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Original Article

Pathology Section

Clinicopathological Concordance of Paediatric Laparoscopic Cholecystectomy at a Single Centre in India

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ABSTRACT

Introduction: The overall incidence of cholecystitis in children appears to be increasing although the exact frequency of acute and chronic cholecystitis among children in India or worldwide remains unknown. The frequency of paediatric cholecystitis has proportionally increased with the childhood obesity and intake of habitual fatty food.

Aim: To present the histopathological concordance of Laparoscopic Cholecystectomy (LC) performed among children for a clinical diagnosis of Gallbladder (GB) disease.

Materials and Methods: A single centre retrospective study was performed including histopathological and relevant clinical data of all paediatric LC performed at Career Institute of Medical Sciences and Hospital, Lucknow, Uttar Pradesh, India, between January 2019 to January 2022. Paediatric patients who had undergone LC in the designated time period for a clinical diagnosis of cholelithiasis and/or inflammatory GB disease with classical signs of inflammation were included. Study population with LC procedure submitted for histological evaluation were identified by performing an electronic search through the archives of Department of Pathology, Career Institute of Medical Sciences and Hospital, Lucknow, Uttar Pradesh, India, followed by a manual review of GB specimens, histopathology slides and reports.

Results: Among 265 patients who underwent LC during this period, there were 62 (23.4%) children. The average age of presentation was 13 years (range 5-18 years), 49 (79%) were girls and 13 (21%) were boys. The clinical diagnosis for which paediatric LCs were performed were cholelithiasis among 51% and cholecystitis among 48%. On histopathological concordance these turned out to be chronic cholecystitis among 98.4% children among which 51% were associated with cholelithiasis. Calculous cholecystitis was more frequent than acalculous cholecystitis. Chronic cholecystitis with cholelithiasis and cholesterolosis was more frequent among adolescent girls.

Conclusion: This study suggests that chronic cholecystitis accounts for the majority of inflammatory diseases among children undergoing LC for a GB disease and may or may not be associated with cholelithiasis. Chronic cholecystitis with cholelithiasis and cholesterolosis seem more frequent among adolescent girls.

Keywords: Children, Cholecystitis, Cholelithiasis, Diagnosis, Inflammatory

INTRODUCTION

The spectrum of GB disorders in the paediatric population has changed over the past three decades [1]. Cholecystitis is defined as inflammation of the GB traditionally divided into acute and chronic subtypes. These subtypes are considered to be separate entities but are closely related in the paediatric age group. Both acute and chronic cholecystitis may also be considered calculous or acalculous, but the inflammatory process remains the same. Most LCs performed for acute cholecystitis show evidence of chronic inflammation, supporting the concept that acute cholecystitis may actually be an exacerbation of chronic distension and GB tissue damage. Although both acute and chronic cholecystitis can be related to cholelithiasis, however in childhood acalculous cholecystitis may be the most frequent form [2]. The exact frequency of acute and chronic cholecystitis among children in India or United State remains unknown [2]. The prevalence of chronic cholecystitis in paediatric age group ranges from 0.13-1.9% including both calculous and acalculous forms [3]. Recent epidemiological studies and case reports have suggested an increase in acalculous form of chronic cholecystitis in the paediatric population [4]. While cholecystitis was previously attributable mainly to haemolytic disease, the frequency of paediatric cholecystitis due to cholelithiasis has proportionally increased with the childhood obesity epidemic suggesting a strong correlation [5]. There however, seems to be more than one factor of concern at play which may include rapid change to urban style feeding habits and fatty food intolerance. As LC is the standard of care for cholecystitis in children, it is also resulting in increased number of LCs performed in paediatric age group [6,7]. Despite the increased frequency of chronic cholecystitis in children and adolescents there is paucity of literature in this regard which results in under estimation of the burden. Most paediatric studies focus on cholelithiasis and biliary dyskinesia rather than inflammatory GB disease [8].

