Cite as: Nowak M, Olejarz Z, Łasińska P, Topa J, Grzybowska-Chlebowczyk U, Basek D, Koszutski T, Więcek S: Retrospective analysis of risk factors and clinical course of cholelithiasis in paediatric patients – a single-centre study. Pediatr Med Rodz 2024; 20 (4): 409–417

Magdalena Nowak[1,2], Zuzanna Olejarz[1], Paula Łasińska[1], Justyna Topa[1], Urszula Grzybowska-Chlebowczyk[3], Dariusz Basek[4], Tomasz Koszutski[4], Sabina Więcek[3,5]

Received: 12.09.2024
Accepted: 27.01.2025
Published: 10.04.2024

Retrospective analysis of risk factors and clinical course of cholelithiasis in paediatric patients – a single-centre study

Analiza obrazu klinicznego kamicy żółciowej u dzieci – badanie jednoośrodkowe

[1] Students' Scientific Society, Department of Paediatrics, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
[2] Department of Paediatric Neurology, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
[3] Department of Gastroenterology, Upper Silesian Child Health Centre, Katowice, Poland
[4] Department of Paediatric Surgery and Paediatric Urology, Upper Silesian Child Health Centre, School of Medicine in Katowice, Medical University of Silesia, Katowice, Poland
[5] Department of Paediatrics, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
Correspondence: Magdalena Nowak, Students' Scientific Society, Department of Paediatrics, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Medyków 16, 40-752 Katowice, Poland, e-mail: nmagdalena533@gmail.com

https://doi.org/10.15557/PiMR.2024.0063

ORCID iDs
1. Magdalena Nowak https://orcid.org/0000-0002-5483-3193
2. Zuzanna Olejarz https://orcid.org/0009-0009-3750-7124
3. Justyna Tołpa https://orcid.org/0009-0003-2429-0962
4. Sabina Więcek https://orcid.org/0000-0001-9870-6674

Abstract

Introduction and objective: In recent years, there has been an increase in the incidence of cholelithiasis in the paediatric population. Most patients have an asymptomatic course of the disease; however, some children may experience serious complications. The aim of this study was to analyse the clinical features, risk factors, and complications in paediatric patients diagnosed with cholelithiasis. **Materials and methods:** A retrospective analysis was conducted on 106 patients, including 59 girls and 47 boys aged 2 months to 17 years, diagnosed with cholelithiasis between 2013 and 2022. **Results:** The study group was stratified into five subgroups based on clinical diagnoses: asymptomatic cholecystolithiasis, symptomatic cholecystolithiasis, complicated cholecystolithiasis, choledocholithiasis with cholestasis, and choledocholithiasis with acute pancreatitis. Younger children exhibited a higher prevalence of asymptomatic cholecystolithiasis compared to older patients. The predominant clinical symptoms included abdominal pain, vomiting, and jaundice. A significant prevalence of overweight and obesity was noted. In 36.6% of patients diagnosed with choledocholithiasis, gallstones were visualised on cholangio-MRI despite normal findings on ultrasound examination. The most common complications were cholecystitis, acute pancreatitis, and cholangitis. The primary risk factors identified in the study population were comorbidities, excessive nutritional status, and a positive family history of cholelithiasis. Additionally, a significant group of children using psychiatric medications was identified. **Conclusions:** An increasing incidence of cholelithiasis is observed in the paediatric population, also in the youngest age groups. Co-occurring diseases, medications, and obesity undoubtedly play a role. The use of psychiatric medications should be considered as a possible risk factor for cholelithiasis in children.

Keywords: children, risk factors, cholestasis, gallstones, cholelithiasis

Streszczenie

Wprowadzenie i cel: W ostatnich latach obserwuje się wzrost częstości występowania kamicy żółciowej w populacji pediatrycznej. U większości pacjentów przebieg choroby jest bezobjawowy, jednak u niektórych dzieci mogą wystąpić poważne powikłania. Celem badania była analiza cech klinicznych, czynników ryzyka i powikłań występujących u dzieci z kamicą żółciową. **Materiał i metody:** Retrospektywna analiza objęła 106 pacjentów, w tym 59 dziewczynek i 47 chłopców, w wieku od 2 miesięcy do 17 lat, u których w latach 2013–2022 rozpoznano kamicę żółciową. **Wyniki:** Grupę badaną podzielono na pięć podgrup według rozpoznania klinicznego: bezobjawowa kamica pęcherzyka żółciowego, objawowa kamica pęcherzyka żółciowego, powikłana kamica pęcherzyka żółciowego, kamica przewodowa z cholestazą i kamica przewodowa z ostrym zapaleniem trzustki. U młodszych dzieci częstszy był bezobjawowy przebieg kamicy pęcherzyka żółciowego w porównaniu ze starszymi pacjentami. Wśród objawów klinicznych dominowały bóle brzucha, wymioty i żółtaczka. Zauważono istotną częstość występowania otyłości i nadwagi. U 36,6% pacjentów z rozpoznaną kamicą przewodową kamienie żółciowe były widoczne jedynie w badaniu cholangio-MRI, przy prawidłowym wyniku badaniu

