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Original Research Article

Prospective observational study to see the presence of micro-organisms in chronic Calculus Cholecystitis in eastern Indian population

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Running Title: Presence of micro-organisms in chronic Calculus Cholecystitis

Abstract

Background : Cholecystitis is one of the commonest biliary pathologies defined as chemical or bacterial inflammation of the gallbladder. Although it occurs in a variety of pathological and clinical forms, cholecystitis associated with gallstones is the most common type, occurring in about 90-95% cases. The objective of the present study is to see most common micro organism in bile culture and their antibiotic susceptibility in eastern Indian population. **Methods :** The present institution based prospective observational study was conducted in the Dept of General Surgery, Burdwan Medical College and Hospital, Burdwan, West Bengal, India between April 2021 to September 2022. Total 75 patients with chronic calculous cholecystitis underwent cholecystectomy were included in the study after applying inclusion criteria and taking informed consent. Statistical data were analysed by using Microsoft Excel and SPSS V.21 software. **Results :** Mean age of 46.05 ±12.15 years. There was a female predominance with 49 females (65.3%) and 26 (34.7%) male out of 75 patients. The mean levels of height, weight and BMI among the study participants were 159.35 ±5.70 cm, 70.35 ±6.80 kg and 27.78 ±3.46 kg/m2 respectively. most patients (60%; 45 out of 75) did not have any co- morbidity while 18 (24%) patients had diabetes mellitus, 9 (12%) patients had hypertension, and 3 (4%) had

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hypothyroidism**. M**ost common clinical symptom among study participants was pain in upper abdomen (64%) followed by dyspepsia (50.7%), nausea and vomiting (16%). The most common indication of chronic calculus cholecystitis was sedentary lifestyle (45.3%) followed by hyperlipidemia (40%), high fat diet (34.7%) and oral contraceptive pills (24%). USG of abdomen confirmed the incidence of cholecystitis in all 75 cases. Out of 75 cases 19 (25.3%) underwent laparoscopic cholecystectomy and 56 (74.7%) underwent open cholecystectomy. Out of 75 cases cholesterol stones (65.3%) were the most common type of stones found among study participants followed by pigmented stones (26.7%) and missed type of stones (8%). **Conclusion :** Bacterial growth in chronic calculus cholecystitis is not very common however the identification of microorganism after cholecystectomy can be used as a useful tool in the management of these patients and consequently reduces the morbidity and mortality.

Keywords : Surgery, Calculus Cholecystitis, Micro-organisms

Introduction :

Gallstone disease (GSD) is a frequent and socially significant public health problem worldwide [1]. Approximately 10–20% of adults in the United States have gallstones, and the prevalence of this disease is constantly growing. The number of cholecystectomies is also increasing and currently numbers more than 750,000 per year. Medical expenses for the prevention and treatment of cholelithiasis [2,3].

More than 175,000 cholecystectomies are performed annually because of cholelithiasis [4,5]. Despite the high worldwide prevalence of GSD, the role of the biliary microbiota in gallstone pathogenesis remains obscure. In 1966, Maki [6] showed the role of bacterial infection in the pathogenesis of pigmented gallstones. Later, in several works, it was demonstrated that changes in the gut microbiota are also one of the etiological factors of cholesterol gallstones [7,- 9].

There is currently an increasing number of studies about the role of the gut microbiome as a key link in the pathogenesis of GSD [10- 16]. The main factors contributing to the formation of gallstones are defective gallbladder motility, metabolism and secretion of cholesterol and bile acids [12]; the gut microbiota is actively involved in the regulation of bile acid metabolism, changing the size and composition of the bile acid pool [13,14]. These associations are being verified by a significantly increasing number of studies confirming the participation of intestinal microbiota in gallstone formation, including works studying the bacterial metabolome and antibiotic resistance genes [10]. In addition, some types of intestinal bacteria can elicit chronic inflammation and reactive oxygen species (ROS)-mediated genotoxicity or secrete DNA-damaging toxins, which also increases the formation of gallstones [17-19].

