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Original Article

Cholecystectomy in children: indications, clinical, laboratory and histopathological findings and cost analysis

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ABSTRACT

Background. The most common indication for cholecystectomy in children is cholelithiasis, and routine histopathological examination is performed on all gallbladder specimens. Currently, selective histopathological examination is suggested instead of routine examination due to the low frequency of gallbladder cancer in adults. The purpose of this study was to evaluate the indications, clinical, laboratory and histopathological findings of the cholecystectomy in children. We also questioned the contribution and cost-effectiveness of routine histopathological evaluation in diagnosis and treatment.

Methods. A total of 114 children underwent cholecystectomy between the years 2008 and 2022. The clinical findings, laboratory, and imaging results of the patients and histopathological findings of the gallbladder specimens were evaluated retrospectively.

Results. Cholelithiasis were diagnosed in 71%, choledochal malformation in 15.8%, hydrops of gallbladder and/or biliary sludge in 12.3%, and hypoplasia of gallbladder in 0.9% of the patients. Histopathologically significant findings were observed in only 3 patients (2.6%); adenomyomatosis in 2 and angiodysplasia and pyloric metaplasia in 1. While the cost of a cholecystectomy and histopathologic examination combined amounted to 27.77% of the minimum wage in Türkiye in 2024, the histopathologic examination alone constitutes just 0.67% of the minimum wage and 2.4% of the operation fee.

Conclusion. In children undergoing cholecystectomy, histopathological examination does not provide any significant contribution to the patient's diagnosis and follow-up management. In children, selective gallbladder histopathological examination might reduce health costs and save time for pathologists.

Key words: cholecystectomy, histopathology, cholelithiasis, adenomyomatosis, children.

With the improved availability of ultrasonography, the prevalence of cholelithiasis in children has increased from 1.9% to 4% between the years 1959 and 2011.[1] At the same time, the number of cholecystectomy procedures performed has increased by 213% over a 9 year period ending in 2012.[2] There is a notable increase in the number of cholecystectomies performed on children, mostly due to the rising incidence of obesity.[3] The symptoms of cholelithiasis are not specific, and examination findings may be subtle in children.[4] In addition, ultrasound findings may show differences between intra- and inter-observers.[4]

Following cholecystectomy, all specimens removed during the operation are routinely sent for histopathological examination in adults, as there is a potential risk of carcinoma. Currently, selective histopathological examination is

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suggested instead of routine examination due to the low frequency of gallbladder cancer in adults.[5] Incidental carcinoma is found in 0.5-1.1% of cholecystectomies performed for cholelithiasis.[5] Individuals with a gallbladder wall thickness of >3 mm and enhanced vascularity have a higher cancer risk.[6] Preoperative abdominal ultrasound and computed tomography studies of gallbladder wall thickness estimation are found to be linearly correlated with histopathology, especially for severe wall thickening (>7 mm).[7]

The occurrence of complications due to underdiagnosis and incorrect treatment of cholelithiasis has an annual risk of 1-2%.[8] Cholelithiasis/cholecystitis is the second most costly disease per hospitalization in pediatric patients after congenital malformation. In the United States, the median total charge per hospitalization for cholelithiasis/cholecystitis is 37,607 US dollars. Healthcare expenditures for biliary tract disease is 16.9 billion US dollars annually, including both adults and children.[9]

The purpose of this study was to evaluate the indications, clinical, laboratory and histopathological findings of cholecystectomy in children. We also questioned the contribution and cost-effectiveness of routine histopathological evaluation to diagnosis and treatment.

Methods

This study included pediatric patients under the age of 18 years who underwent cholecystectomy at Dr. Sami Ulus Maternity and Child Health and Diseases Training and Research Hospital between January 2008 and December 2022. Data were collected retrospectively, including patients' age at the time of cholecystectomy, sex, body mass index (BMI) Z-score, indications for cholecystectomy, presence of single or multiple stones, underlying hematological diseases, accompanying symptoms, complete blood count (CBC) and biochemical parameters. There were no patients who underwent cholecystectomy for acute cholecystitis.