The aim of this study was to present the clinicopathological concordance of LCs performed among children at a single centre.

MATERIALS AND METHODS

This was a single centre retrospective study performed on GB specimens, at Career Institute of Medical Sciences and Hospital, Lucknow, Uttar Pradesh, India, between January 2019 to January 2022. Analysis of data was done from January 2022 to June 2022. The study was approved by the Institutional Ethics Committee (IEC) for Scientific Research vide reference number CIMSH-IEC-R 25/2018.

Inclusion criteria: Initially all patient who had undergone LC in the designated time period for a clinical diagnosis of cholelithiasis and/or inflammatory GB disease with classical signs of inflammation were included. Thereafter the target paediatric age group of 0-18 years according to Indian Association of Paediatricians were identified for further study [9]. Inclusive symptoms considered indicative of inflammation were right upper quadrant abdominal pain radiating to mid back or right scapula, fever, nausea, vomiting and abdominal discomfort related to intake of fatty food. Inclusive clinical and laboratory parameters considered to be consistent with GB disease included positive Murphy's sign, elevated white blood cell count, elevated C-reactive Protein (CRP) and radiological evidence of the

clinical diagnosis on ultrasound (US), Computerised Tomography (CT), or Hepatobiliary Iminodiacetic Acid scan (HIDA).

Exclusion criteria: Paediatric LC performed in children as part of other complicated procedures such as those for GB polyps, biliary atresia or resection of choledochal cyst were excluded from the study.

Study Procedure

Study population with LC procedure submitted for histological evaluation were identified by performing an electronic search through the archives, followed by a manual review of GB specimens, histopathology slides and reports independently to resolve any discrepancy. Relevant clinical data was collected using appropriate International Classification Of Diseases (ICD 10) for medical diagnosis [10]. Entire data was rechecked manually to delete duplications, processed and analysed in Microsoft excel format. Concordance of clinical diagnosis and histopathological diagnosis was examined case by case.

The paediatric LC specimens for histopathological examinations were fixed in 10% neutral buffered formalin, embedded in paraffin wax and cut into 5 mm sections. Three sections were taken from each specimen one each from cystic duct, body and fundus of GB. Tissue sections were stained with Haematoxylin and Eosin (H&E). The histopathological evaluation was done based on the following defined criteria. Histopathological diagnosis of acute cholecystitis was made if the GB was grossly enlarged, oedematous with turbid bile and serosal exudate. These gross features were validated against the histological evidence of transmural oedema, neutrophilic infiltration and haemorrhage, serosal fibrin with subserosal haemorrhage and mucosal ulceration. A diagnosis of chronic cholecystitis was made if GB grossly showed evidence of chronic inflammation such as serosal adhesions or sub serosal fibrosis and a wall thickening of more than 3 mm. These gross features were validated against the histological evidence of increased mononuclear inflammatory infiltrate in lamina propria extending into muscularis propria and pericholecystic tissue, hypertrophy of muscularis propria, accentuation of Rokitansky Aschoff sinuses and mural fibrosis. Cholesterolosis was diagnosed when mucosal surface of the specimen grossly showed fatty streaks and lamina propria showed lipid laden foamy histiocytes histopathologically [11].

STATISTICAL ANALYSIS

Data was entered and analysed using commercial software Statistical Package for Social Science (IBM SPSS Statistics, version 23.0. Armonk, NY: IBM Corp).The Mann-Whitney U-test was used for comparison of variables. Categorical variables were compared by the Chi-square test, presented as counts and percentages, and a p-value <0.05 was considered significant.

