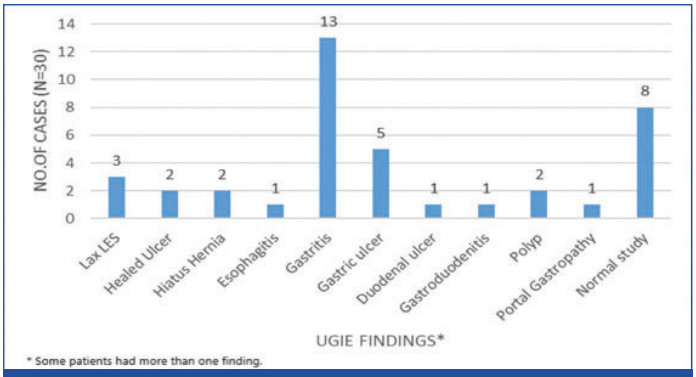
The present study population included 9 (30%) male patients and 21 (70%) female patients. Based on the symptomatology, the identified typical and atypical groups had equal presentation with belching as common presenting symptoms shown in [Table/Fig-3].

Presentation of symptoms	No. of individuals* (n)
Typical	15
Abdominal pain/discomfort	12
Nausea/vomiting	22
Anorexia	20
Heartburn	17
Belching	23
Food intolerance	9
Early satiety	8
Bloating	15
Flatulence/diarrhoea	3

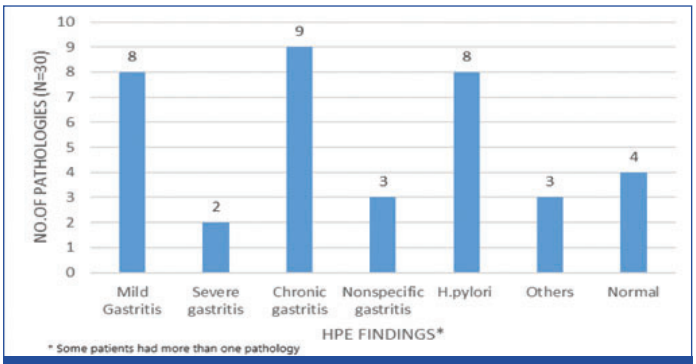
[Table/Fig-3]: Distribution of presenting symptoms (N=30).
*symptoms co-exist in individuals

A total of 26 (89.7%) patients out of the study population had UGI pathology. This included 22 individuals by visual detection and four more individuals by biopsy sampling. The commonest pathology on UGIE was gastritis in 13 (33.3%) patients followed by gastric ulcer in 5 (14.7%) patients [Table/Fig-4]. HPE of biopsy samples identified gastritis 22 (55%) as the commonest pathology. Other findings such as xanthoma and inflammatory polyp were seen in two patients. Four patients had a normal HPE. Special staining on biopsy samples identified 8 (20%) patients with HP infection [Table/Fig-5]. On PCR, 16 (53.3%) samples were HP positive. The sensitivity of HPE was 50% compared to PCR for HP detection in the present study while specificity was 100%.

The follow-up based on questionnaire on 14th, 30th, 60th, 90th and 180th day following surgery. This was plotted against x-axis on the graph. While, the number of individuals positive for PCS

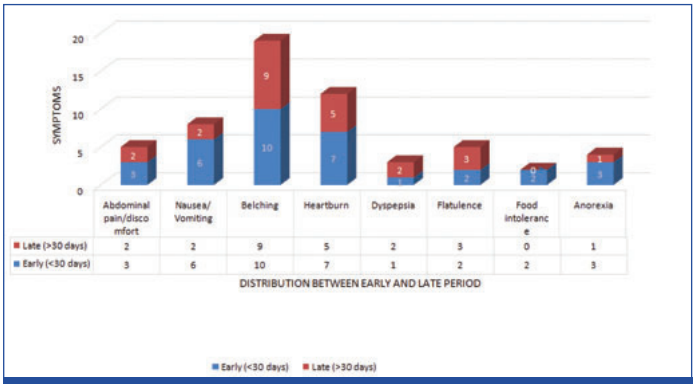


[Table/Fig-4]: Preoperative Upper Gastrointestinal (UGI) findings.

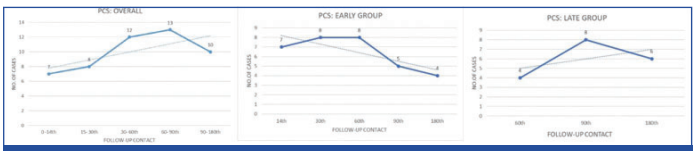


[Table/Fig-5]: Histopathological findings.

(early and late groups) formed the y-axis. In the present study, 16 patients had PCS. Out of these eight had early PCS and eight had late PCS. The most common symptom in both groups was belching (38.5% and 34.6%, respectively) followed by heartburn (27% and 19.23%, respectively) [Table/Fig-6]. A total of 10 of these patients continued to have symptoms at the end of study period of six months. The follow-up data in early PCS showed a trend in reduction of PCS overtime, while the late PCS showed an increasing trend at the end of the study period [Table/Fig-7]. All patients (16) with PCS were found to have UGI pathology. Ten patients without PCS also had UGI pathology. The relationship between PCS and UGI pathology was statistically significant (p=0.022) [Table/Fig-8].



[Table/Fig-6]: Distribution of symptoms based on duration.



[Table/Fig-7a]: Trend of PCS over time.