Additionally, macroscopic features of the gallbladder, such as cystic lesions, fibrotic, fragmented, irregular and diffuse wall thicknesses, were noted from pathology reports. Hydrops of the gallbladder refers to an enlarged gallbladder due to obstruction of the cystic duct, typically caused by an impacted stone or stricture. Moreover, microscopic features such as inflammation (granulomatous, xanthogranulomatous, follicular), epithelial atrophy or hyperplasia, cholesterolosis, dysplasia, metaplasia (pyloric, intestinal), eosinophilic or lymphoeosinophilic infiltration, stones, ulceration, erosion in the gallbladder, presence of denuded epithelium, serositis, adenoma (tubular), adenocarcinoma, adenomyomatosis, gangrene, ischemia, cholesterol polyp, hyperplastic polyp, mucocele, pancreatic heterotopia, hyperplastic Luschka ducts, and porcelain calcification were evaluated by hematoxylin and eosin staining. The gallstones, composed mainly of cholesterol, appears yellow and the dark brown and black stones contain mostly bilirubin. So, the colors of the gallstones were also noted.

Statistical analysis

The descriptive statistics for the data included the median, 25th to 75th interquartile range for gallbladder macroscopic features including longest gallbladder dimension and gallbladder wall thickness, CBC and biochemical parameters; mean and standard error values were reported for BMI Z-score. The parametric assumptions were tested using the Shapiro-Wilk Test and the Levene Test. The Mann-Whitney U test was performed for variables where the parametric assumptions were not met, chi-square test was used for quantitative data, and the Student t test was performed for variables for which the parametric assumptions were met at the 0.05 level of significance. The program IBM SPSS Statistics for Windows, version 22.0. Armonk, NY: IBM Corp, 2013 was used for statistical analyses.

This study was approved by Ankara Bilkent City Hospital Ethics Committee (Date: 01.03.2023, Number: E2-23-3472).

Results

A total of 114 children underwent cholecystectomy, of whom 100 (88%) were female and 14 (12%) male. Fourteen of these patients underwent cholecystectomy in the first 5 years (January 2008-December 2012), and 100 patients underwent cholecystectomy in the last 10 years (January 2013-December 2022). The most common indication for cholecystectomy was cholelithiasis (Table I). The median age and BMI Z-score of patients were higher in those with cholelithiasis, and cholelithiasis was more frequently observed in girls (p<0.05) (Table II and Table III). Hemolytic anemia was present in 12 (10.5%) patients. Among these cases, 8 patients had hereditary spherocytosis, one had hereditary elliptocytosis, one had sickle cell anemia, one had transfusion dependent beta-thalassemia and one had congenital dyserythropoietic anemia. Out of 83 children with cholelithiasis, the color of the stones was noted in 62 patients. Among these, 23 had green stones, 20 had yellow stones, and 19 had black stones. Among the patients with hemolytic disease, green and/or green-black stones were observed in 7 patients, black stones in 3 patients and yellow stones in one patient, one patient however was missing color information. Green gallstones were observed in 2 patients with choledochal malformations type 1 or type 2.

There was no statistically significant difference in the presence of hemolytic anemia, and symptoms of nausea and vomiting, between patients with or without cholelithiasis (p> 0.05). However, the rate of abdominal pain was higher in those with cholelithiasis (p< 0.05) (Table II). The laboratory results indicate that individuals with cholelithiasis had reduced levels of platelet count, alkaline phosphatase and aspartate aminotransferase (p< 0.05) (Table III).

Histopathological examination revealed chronic cholecystitis in all but 7 patients. Of these 7 patients without chronic cholecystitis, 2 had multiple gallstones, 1 had a hypoplastic gallbladder, and 3 had a type 1 choledochal malformation. One patient with overt clinical symptoms of cholecystitis underwent cholecystectomy, and the histopathology of the gallbladder was found to be normal. The macroscopic pathological examination indicated the presence of hydrops in 3 cases and the histopathological examination indicated cholesterolosis in 12 patients with cholelithiasis. Two patients without cholelithiasis exhibited hydrops, and two others showed

Table I. Indications for cholecystectomy (N=114).

Preoperative Diagnosis	Number (%)
Multiple gallstones	60 (52.6%)
Single gallstone	21 (18.4%)
Choledochal cyst type 1	16 (14.0%)
Hydropic gallbladder and/or biliary sludge	14 (12.3%)
Choledochal cyst type 2	2 (1.8%)
Hypoplastic gallbladder	1 (0.9%)

Table II. Comparison of sex, diagnosis of hemolytic anemia, and symptoms in patients with and without cholelithiasis.