RESULTS

Among total of 265 patients who underwent LC during this period there were 62 (23.4%) children who underwent LC for cholelithiasis and/or inflammatory GB disease. The average paediatric age of presentation was 13 years (range 5-18 years) with highest frequency among girls [Table/Fig-1]. All patients studied presented with complaints of abdominal pain. Ten children (16.1%) clinically presented with acute symptoms with an average duration of pain for two days. Twenty children (32.3%) presented with chronic symptoms with an average duration of pain for six months. The clinical presentation among rest of the 32 (51.6%) was variable with nausea, vomiting and abdominal discomfort related to intake of fatty food. One patient of acute cholecystitis who presented clinically with high grade fever, raised CRP and leukocytosis had received antimicrobial treatment and none of the patients with clinical diagnosis of cholecystitis or cholelithiasis had received preoperative antimicrobial drugs. Among 56 children (90.3%) who had preoperative US suggestive of cholelithiasis all turned out to be associated with chronic cholecystitis and among five children (8.1%) who underwent preoperative CT suggestive of cholecystitis all turned out to be chronic cholecystitis on histopathological examination. One child (1.6%) who underwent preoperative US and HIDA suggestive of acute cholecystitis with cholelithiasis turned out to be the same on histopathological examination [Table/Fig-2]. On gross examination there was no significant variation in size and volume of GB within the studied paediatric age group. Overall 61 (98.4%) cases turned out to be chronic cholecystitis and 1 (1.6%) turned out to be acute cholecystitis on histopathological examination. Among 10 (16.1%) cases with a clinical diagnosis of acute cholecystitis, only one case turned out to be acute calculous cholecystitis while remaining nine were chronic cholecystitis on histopathological examination. The clinical diagnosis of cholelithiasis among 32 (51.6%) and cholecystitis among 30 (48%) turned out to be chronic cholecystitis among 98.4% on histopathological concordance, among which 51% were associated with cholelithiasis and 22 (69%) were accompanied with cholestrolosis [Tables/Fig-3]. Chronic cholecystitis with cholelithiasis and cholesterolosis was more frequent in girls (79%). One out of 10 (16%) patients clinically presenting with acute cholecystitis, 14 out of 20 (70%) clinically presenting with chronic cholecystitis and 30 out of 32 (94%) presenting with cholelithiasis were associated with cholesterol stones. The remaining in each category were pigment stones. Representative ultrasound, gross and microscopy are presented in [Table/Fig-4,5], respectively.

Age group (years)	Gender	
	Males, n (%)	Females, n (%)
5-9	1 (1.6)	1 (1.6)
10-14	5 (8.1)	10 (16.1)
15-18	7 (11.3)	38 (61.3)
p-value	<0.001	

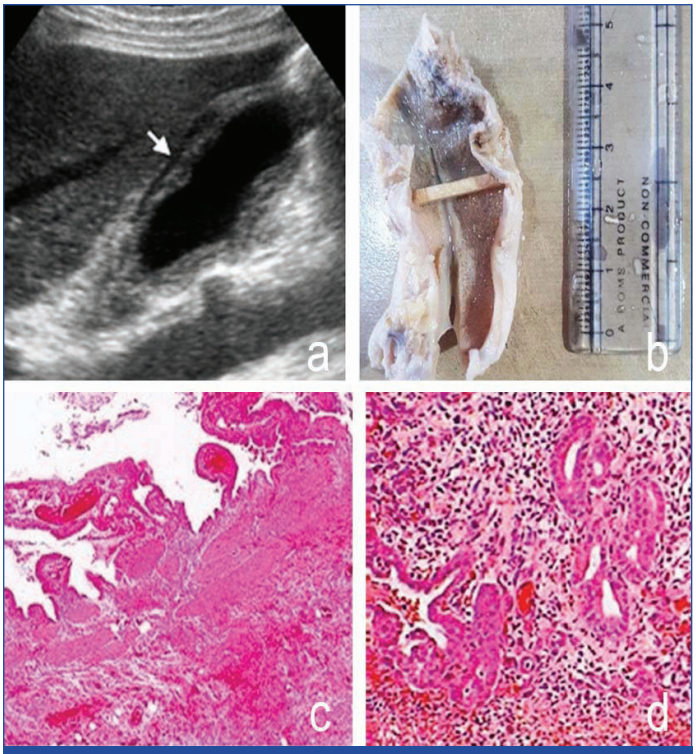
[Table/Fig-1]: Age and gender distribution.