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With this background the present study has been carried out to see most common micro organism in bile culture and their antibiotic susceptibility in eastern Indian population.

Materials and Methods

Present institution based prospective observational study was conducted in the Dept of general surgery, Burdwan Medical College and Hospital, Burdwan, West Bengal, India between April 2021 to September 2022.

Patients with chronic calculous cholecystitis underwent cholecystectomy (lap / open cholecystectomy) and admitted through General Surgery OPD / Emergency fulfilling inclusion criteria were allotted in any study group and those were not fulfilling the criteria were excluded from the study.

This formula ($n = Z^2P (1 – P)/ d^2$) used by Unisa S, Jaganth P, Roy TK et al in their study titled "Population based study to estimate prevalence and determine risk factors of gallbladder diseases in the rural Gangetic basin of North India.[20] Due to limited time 75 samples were included in the study.

Inclusion Criteria :

- Patients in the age group of 18-75yrs
- Patients who underwent cholecystectomy in BMCH during the study period
- Clinical features suggestive of cholecystitis
- Radiological features suggestive of calculous cholecystitis

Exclusion Criteria :

- Patients with acalulous cholecystitis
- Patient who are not fit or not willing for the surgery
- Patients who were having major CVS/GI/Renal disorders
- Patients presenting with complication like CBD stones, gallstone pancreatitis, septic complications

The Proposed study was to treat patients who came with acute cholecystitis then depending on the clinical condition and severity the patient was managed. In case of mild to moderated pain conservative management was given and later after 6 weeks of acute attack the patient was planned for laparoscopic or open cholecystectomy. Thus to see the presence of microorganisms in chronic calculus cholecystitis was assessed among Eastern Indian population.

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All patients were investigated with haemogram, ECG, LFT, blood sugar, blood urea, serum creatinine, urine analysis, blood group, chest x-ray, ultrasound scan of the abdomen. Relevant investigations and specialist consultations were taken for patients with associated medical illness and their control was achieved. Risk and complications of the condition as well as the types of surgical options available and their benefits and complications were explained to the patients, and consent was taken.

The necessary preoperative work up and preoperative antibiotics were given. After opening the abdomen, the pathological features and anatomical variations were noted and documented. Since patients with CBD stones were excluded from the study, routine CBD exploration and intraoperative cholangiogram was not performed.

After cholecystectomy, the removed gallbladder was sent for histopathological examination and the gallstones for chemical analysis, bile is sent for gram stain and culture and sensitivity. All the patients received routine post-operative care. Patient was monitored in the post-operative period to note the development of any complication and suitable treatment given according to the need.

Method of Data Analysis Plan : The data was analyzed with the help of computer software SPSS 21.0 for windows. Descriptive statistics were performed in the collected data. Chi square test was used to ascertain statistical significance among the proportions. Incidence along with 95% confidence limits was calculated to express magnitude. Chi square test, Fischer Exact test and other relevant parametric and non- parametric tests were done. Proportions were calculated to assess the qualitative outcomes to compare the outcome by characteristics of the subjects. A p value of <0.05 was considered as statisticallysignificant unless proved otherwise.

Ethical considerations- Study was initiated after obtaining the informed consents from the participants and ethical clearance from the institutional ethical committee.

Results

Table 1: Age and gender wise distribution of the study participants

Age Group	Frequency	Percentage
18-30 years	8	10.7
31-40 years	14	18.7
41-50 years	30	40.0
51-60 years	13	17.3

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61-70 years	8	10.7
>70 years	2	2.7
Total	75	100.0
Mean Age	**46.05 ±12.15**	
Gender		
Total	**75**	**100.0**
Male	26	34.7
Female	49	65.3
Total	**75**	**100.0**