		Gallstone		Total	P
		Absent n=31 (27.2%)	Present n=83 (72.8%)		
Sex (%)	Female	24 (24%)	76 (76%)	100	0.041
	Male	7 (50%)	7 (50%)	14	
Hemolytic anemia (%)	Negative	30 (29.4%)	72 (70.6%)	102	0.121
	Positive	1 (8.3%)	11 (91.7%)	12	
Abdominal pain (%)	Negative	19 (46.3%)	22 (53.7%)	41	0.001
	Positive	12 (16.4%)	61 (83.6%)	73	
Nausea and/or vomiting (%)	Negative	21 (29.2%)	51 (70.8%)	72	0.535
	Positive	10 (23.8%)	32 (76.2%)	42	

Table III. Comparison of age, BMI Z-scores, complete blood count, biochemical parameters, and macroscopic pathological examination of the gallbladder in patients with and without cholelithiasis.

	Gallstone						P
	Absent			Present			
	Q1	Median	Q3	Q1	Median	Q3	
Age, years	3	7	13	11	15	17	**< 0.001**
BMI Z score (mean±SD)		-0.4±0.2			0.7±0.2		**< 0.001**
Hemoglobin g/dl	11.7	12.5	13.7	12.4	13.2	14	0.093
White blood cell, $x10^6$/L	6700	7450	8700	5780	7160	8760	0.226
Platelets, $x10^9$/L	260	320	405	236	289	334	0.020
Eosinophil count, $x10^6$/L	100	180	220	90	140	220	0.259
Eosinophil, %	1.7	2.1	3.2	1.2	2.0	2.6	0.333
ALT, U/L (Normal range 0-32)	13	19	36	11	15	21	0.055
AST, U/L (Normal range 0-36)	24	31	42	17	22	25	**< 0.001**
Alkaline Phosphatase, U/L (Normal range 128-420)	156	228	275	86	144	185	**< 0.001**
GGT, U/L (Normal range <73)	12	14	142	11	14	21	0.147
Total bilirubin, mg/dL (Normal range 0.3-1.2)	0.3	0.6	1.1	0.5	0.6	1	0.388
Direct bilirubin, mg/dL (Normal range 0-0.2)	0.1	0.2	0.3	0.1	0.1	0.3	0.567
Gallbladder longest dimension, cm	5	6	8	5.5	6.5	8	0.122
Gallbladder wall thickness, cm	0.2	0.3	0.4	0.2	0.2	0.3	0.116

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma glutamyl transferase, Q1: 25th quartile, Q3: 75th quartile; SD, standard deviation.

cholesterolosis, both of whom had a choledochal malformation. In a patient with a choledochal malformation with pancreaticobiliary junction Todani 1A, Komi 3 anomaly; mononuclear inflammatory cell infiltration and Rokitansky-Aschoff sinus, and pyloric metaplasia were observed in the mucosa. In the mucosa and the submucosa, diffuse increased vascularization, dilatation of venous vessels and thick-walled arterial structures were observed, indicating angiodysplasia. The surface epithelium of hypoplastic gallbladder was not visible in most areas and the epithelium was flattened partially in a patient. Fibrosis was observed in the subepithelial area and Rokitansky-Aschoff sinus as well as inflammatory cells in the fibrous tissue. Another patient with a choledochal malformation, showed an enlarged and cystic appearance of the Rokitansky-Aschoff sinus. Adenomyomatous hyperplasia was noted in 2 patients: one presented with a polyp in the gallbladder and the other presented with multiple stones. Both patients had symptoms of abdominal pain, and the length of the removed gallbladder was 5 cm in both. The wall thickness of the gallbladder of the patient who underwent surgery for the polyp was 0.3 cm and the wall thickness of the gallbladder of the other patient was 0.5 cm. In a patient with a choledochal malformation, areas of hemorrhage and ischemia were observed in the serosa. A gallbladder perforation was observed in a patient diagnosed with calculous cholecystitis. Elevated levels of amylase and lipase were seen in 5 patients, while 4 patients were diagnosed with type 1 choledochal malformation and one patient had multiple gallbladder stones.