Values	Clinical and laboratory findings N=62			Radiological findings N=62		
	Murphy's sign	Elevated WBC	Elevated CRP	US	CT	HIDA
N (62)	59	58	30	56	5	1
%	95.2	93.5	48.4	90.3	8.1	1.6
	p-value >0.05					

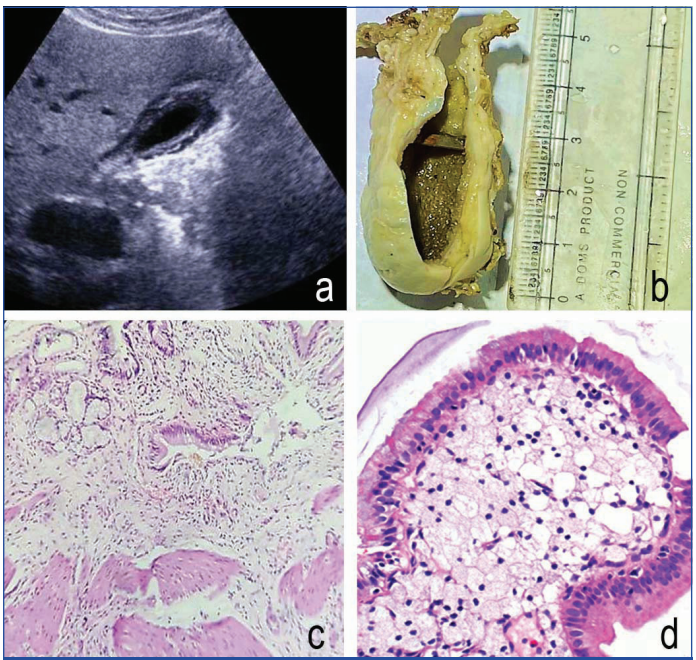
[Table/Fig-2]: Clinical, laboratory and radiological findings among children undergoing LC.

Clinical diagnosis N=62	N	%	Histopathological concordance N=62							
			Acute calculous cholecystitis		Chronic cholecystitis		Chronic cholecystitis with cholelithiasis		Chronic cholecystitis with cholelithiasis and cholesterolosis	
			N	%	N	%	N	%	N	%
Acute cholecystitis	10	16.1	1	10	9	90	-	-	-	-
Chronic cholecystitis	20	32.3	-	-	20	100	-	-	15	75
Cholelithiasis	32	51.6	-	-	-	-	32	100	22	69
p-value	<0.001		<0.001		<0.001		<0.001		<0.001	

[Table/Fig-3]: Clinicopathological concordance of paediatric LC.



[Table/Fig-4]: a) Ultrasound abdomen of 12-year-old boy showing distention of GB lumen and thinning of the wall clinically diagnosed as acute; b) Gross image of paediatric LC specimen of same patient showing enlarged, edematous and congested GB. Serosa is focally covered with purulent exudate; c) Photomicrograph showing mucosal ulceration, congestion and mural haemorrhage diagnosed as acute cholecystitis on microscopy. (H&E stain, 20x); d) Photomicrograph showing mural neutrophilic infiltration. (H&E stain, 40x).



[Table/Fig-5]: a) Ultrasound abdomen of a 15-year-old girl showing shrunken lumen, rigidity and thickening of GB wall; b) Gross image of paediatric LC specimen showing enlarged GB with wall thickness >3 mm and serosal adhesions; c) Photomicrograph showing mural fibrosis and chronic inflammatory infiltrate. (H&E stain, 20x); d) Photomicrograph showing lipid laden macrophages in the lamina propria (H&E stain, 40x).