In the present study age range of the study participants varied from 21 to 74 years. Majority of the patients in the present study were aged from41 to 50 years (40%) followed by 31-40 years (18.7%) and 51-60 years (17.3%) with a mean age of 46.05 ±12.15 years. There was a female predominance with 49 females (65.3%) and 26 (34.7%) male out of 75 patients. (Table 1)

Table 2: Distribution of the study participants according to anthropometric variables

Anthropometric Variables	Mean	±SD
Height (cm)	159.35	±5.70
Weight (kg)	70.35	±6.80
BMI (kg/m^2)	27.78	±3.46

The mean levels of height, weight and BMI among the study participants were 159.35 ±5.70 cm, 70.35 ±6.80 kg and 27.78 ±3.46 kg/m2 respectively. (Table 2)

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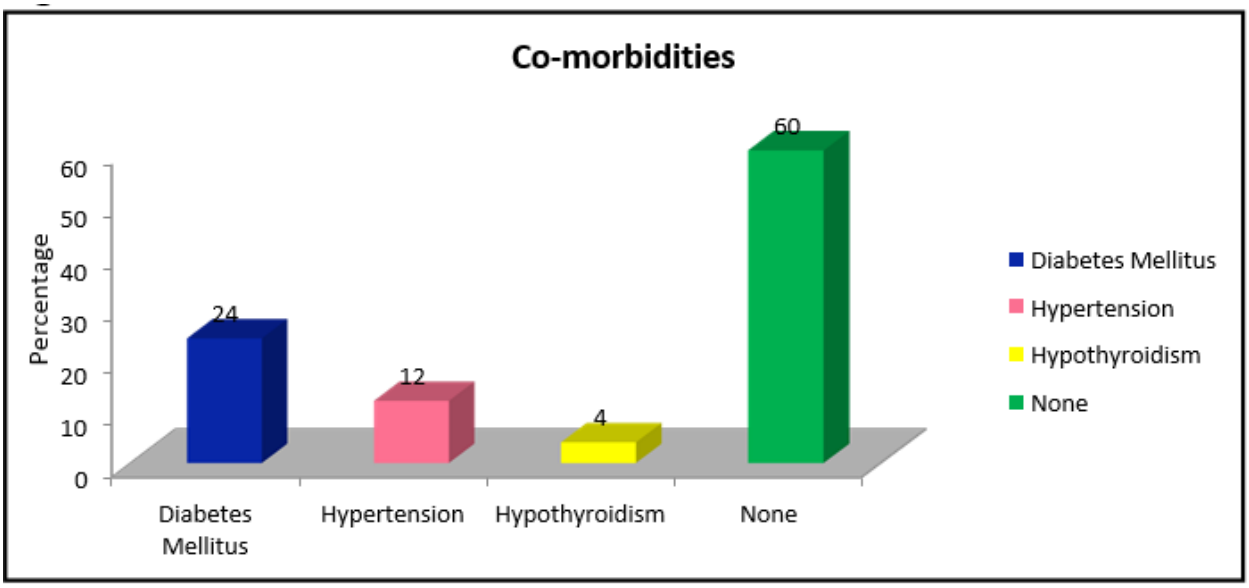
Figure 1 : Distribution of the study participants according to co-morbidities



In present study, most patients (60%; 45 out of 75) did not have any co- morbidity while 18 (24%) patients had diabetes mellitus, 9 (12%) patients had hypertension, and 3 (4%) had hypothyroidism. (Figure 1)

Table 3: Distribution of the study participants according to clinical symptoms and duration

Clinical Symptoms	**Frequency**	**Percentage**
Pain in upper abdomen	48	64.0
Dyspepsia	38	50.7
Nausea/ Vomiting	12	16.0
Fever	3	4.0
Asymptomatic	24	32.0
Duration of Symptoms		
<6 months	26	37.7
6-12 months	31	41.3
>12 months	18	24.0
Total	**75**	**100.0**
Mean ±SD	8.38 ±5.40	

The most common clinical symptom among study participants was pain in upper abdomen (64%) followed by dyspepsia (50.7%), nausea and vomiting (16%) and fever (4%) while 32% cases were asymptomatic. Regarding the duration of symptoms, we found majority of the study

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subjects had duration of symptoms for6-12 months (41.3%) followed by ,6 months (37.7%) and >12 months (24%) with a mean duration of symptom of 8.38±5.40 months. (Table 3)

Table 4: Indication of Chronic Calculus Cholecystitis, type of surgery and type of stones.