ultrasonograficznego. Najczęstszymi powikłaniami kamicy żółciowej były zapalenie pęcherzyka żółciowego, ostre zapalenie trzustki i zapalenie dróg żółciowych. Główne czynniki ryzyka w badanej grupie stanowiły choroby współistniejące, nieprawidłowy stan odżywienia i dodatni wywiad rodzinny w kierunku kamicy żółciowej. Dodatkowo zidentyfikowano znaczącą grupę dzieci stosujących leki psychiatryczne. **Wnioski:** Obserwuje się zwiększoną częstość występowania kamieni żółciowych w populacji pediatrycznej, również w najmłodszej grupie wiekowej. Niewątpliwie wpływ na ten stan mają choroby współwystępujące, przyjmowane leki i otyłość. Stosowanie leków psychiatrycznych należy brać pod uwagę jako możliwy czynnik ryzyka kamicy żółciowej u dzieci.

Słowa kluczowe: dzieci, czynniki ryzyka, cholestaza, kamienie żółciowe, kamica żółciowa

BACKGROUND

The term "cholelithiasis" refers to the presence of deposits that form in the bile system, usually in the gallbladder and less commonly in the bile ducts. Although this condition is considered much less common in children than in adults, an increasing trend has been observed in the paediatric population in recent years[1–4]. The literature reports the prevalence of cholelithiasis in the children and adolescent population as approximately 0.1% to 1.9%. In Poland, detailed studies specifically examining the prevalence of paediatric cholelithiasis are currently lacking. Notably, there is a concerning global trend of cholelithiasis being diagnosed in increasingly younger patients, which correlates with the rising rates of childhood obesity and associated metabolic disorders[3,5,6]. Studies have also demonstrated a correlation between increasing age and the prevalence of cholelithiasis in children[5].

Most children with cholelithiasis have at least one risk factor for gallstone development, such as female sex, familial history, obesity, prior bariatric surgery, haemolytic anaemia (mainly caused by thalassemia or sickle cell disease), drug exposure (ceftriaxone treatment, diuretic therapy, parenteral nutrition), or other comorbidities (congenital heart disease, prematurity, malabsorptive gastrointestinal conditions, non-alcoholic fatty liver disease, primary sclerosing cholangitis)[1–27]. Additionally, research indicates a possible relationship between microbiota abnormalities and cholelithiasis[10,28,29].

In recent decades, the incidence of cholelithiasis in children has increased, primarily due to the epidemic of paediatric obesity. A recent study has shown that the number of paediatric cholecystectomies has increased significantly over the past 20 years, along with an increase in the average body mass index (BMI) of the studied population. This likely indicates a link between the rising obesity rates and the increasing prevalence of symptomatic cholelithiasis in children. In addition, the same study reported that diagnoses such as hereditary spherocytosis decreased from 63.6% to 11.8% of indications for cholecystectomy, while the proportion of cholesterol stones increased from 27.3% to 70.6%[30]. Multiple studies have established an association between obesity and the occurrence of cholelithiasis. The main factors contributing to gallstone formation are the oversaturation of bile with cholesterol and gallbladder dysmotility. Cholesterol supersaturation can be caused by increased cholesterol synthesis or enhanced hepatic cholesterol uptake. Obese individuals have increased hydroxy-3-methylglutaryl-coenzyme A activity and, consequently, higher hepatic secretion of biliary cholesterol. Excess cholesterol precipitates and forms stones. Cholesterol is also stored in the gallbladder wall, causing stiffness and impairing gallbladder peristalsis. The remaining bile in the gallbladder increases the likelihood of cholesterol crystals formation[8,31,32].

In most cases, cholelithiasis in the paediatric population has an asymptomatic course[24,33]. The most common symptoms are jaundice, vomiting, nausea, abdominal pain, and abdominal distension[1,13,24,34,35]. Symptomatic cholelithiasis in children is associated with high rates of common extrahepatic cholestasis and pancreatitis[36]. In some cases, complications may present as the first symptom of the disease. In such instances, a severe and life-threatening course is possible[2,23].