DISCUSSION

This study shows that LCs performed for paediatric cholecystitis to be a much more prevalent disease than previously described. Overall 61 (98.4%) cases turned out to be cholecystitis and 1 (1.6%) turned out to be acute cholecystitis on histopathological examination. Among 10 (16.1%) cases with a clinical diagnosis of acute cholecystitis only one case turned out to be acute calculous cholecystitis while remaining nine were cholecystitis on histopathological examination. Other clinical diagnosis were; 32% of children presented with chronic cholecystitis, 16% with acute onset of symptoms and 51% with cholelithiasis. These findings were consistent with those reported by Blackwood PB and Grabowski J [8]. The study result also demonstrates that the majority of the children have chronic cholecystitis regardless of their clinical presentation. The average paediatric age of presentation was 13 years (range 5-18 years) with highest frequency among girls.

In adolescence, differences in the frequency of cholecystitis based on race, genetics, and gender are becoming more evident as was also noted from this study that adolescent Indian girls seem much more at risk of developing the disease than boys. Gowda DJ et al., reported an average age of 9.4 years for Indian children undergoing LC for GB disease while in the present study it was 13 years. This could be partly explained by the rapid change in life style and feeding habits since the previous study exacerbated by easy access and delivery of fatty food through food applications [12]. Among 6040 paediatric cholecystectomy performed between 1993-2012 Murphy PB et al., reported mean age as 14.3 years with 79.6% of children being girls. The crude incidence per 100,000 person-years increased from 8.8-13.0 ($p<0.001$) from 1993 96–2009–12, respectively. The gender-specific incidence showed a larger increase among girls from 14.7-21.1 per 100,000 children-years ($p<0.001$) [13]. Walker SK et al., also reported an increase in the incidence of paediatric cholecystitis from 1997-2009, but the study does not specify the subtypes of cholecystitis or age and gender related distribution. They also found that 53% of the children were either obese or overweight [14]. Obesity and Hispanic ethnicity are strongly correlated with symptomatic paediatric gallbladder disease [15]. It is becoming evident that the overall incidence of paediatric cholecystitis appears to have increased in the last three decades and with this increasing incidence, it is imperative that we understand the underlying pathophysiology in order to better treat these children. High consumption of fatty foods by young children may be the leading cause. In children with chronic haemolysis (eg, haemolytic anemias) the incidence of cholecystitis is much higher than in the general population. Biliary sludge and/or cholelithiasis are implicated among 1 in 5 children with haemolytic anemia before their adolescent years. Obesity alone accounts for some 8-33% of cholelithiasis observed in children [16]. The changing demographic of cholecystitis among paediatric age group is a neglected aspect of the obesity epidemic. Other than a high caloric intake that leads to obesity, any importance of the dietary content is unclear and difficult to analyse in context of paediatric cholecystitis. Diets specifically high in cholesterol, fatty acids, carbohydrates or legumes seem to increase the risk of cholelithiasis and may therefore be implicated in causing calculous cholecystitis indirectly. In contrast, unsaturated fats, coffee, fibre, ascorbic acid (vitamin C), and calcium reduce the risk [17]. Certainly, the shift to a more Western diet, high in refined carbohydrates and unsaturated fats and low in fibre, best explains the profound increase in cholestrolosis and cholesterol stones amongst American Indians (unmasking their presumed genetic burden) and in European countries. This dietary change also might account for the shift from pigment to cholesterol stones in Asian countries [17].