Indications	**Frequency**	**Percentage**
Sedentary Lifestyle	34	45.3
Hyperlipidemia	30	40.0
High Fat Diet	26	34.7
Oral Contraceptive pills	18	24.0
Type of surgery		
Laparoscopic Cholecystectomy	19	25.3
Open Cholecystectomy	56	74.7
Type of stones		
Cholesterol Stone	49	65.3
Pigmented Stone	20	26.7
Mixed Type Stone	6	8.0

The most common indication of chronic calculus cholecystitis was sedentary lifestyle (45.3%) followed by hyperlipidemia (40%), high fat diet (34.7%) and oral contraceptive pills (24%). In the present study, USG of abdomen confirmed the incidence of cholecystitis in all 75 cases. Out of 75 cases 19 (25.3%) underwent laparoscopic cholecystectomy and 56 (74.7%) underwent open cholecystectomy. Out of 75 cases cholesterol stones (65.3%) were the most common type of stones found among study participants followed by pigmented stones (26.7%) and missed type of stones (8%). (Table 4)

Table 5: Type of stones and Isolated Micro-organism in Bile culture findings

Bile Culture Findings (n=75)	**Frequency**	**Percentage**
Positive	11	14.7
Negative	64	85.3
Total	**75**	**100.0**
Micro-organism in Bile culture findings (n=11)		
E. Coli	5	45.5
Klebsiella	3	27.3
Pseudomonas	2	18.2

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Enterococcus	1	9.1
Total	**11**	**100.0**

On culture of the bile, bacterial growth was seen in 14.7% (227 out of 266) patients while 85.3% (64 out of 75) were negative for bile culture. Out of 11 cases of isolated micro-organism E. Coli was the most common one (45.5%) followed by Klebsiella (27.3%), Pseudomonas (18.2%) and Enterococcus (9.1%). (Table 5)

Table 6: Antibiotic Susceptibility

Antimicrobial agents	***Escherichia coli* (n=5)**		***Klebsiella* (n=3)**		***Pseuodomonas* (n=2)**		***Enterococcus* (n=1)**	
	S	**R**	**S**	**R**	**S**	**R**	**S**	**R**
Ampicillin	2	3	1	2	1	1	0	1
Amikacin	5	0	3	0	2	0	1	0
Ceftriaxone	4	1	2	1	1	1	1	0
Cefotaxime	4	1	3	0	2	0	1	0
Meropenem	5	0	3	0	2	0	1	0
Gentamycin	5	0	2	1	1	1	1	0

Of the 11 patients in whom organisms were isolated, antibiotic susceptibility is shown in Table 6. Amikacin and Meropenem were found to be the most sensitive antibiotics in the present study with 100% sensitivity to all the miscroorganisms

Discussion :

Chronic calculus cholecystitis is usually associated with gall stones. Gallstones are most common biliary pathology and are major cause of morbidity and mortality throughout the world. Incidence of gallstone increases with age; it is more common in female than male.[21,22] Gallstone diseases are responsible for about 95% of biliary tract abnormalities.[23] The prevalence rate of gall bladder disorders varies between 15-25% in developing countries.[24] It varies between 5-10% in India.[24] The rate of increase of incidence is due change in the dietary habits and life style of the individuals.[25]

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Primarily gallstones can be divided into two major groups. Firstly pure gallstones contributing 10% and secondly is mixed or combined gallstones which accounts for 90% of gallstones. Mixed gallstones frequently associated with cholecystitis.[26]