Most patients with asymptomatic cholelithiasis exhibit no laboratory abnormalities. Elevated cholestasis indicators can be found in patients with biliary obstruction – choledocholithiasis. Raised serum amylase activity is diagnostic of acute biliary pancreatitis. Increased inflammatory parameters are observed in some patients, particularly those with cholecystitis, cholangitis, or pancreatitis. To confirm a diagnosis, abdominal ultrasonography is the initial investigation of choice[6,33,37]. Magnetic retrograde cholangiopancreatography (MRCP) is more sensitive for detecting bile duct and pancreatic abnormalities and can be used when ultrasound findings are inconclusive[6,37]. Endoscopic retrograde cholangiopancreatography (ERCP) is both a diagnostic and therapeutic procedure[6].

Treatment aims to relieve the symptoms of cholelithiasis and to minimise the risk of complications and recurrence. Laparoscopic cholecystectomy is the gold-standard treatment for symptomatic cholelithiasis[6,23,24,37,38]. Accepted treatment techniques also include ERCP and exploration of the common bile duct (CBD), performed either openly or laparoscopically (laparoscopic common bile duct exploration, LCBDE)[20,37,39].

This study aims to analyse the risk factors, clinical course, and complications of cholelithiasis and to provide insights

DOI: 10.15557/PiMR.2024.0063

into the clinical implications that may be relevant for the diagnosis and management of cholelithiasis in paediatric patients treated at the Department of Paediatrics and the Gastroenterology Outpatient Clinic of Upper Silesian Child Health Centre, Medical University of Silesia in Katowice, from 2013 to 2022.

METHODS

The retrospective analysis included medical records of 106 children aged 2 months to 17 years (mean age 11.65 ± 5.09 years) with the diagnosis of cholelithiasis. These patients were treated at the Department of Paediatrics and the Paediatric Gastroenterology Outpatient Clinic of Upper Silesian Child Health Centre, Medical University of Silesia in Katowice, between 1 January 2013 and 31 December 2022. Inclusion criteria comprised a diagnosis of cholelithiasis confirmed by imaging tests (ultrasonography and/or cholangio-MRI) and patient age in the range of over 30 days and under 18 years. Exclusion criteria included the absence of gallstones on imaging tests and lack of patient consent. The primary outcome was the clinical course of cholelithiasis, including the age at diagnosis. The secondary outcome included possible risk factors for cholelithiasis in the paediatric population. Data evaluated included hospitalisation duration, clinical symptoms, nutritional status, and laboratory tests (indicators of cholestasis, parameters of hepatocyte damage, and inflammation parameters). Moreover, imaging test results, course of treatment, complications, and risk factors were analysed.

Patients underwent various treatment methods for cholelithiasis, including ERCP, laparoscopic cholecystectomy, and pharmacological treatment.

The ERCP procedure was performed using the Olympus TJF-145 device under general anaesthesia administered by the anaesthesiology team. The endoscope was advanced into the duodenum, the ampulla of Vater was visualised, and the bile ducts were catheterised for cholangiopancreatography. When required, the ERCP procedure was extended to include sphincterotomy, stone extraction with a Dormia basket, or stent placement in narrow bile ducts.

Cholecystectomy was performed using the laparoscopic method under general anaesthesia in the paediatric surgery department. Insufflation was performed with a Veress needle inserted below the umbilicus, maintaining the pressure in the pneumoperitoneum at 10–12 mm Hg. The standard surgical approach with four ports was used (a 10 mm trans-umbilical port, a 10 mm port in the midline below the xiphoid process of the sternum, and two 5 mm ports in the right subcostal area – in the midclavicular line and slightly laterally). After dissection, the cystic duct and cystic artery were clipped in two places and cut between them. The gallbladder was then separated from the liver bed and removed through the umbilical incision. In cases of a large gallbladder with numerous deposits, a laparoscopic bag was used.

Based on the clinical presentation, the patients were divided into five subgroups:

- subgroup 1: asymptomatic cholecystolithiasis – 30/106 patients (28.3%);
- subgroup 2: symptomatic uncomplicated cholecystolithiasis – 25/106 patients (23.58%);
- subgroup 3: complicated cholecystolithiasis – 7/106 patients (6.6%);
- subgroup 4: choledocholithiasis with cholestasis – 32/106 patients (30.19%);
- subgroup 5: choledocholithiasis with acute pancreatitis – 12/106 patients (11.32%).