Although paediatric patients may initially appear with acute cholecystitis, cholelithiasis symptoms frequently precede those of cholecystitis. Biliary colic is caused by cholelithiasis. Patients may report right upper quadrant intermittent abdominal discomfort of varying intensity that may radiate to the scapular region of the back, or pain may be generalised or restricted to the epigastrium. Regarding chronic cholecystitis patients usually present with biliary colic, with an intermittent and indolent history of pain and positive Murphy's sign. Therefore, differentiation must be made on the basis of findings from the physical examination and diagnostic test [2]. Most of the patients in present study presented with nausea, vomiting and pain in the right upper abdomen radiating to scapula. Only one patient presented with fever that turned out to be acute cholecystitis on histopathological examination. Pelizzo G et al.,

observed severe damage of the GB in their study groups, including signs of chronic inflammation suggesting that children may have milder episodes of self-limited GB inflammation compared with adults, which may lead to delayed surgical intervention and morbidity [18]. Cholelithiasis and chronic cholecystitis are independent risk factors for carcinoma of the GB and are therefore reasons for intervening earlier on symptomatic children [19]. Interestingly the present study also identified a discrepancy in the preoperative US diagnostic work-up of children for inflammatory GB disease. In the present study 90% of children underwent a preoperative US out of which 51% were diagnosed radiologically as cholelithiasis without specifying acute or chronic inflammation. These turned out to be associated with chronic cholecystitis on histopathological examination. The lower sensitivity of preoperative US for picking up GB inflammation further masks and complicates the rising number of paediatric cholecystitis. A recent study found that US findings have sensitivities as low as 6% for cholecystitis in the paediatric population compared to the adult population where sensitivities are as high as 96% [20]. Consistent with the histopathological findings in the present study demonstrating chronic cholecystitis among 98.4% and acute CC among 1.6% children, Tsai J et al., reported 83% children with histopathologic diagnosis of chronic CC and 8% as acute cholecystitis. The slight increase in the present study can be explained by the variation in dietary habits, life style and patient phenotype. As suggested by Tsai J et al., these findings indicate that children undergo multiple episodes of inflammation that are not significant enough to be seen radiologically, yet still produce enough pain that these children present to the hospital for evaluation. As a result of this more indolent course, physicians may be delaying appropriate surgical intervention. This in turn may be increasing paediatric emergency department and primary care visits, adding to the overall healthcare costs [20].

Cholecystitis likely results from prolonged or recurrent episodes of acute inflammation and though most often found in the context of cholelithiasis, it can also be present in absence of cholelithiasis. The understanding of cholelithiasis has progressed significantly since the characterisation of the most likely candidates as being fair, fat, fertile, 40-year-old females. Although cholelithiasis in children is a rare disease with a prevalence between 0.13-0.22% [21]. The current trend indicates that it is primarily a disease of adolescent girls, which may partly be related to increase in estrogen levels. In the present study too, it was observed that chronic cholecystitis with cholelithiasis and cholesterolosis was more frequent in girls (69%). Gokce S et al., reported that the most common complications of cholelithiasis are cholecystitis, choledocholithiasis, and pancreatitis [22]. In the current study too, 51% of the children had cholecystitis in presence of cholelithiasis. Lee YJ et al., reported 16.9% of cholelithiasis in their study to be associated with cholecystitis. This variation could be partly explained by the differences in the phenotypes of study populations. Conditions such as metabolic disorders, parenteral nutrition, cystic fibrosis, haemolytic diseases and malignancies are strongly correlated with paediatric gallstones [23-26]. On the contrary Enayet A et al., reported the possible aetiology for cholelithiasis among Egyptian children as largely idiopathic (28.6%) followed by G6PD deficiency (14.3%) and hyperlipidaemia (11.4%) [27]. Cholelithiasis is also detected more frequently than in previous years because of the increased use of US [28].