Ultrasonography of abdomen is the accurate diagnostic procedure for the identification of the disease condition. The management of the disease includes non-surgical and surgical modalities. Non-surgical treatment includes dissolution of gallstones with bile salts, extracorporeal shock wave lithotripsy (ESWL) and invasive contact dissolution with organic solvents. The surgical procedures include cholecystectomy, either open or laparoscopic. Cholecystectomy is done more commonly for chronic calculous cholecystitis as compared to acute cases.[27]

Various studies proved that bacteria plays a significant structural and functional role in the development of pigment and cholesterol gallstones.[28,29] Bile which in normal is sterile is about ½ of the cases bacteria can be cultured from the gallbladder bile.[6] Infective factor seems to be a major cause of formation of gallstones. Moynihan's aphorism that "Gall stone is a tomb stone erected in the memory of the organism within it" is true even today.[22]

The incidence of cholelcystitis increases with age and it is more common in females. This statement was supported by the findings of our study. In the present study age range of the study participants varied from 21 to 74 years. Majority of the patients in the present study were aged from41 to 50 years (40%) followed by 31-40 years (18.7%) and 51-60 years (17.3%) with a mean age of 46.05 ±12.15 years.

In a study conducted by Zuhair et al peak age of incidence was reported between 41-50 years. Study by Ranshoff reported the same results.[30,31] This was in accordance with the findings of Gupta et al.[23] Singh KK et al in their study also reported majority of the patients were between 41-50 years (38%).[32]

Study have shown an increase in the prevalence of gallstone with age probably because of decrease in activity of cholesterol reductase and increase in activity of HMG CoA reductase.[37]

There was a female predominance with 49 females (65.3%) and 26 (34.7%) male out of 75 patients. Similar female predominance was reported by Gupta et al in a study on morphological spectrum of gallstone and bacteriology of bile in cholelithiasis.[23] Khedkar et al reported female predominance with cholelithiasis which is consistent with the study conducted.[33] Singh KK et al in their study reported female preponderance (69%) was observed in their study.[32] Similar

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observation was made by Lokesh et al.[34] Gandhi et al also reported that majority of patients with cholelithiasis were female (92%).[35]

Regarding the type of gallstones we found that Out of 75 cases cholesterol stones (65.3%) were the most common type of stones found among study participants followed by pigmented stones (26.7%) and missed type of stones (8%).

Similarly Mayurkumar J Dudhat et al in their study reported cholesterol, pigment and mixed stones are 48, 14 and 7 respectively in female patients, where 20, 8 and 3 respectively in male patients.[36]

Singh KK et al in their study observed among the type of gallstones, cholesterol type was seen in 68% cases.[32]

Gandhi et al in accordance to the finding of the present study reported cases with cholesterol type of gallstone were found to be predominant 52%, followed by mixed stone 30%, cases with black pigment type of gallstone were 10% and cases of combined pigment stone were 8%.[35]

However, Gupta et al in contrast to the present study reported gallstone was classified according to their morphological appearance and cases with mixed type of gallstone was found to be predominant 50%, followed by cholesterol stone 30%. Cases with combined type of gallstone were 12% and cases of pigment stone was 8%.[23]

In contrast to the present study literature from Chennai, Jayanthi V et al found maximum cases of pigment type of gallstone.[37] The variation in different types of gallstones varies significantly in different parts of India.

The most common clinical symptom among study participants was pain in upper abdomen (64%) followed by dyspepsia (50.7%), nausea and vomiting (16%) and fever (4%) while 32% cases were asymptomatic. This was similar to the finding of Wani et al.[35]

If the bile duct gets obstructed, then bacteria can proliferate within the stagnant bile. Bacteria can then enter the circulation leading to a systemic infection. Bacteria can be isolated from the bile or gallbladder in about 30% of cholelithiasis patients. Few studies have found that certain bile bacteria like *Helicobacter pylori* can induce cholesterol gallstone formation.[38]