There was no significant difference in gallbladder wall thickness and length between patients with and without cholelithiasis (p> 0.05) (Table III). In 9 patients, the gallbladder wall was thick (>0.3 cm) on ultrasound, and on macroscopic examination the thickness of the gallbladder wall was 0.3-0.4 cm in 8 patients and 0.7 cm in one. Hydrops of the gallbladder were observed in 7 patients on ultrasound and macroscopically the size of

the gallbladder was 5-7.5 cm in 5 patients and 9.5-10 cm in 2. Our patients did not exhibit any clinical manifestations such as xanthogranulomatous inflammation, dysplasia, eosinophilic or lymphoeosinophilic infiltration, ulceration in the gallbladder, tubular adenoma, adenocarcinoma or pancreatic heterotopia.

In Türkiye, the cost of a histopathologic study of the gallbladder alone amounts to 114 Turkish Liras (TL) (0.67% of minimal wage), equivalent to around 3.5 US dollars, reimbursed by the Turkish Social Security Institution. However, when considering the combined expenses of cholecystectomy and histopathologic investigation, the entire cost reaches 4722 TL, equivalent to approximately 147.5 US dollars and 27.77% of the minimum wage in Türkiye (17002 TL, approximately 528 US dollars). Hence, histopathologic examination constitutes 2.4% of the total expenditure.

Discussion

Cholecystectomy is indicated in children for symptomatic cholelithiasis, asymptomatic cholelithiasis with hemolytic diseases, acute cholecystitis that does not respond to medical management, chronic cholecystitis causing recurrent symptoms, gallbladder polyps larger than 1 cm or symptomatic polyps, gallbladder anomalies, and cholecystitis with pancreatitis.[10] Prolonged symptom duration, signs of systemic inflammation, history of lithotherapy, and gallbladder wall thickening of 3 mm or more have been identified as indications for immediate surgery.[10] A recent systematic review and meta- analysis showed that, the most common indications for laparoscopic cholecystectomy in children are cholelithiasis, cholecystitis, and biliary dyskinesia.[11] In the present study the most common indication for cholecystectomy was cholelithiasis followed by choledochal cyst and hydropic gallbladder and/or biliary sludge.

The current study revealed that individuals with cholelithiasis had a higher median age, more frequent abdominal pain, and a higher BMI Z-score (p<0.001). Also, cholelithiasis was more frequently observed in girls (p<0.05), in line with other pediatric studies.[2] Black pigment gallstones, also known as calcium bilirubinate stones, are typically associated with hemolytic disease.[12] However, in our cohort, green and green-black pigment stones were more common among patients with hemolytic disease. Two patients with choledochal malformation had green gallstones, despite the usual description of brown gallstones in such patients.[12]

The length and wall thickness of the gallbladder did not differ significantly (p>0.05) between those with and without cholelithiasis. The gallbladder wall is defined as thick and suspicious for cancer if it measures more than 0.3 cm on ultrasound or macroscopic examination.[13] The median gallbladder wall thickness was 0.3 cm or less in patients with and without cholelithiasis in this study.

The study revealed that Rokitansky-Aschoff sinus was present in three children (2.6%) and adenomyomatous hyperplasia was present in two children (0.17%). These rates are much lower compared to adults, where Rokitansky-Aschoff sinus has been reported in 65% and adenomyomatous hyperplasia in 5% of cases.[14,15] There was no muscular layer hypertrophy and epithelial proliferation in the patients with Rokitansky-Aschoff sinus. Adenomyomatosis is rare in children, and progression to carcinoma has not been reported.[16] Carcinoma has been observed in 0.06% of dysplasia-preceding pyloric metaplasia cases and in 0.04% of intestinal metaplasia cases in cholecystectomy specimens from adolescents and young adult patients aged 11-20 years.[17] In this study, one patient (0.87%) aged 3.5 years with an anomaly of the pancreaticobiliary junction anomaly (Todani 1A, Komi 3), had pyloric metaplasia, increased vascularization in the mucosa and submucosa and angiodysplasia of the gallbladder. As documented in prior studies, 3 patients were found to have angiodysplasia in the gallbladder.[18] One of these patients was a 78-year-old male in whom multiple

angiodysplasias were also observed in the gastrointestinal tract. The other two female patients were 29 and 36 years old and one of them had an association with cholelithiasis.[18] Apart from these cases, angiodysplasia of the gallbladder has not been reported in the literature. According to our findings, 2 patients with adenomyomatous hyperplasia and one patient with angiodysplasia and pyloric metaplasia did not develop any further clinical manifestations subsequent to cholecystectomy.