Paediatric acute acalculous cholecystitis is estimated to represent 50% of all cases of acute cholecystitis in this population which may be stimulated by a recent viral illness or may be associated with multiple injuries, burns GB ischaemia, sepsis, dehydration or chronic diseases [29]. Acute calculous cholecystitis may result from biliary obstruction or impaction of gall stones at GB neck with superadded bacterial infections such as *Brucella* spp., *C. jejuni*, *C. burnetii, Leptospira* spp., *Mycobacterium* spp., *Salmonella* spp., and *V. cholerae*, yeasts (*Candida* spp.), viruses (HAV, HBV, EBV, CMV, and Flavivirus), and parasites (*Plasmodium* spp., *A. lumbricoides*, and *Echinococcus* spp.). Chronic acalculous cholecystitis is related to chronic biliary sludge post habitual consumption of fatty food and fatty food intolerance [8,12]. The aetiology and predisposing factors of cholecystitis and cholelithiasis in children are interrelated and may ultimately have an influence on interdisciplinary therapeutic decisions and management.

The incidence of paediatric LCs has risen. According to a UK study, the frequency ranges between 0.78 and 2.7/100,000 in children under 16 years [12]. The most frequent indication for cholecystectomy in paediatric age group remains radiological evidence of cholecystitis and or cholelithiasis. Pelizzo G et al., reported that both elective and urgent LC are safe and feasible in children. The clinical parameters and US criteria currently used in adults to define the timing of LC do not allow the severity prediction of the GB histopathological condition and consequently the surgical outcome in children [18].

The 2007 Tokyo Guidelines grade the severity of acute cholecystitis to help guide its treatment into mild, moderate, and severe as follows: Mild (grade I); defined as acute cholecystitis with limited GB disease and no dysfunction, making LC a low-risk procedure, Moderate (grade II): defined as acute cholecystitis with extensive GB disease, raised WBC count, palpable, tender mass in upper right quadrant and duration of symptoms longer than 72 hours and Severe (Grade III): defined as acute cholecystitis with multiple organ dysfunction such as, cardiovascular dysfunction, neurological, respiratory, renal, 1 hepatic and haematologic dysfunction [30]. Various stages of cholecystitis have been described. Stage 1 (oedematous), corresponding to 2-4 days when GB tissue is intact with oedema in subserosal layer and dilated capillaries and lymphatics. Stage 2 (necrotising), corresponding to 3-5 days, when extensive oedematous and haemorrhage cause necrosis due to compromised blood flow. Stage 3 (suppurative), corresponding to 7-10 days when there is active inflammation with necrosis and suppuration in wall along with fibrous thickening and formation of intramural abscesses. Stage 4 (chronic) resulting from repeated episodes of cholecystitis and characterised by mucosal atrophy, wall fibrosis, neutrophil/lymphocyte/plasma cell infiltration [31].

To the best of author's knowledge, there are no studies presenting the clinicopathological concordance for paediatric LC from India which highlights the strength of this study. Some of the other strengths of this study include the robust design and transparency.

Limitation(s)

This study has certain limitations and results should be interpreted accordingly. The main one being that it was a retrospective study with a relatively small size of study population over a short period of time which in turn limits the application value of these results. Also this being a single institution study the criteria used in the assessment of cholecystitis, clinically, radiologically and on histopathology may vary with other institutions. Institutional preoperative imaging sensitivity may also vary slightly based on the expertise of those performing and interpreting the imaging studies. Representing the diverse patient spectrum in children with cholecystitis, the case mix and the variety of complications additionally limit the possibility to draw strong conclusions because of even smaller case numbers within subgroup analyses. Therefore, a larger cohort of children is mandatory to study possible associations. Variability in the upper age limit for children in different countries may also be perceived as selection bias.

CONCLUSION(S)

Chronic cholecystitis accounts for the majority of inflammatory diseases among children undergoing LC for a clinical presentation of GB disease regardless of association with cholelithiasis. The study also reflects a demographic change in the frequency of cholecystitis

noticed among Indian children which needs to be highlighted to maintain clinical awareness. Underrated GB inflammation may delay surgical intervention, increase paediatric emergency inflow and lead to complicated surgeries. In view of the fact that greater tissue damage is caused by increased inflammatory response, it is important to consider early intervention among children presenting with symptoms of cholecystitis.

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