The incidence of bile and gallstone infection varies considerably from area to area in the world and also among different countries in a given area.[39] In the present study the incidence of

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positive bile culture was 11.7% (45 out of 75 cases). Which is much lower than Gupta et al where they reported the positive bile culture was 40%, which is considerably higher than reported by Yaqin and Sultan.[40] Other studies show this positivity ranges from 16.4% to 46%. Other studies have shown bacterial isolation rate between 23 to 47% in cases of chronic cholecystitis with cholelithiasis.[41]

However similar to the present study in the study by Ahmad M et al, only 23.6% patients showed positive growth on bile culture.[42]

In contrast Gomes et al in Sri Lanka grew *E coli* in 40 % and a high 35% of *Klebsiella* species.[43]

The microorganisms predominantly found are gram-negative aerobes like E.coli, Klebsiella, Proteus and Pseudomonas; gram-positive cocci are also present in substantial numbers like the *Streptococci*, *Enterococci* and *Staphylococci*. Anaerobes found in the bile are anaerobic Streptococci, Clostridium welchii and Bacteroids fragilis.[44] Out of 11 cases of isolated micro-organism in the present study *E. Coli* was the most common one (45.5%) followed by *Klebsiella* (27.3%), *Pseudomonas* (18.2%) and *Enterococcus* (9.1%).

Gupta et al also in their study reported *E.coli* was found to be the commonest organism in their study, and it also reported in previous studies.[23]

Singh KK et al in their study reported *E. coli* was found to be the common organism isolated from the bile culture of many patients (50%). Similar incidence was noted in previous studies.[23,27,32,34]

Regarding the antibiotic susceptibility we found Amikacin and Meropenem were found to be the most sensitive antibiotics in the present study with 100% sensitivity to all the miscroorganisms [Table 6].

A cross sectional study by Ahmad F et al reported *E. coli* was the most common bacteria isolated from such patients while other commonly reported bacterial were *Klebseilla* (17.16%), *Salmonella* (12.68%) and *Shigella* (6.34%) and in more than 50% cases all four bacterial species were found to be sensitive to cefuroxime, ceftriaxone, ciprofloxacin and amoxicillin.[45]

Shankaran R et al in their study observed all the cultures were sensitive to amikacin and meropenem, 97.44% to imipenem, and only 43.39% were sensitive to ampicillin.[46]

Based on the above observation we can suggest that that middle aged females are more prone to

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develop chronic calculus cholecystitisand the most common symptom is pain in upper abdomen, the most common indication for the cholecystitis was sedentary lifestyle. The incidence of bacterial infection in the present study was 14.7%. The most common type of gall stone was cholesterolstones and most common isolated microorganism was *E. Coli* followed by *Klebsiella*. Also culture of bile at Cholecystectomy is helpful because appropriate antibiotic can be administered in cases of culture being positive, hence avoid serious complication.

Conclusions

Acute cholecystitis is defined as an acute inflammation of the gall bladder. It is one of the most common inpatient diagnoses at surgical departments and in a vast majority of patients it arises as complications of cholelithiasis (calculous cholecystitis). Bacterial growth is believed to represent a secondary complication and not the initiating event of the disease. Bacterial Infection is considered an important negative prognostic factor, and antibiotics are included in treatment recommendations for all grades of severity.

Hence the present study was conducted with the aim to see the incidence of biliary micro-organism and most common biliary micro-organisms and resistance to antibiotics in patients with cholecystitis, as well as to predict situations that do not require the use of prophylactic antibiotics.

Based on the observation of the present study we can suggest that middle aged females are more prone to develop chronic calculus cholecystitisand the most common symptom is pain in upper abdomen, the most common indication for the cholecystitis was sedentary lifestyle. The incidence of bacterial infection in the present study was 14.7%. The most common type of gall stone was cholesterolstones and most common isolated microorganism was E. Coli followed by Klebsiella.

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Ethical approval: The study was approved by the institutional ethics committee

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