The criteria for diagnosing gallbladder hydrops typically include gallbladder distention with an anterior-posterior diameter >5 cm and with clear fluid content, and irrespective of acute inflammation and gallbladder wall thickness.[12] In this study, 5 patients had gallbladder hydrops upon macroscopic inspection. Among them, 2 presented with a solitary gallstone, 2 presented with several stones, and one presented with a choledochal malformation. Since the size of the gallbladder in children varies according to age, height, weight and body surface area, it is not appropriate to use parameters such as a diameter >4.5-5 cm to diagnose a hydropic gallbladder.[4] In our research, we assessed the length of the gallbladder and observed no difference between the patients with and without cholelithiasis. A review of 134 cholecystectomy specimens identified 8 cases (6%) of eosinophilic cholecystitis and 3 cases (2.2%) of lymphoeosinophilic cholecystitis in children.[19] In our study, we did not encounter any patients exhibiting eosinophilic or lymphoeosinophilic infiltration.

For a comprehensive histopathological evaluation, specimens from the fundus, corpus, and parts of the cystic duct-neck should be examined. One study found that taking samples from all three parts with longitudinal sectioning led to a higher number of mucosal lesions and preinvasive lesions.[20] In our study, classical sampling was performed with samples from three parts placed in one cassette, which may have resulted in the failure to detect some mucosal lesions. In fact, in both types of sampling, samples are taken from three parts of the gallbladder, and if dysplasia is detected in these samples, examination of the entire gallbladder is recommended.[21]

Even in Asian countries, where incidental gallbladder carcinomas are common, histopathological examination is recommended in selected cases.[22] Routine histopathological examination is also not recommended by the Dutch national guidelines devised in 2014.[23] However, in 2018 a study conducted in the Netherlands found that the rates of histopathological examination of cholecystectomy specimens did not decrease between 1990 and 2015.[23] The histopathology rate could be reduced by 90% by sending macroscopically suspicious specimens for further evaluation.[24]

The study's limitations stem from its reliance on retrospective histopathology reports, where each gallbladder sample was evaluated by more than one pathologist. The reporting pathologists may have considered some histopathological abnormalities as unimportant and not worth reporting. Despite conducting the study in a single center, the population encompassed patients from various regions of Türkiye, thereby reflecting the country's demographic structure.

Implementing histological investigations selectively, based on clinical and macroscopic observations before and during surgical procedures, can potentially reduce healthcare costs. In children undergoing cholecystectomy, histopathological examination does not provide any significant contribution to the patient's diagnosis and follow-up management. Despite this, pathology departments routinely receive samples removed during surgery and are exposed to excessive workload. Although the financial burden of histopathological examination is negligible in Türkiye, it may be high in other countries. In low-risk areas for gallbladder cancer; more than half of the studies implemented a more selective policy;

while studies in high-risk areas emphasize that all gallbladder specimens should be evaluated by a pathologist.[24] Even in high-risk areas, the incidence of truly incidental gallbladder cancer is 0.44% and if surgeons examine gallbladders systematically, it drops to 0.08%.[24] Surgeons might miss incidental cancer, and they might fear medicolegal consequences. The FANCY study showed that 0.22% of 10041 gallbladder specimens had cancer. Surgeons could have held back histopathologic examination for 78.1% of the specimens, saving €70.35 per person by using selective instead of routine examination.[25] Studies are needed to pinpoint suspicious macroscopic features in gallbladder specimens from children and to limit histopathological examination to these specific cases. In children, selective gallbladder histopathological examination might reduce health costs and save time for pathologists.

Ethical approval

The study was approved by Ankara Bilkent City Hospital Ethics Committee (date: 01.03.2023, number: E2-23-3472).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: AÜA, NG, AK, data collection: AÜA, NG, GŞ,; analysis and interpretation of results: FÖH,AT, draft manuscript preparation: AÜA, NG, AK. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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