Out of 16 patients presenting with PCS, 12 (75%) individuals were positive for *H.pylori* on PCR. Among 14 individuals without PCS, 4 (28.6%) patients were identified to have associated *H.pylori* infection on HPE itself. These individuals received eradication therapy. None of these developed PCS. The 12 (75%) patients

Overall PCS (n=16)	UGI abnormality		Total n (%)	p-value
	Present n (%)	Negative n (%)		
Postitive	16 (100)	0	16 (100)	0.022
Negative	10 (71.4)	4 (28.6)	14 (100)	
Total	26	4	30	

[Table/Fig-8]: PCS and UGI pathologies showing significant association.
PCS: Post-cholecystectomy syndrome; UGI: Upper gastrointestinal

diagnosed later by PCR alone did not receive eradication therapy preoperatively and all of them developed PCS. Four patients who were asymptomatic were also found to be HP positive. The relationship between PCS and *H.pylori* infection was also statistically significant (p=0.026) shown in [Table/Fig-9]. The early and late groups were analysed separately to look for the presence of UGI pathologies and *H.pylori* infection. Fischer-exact test used showed p-value=0.27 (insignificant) for both groups, while similar result for *H.pylori* infection for both groups.

Overall PCS (n=16)	*H.pylori* infection		Total n (%)	p-value
	Positive n (%)	Negative n (%)		
Postitive	12 (75)	4 (25)	16 (100)	0.026
Negative	4 (28.6)	10 (71.4)	14 (100)	
Total	16	14	30	

[Table/Fig-9]: PCS and *H.pylori* showing significant association.

DISCUSSION

Cholelithiasis is common with an estimated prevalence of gallstone disease in India has been reported as 2% to 9% [21-24]. Although, laparoscopic cholecystectomy is the gold standard treatment, it has been seen that a proportion of individuals present with PCS [6]. Several studies have identified the causes of PCS to arise from the biliary tract and UGI pathology. It has been reported that, detecting and managing UGI pathology by preoperative UGIE can reduce the incidence of PCS [4,11]. In the study population, the incidence of cholelithiasis was found to be highest in the 4th-6th decade age group. This is similar to the study conducted by Parambil SM et al., who showed majority of patients belonged to 31-50 years of age with a mean age of 44±13.33 years [25]. Several studies have shown that, an increase in frequency was noted in patients more than 40 years of age [8,23,24]. Women were twice more the number of men in the present study. This also was similar to data collected by Bellad AKP and Asha MC and Parambil SM et al., [4,25]. The evaluation of gallstone patients based on symptomatology has shown an equal distribution between the typical and atypical groups in Indian population which was in accordance with other Indian based studies [5,26,27].

The present study found gastritis to be the commonest pathology (33.3%). This was similar to another study on Indian population. This study had a study population of 216 individuals divided between typical 98 (42.5%) and atypical 118 (57.5%) groups. The common UGI pathology identified using endoscopy was gastritis in typical group 30 (30.6%) and 48 in atypical group (40.67%) [28]. A prospective study, that performed UGIE on select patients presenting with atypical symptoms showed that, the common pathology were gastritis (69.8%), duodenitis (16.3%) and oesophagitis (9.3%) [29]. This was much higher than the incidence of gastritis (33.3%) in the present study, this may be because all the patients non selectively underwent endoscopy regardless of typical or atypical symptoms. The HPE of gastric biopsy samples showed findings in 26 (52%) individuals with gastritis as the most common finding. This was similar to other Indian studies showing gastric pathologies as common findings in preoperative evaluation. In a study, out of 80 individuals, who underwent endoscopy prior

to cholecystectomy, the most site of pathology was stomach and identified as gastritis (72.5%). Another study conducted on 2,800 individuals, preoperative endoscopy showed abnormalities in 1,187 (42%) of which 735 (26.3%) had gastritis [30,31]. A total of 16 out of 30 patients developed PCS, of which eight had early PCS and eight had late PCS. The authors found a significant association between preoperative UGI detected pathology and overall PCS (p=0.022). This was similar to the study by Jaunoo SS et al., where they suggested that, majority could be due to organic disorders of the GI system [32]. *H.pylori* detected by PCR also showed a significant association with overall PCS (p=0.026). When the trend of PCS over time was analysed, it was found that, early PCS number tend to decrease whereas, late PCS tend to persist over time. Since, the authors did not find any difference between UGI pathology or *H.pylori* infection occurrence in these two groups (p=0.27 and 0.074, respectively), the authors concluded that, late PCS may be more due to extra-gastric pathology. Other studies have implicated extra-gastric pathology in the occurrence of PCS [6,7,33]. In the present study, patients who were treated for *H.pylori* after preoperative identification by HPE did not develop PCS. However, the 12 patients, who were diagnosed to be HP positive on PCR much later and therefore, did not receive treatment, and all developed PCS. Even though, the numbers are small, this strongly suggests that, preoperative identification and treatment of *H.pylori* goes a long way to prevent PCS. The study recommends the use of PCR technique and kit method for identifying *H.pylori* and further study in the area of population-based species to aid eradication of *H.pylori*.

Limitation(s)

Sample size was limited due to COVID-19 pandemic. The trend of post-cholecystectomy symptoms shows vital relation to symptomatic gallstone disease although, a statistical analysis could not be drawn.

CONCLUSION(S)

There is a high incidence of PCS in symptomatic GSD. This was equally divided into early and late groups. The behaviour of groups was different, where early PCS tended to reduce over time, while the late and overall PCS tended to increase. The endoscopic biopsy sampling to detect *H.pylori* using histopathology is less reliable compared to PCR. There is a significant association between UGI pathologies and *H.pylori* infection in the occurrence of PCS and with treatment of these pathologies and *H.pylori* infection is likely to prevent PCS.

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