Statistical analysis was performed using Statistica 13.3 software. Missing data were handled by excluding participants who had one or more missing values during calculations (complete case analysis). Quantitative variables were presented in the form of arithmetic mean and standard deviation or median and interquartile range. Qualitative variables were presented in the form of absolute values and percentages. Intergroup differences for quantitative variables were assessed by analysis of variance or the Kruskal–Wallis test. The chi-square test was used for qualitative variables. The normality of data distribution was assessed by the Shapiro–Wilk test. The criterion of significance was assumed at the level of $p < 0.05$.

RESULTS

Patients' characteristics

A total of 106 paediatric patients, including 59 (55.66%) females and 47 (44.34%) males, with a slight female predominance (1.2:1), were diagnosed with asymptomatic cholecystolithiasis (30/106), symptomatic uncomplicated cholecystolithiasis (25/106), complicated cholecystolithiasis (7/106), choledocholithiasis with cholestasis (32/106), choledocholithiasis with acute pancreatitis (12/106). There were 61 patients (57.54%) treated at the Department of Paediatrics and 45 patients (42.45%) receiving treatment at the Paediatric Gastroenterology Outpatient Clinic. The mean age of the patients was 11.65 ± 5.09 years, with

Variables		Total (*N* = 106)
Gender	Female	59/106 (55.7%)
	Male	47/106 (44.3%)
Age	0–2 years	9/106 (8.5%)
	2–10 years	25/106 (23.6%)
	>10 years	72/106 (67.9%)
Diagnosis	Asymptomatic cholecystolithiasis	30/106 (28.3%)
	Symptomatic uncomplicated cholecystolithiasis	25/106 (23.6%)
	Complicated cholecystolithiasis	7/106 (6.6%)
	Choledocholithiasis with cholestasis	32/106 (30.2%)
	Choledocholithiasis with acute pancreatitis	12/106 (11.3%)

Tab. 1. Clinical characteristics of the study group

 DOI: 10.15557/PiMR.2024.0063

	Median age at diagnosis (IQR) ($p < 0.01$)	
Diagnosis	Asymptomatic cholecystolithiasis	3.5 years (IQR: 1–10)
	Symptomatic uncomplicated cholecystolithiasis	10 years (IQR: 5–12)
	Complicated cholecystolithiasis	14 years (IQR: 10–15)
	Choledocholithiasis with cholestasis	14 years (IQR: 9–15)
	Choledocholithiasis with acute pancreatitis	14 years (IQR: 13–16)

Tab. 2. Median age at diagnosis by subgroups

ages ranging from 2 months to 17 years. Children over 10 years of age constituted the largest group of patients. General information is shown in Tab. 1.

Among the hospitalised patients, the mean hospitalisation time was 9.92 ± *SD* 5.8 days. The difference in hospitalisation times between the groups, divided according to diagnosis, was at the limit of statistical significance ($p = 0.06$). The longest hospitalisation time, 12.5 ± *SD* 7.78 days, was observed in the group of patients with choledocholithiasis with acute pancreatitis, compared to 10.83 ± *SD* 6.1 days in patients with choledocholithiasis and 7.03 ± 2.35 days in those with symptomatic uncomplicated cholelithiasis.

In the entire study group, cholelithiasis was diagnosed at a median age of 11 years (interquartile range, IQR: 3–14). The age of diagnosis differed between the individual groups of patients ($p < 0.01$). Younger children more often presented with an asymptomatic or uncomplicated course of cholecystolithiasis, while older children had higher rates of complications, choledocholithiasis, and acute pancreatitis. Detailed data are presented in Tab. 2.

Clinical features

In the total group, 69/106 (65.09%) patients were symptomatic. The most common presenting symptoms were abdominal pain, vomiting, and jaundice. Only 19/45 (42.22%) patients from the outpatient clinic group showed symptoms, compared to 50 (82%) children from the hospital group. The leading symptoms are presented in Tab. 3.

Clinical symptoms	Total
Abdominal pain	71/106 (66.98%)
Vomiting	31/106 (29.24%)
Jaundice	21/106 (19.81%)
Itchy skin	20/106 (18.87%)
Acholic stools	4/106 (3.77%)
Fever	3/106 (2.83%)

Tab. 3. Clinical symptoms of cholelithiasis

	Percentile range	Total
Body mass index	<3	3/95 (3.16%)
	3–10	5/95 (5.26%)
	10–90	47/95 (49.47%)
	90–97	14/95 (14.74%)
	>97	26/95 (27.37%)

Tab. 4. Body mass index of the study group

Nutritional status

The nutritional status of patients was assessed using BMI values referenced to percentile charts. Normal BMI was found in 47/95 (49.47%) patients. Among 40/95 (42.11%) patients with high BMI, 14/95 (14.74%) children were overweight and 26/95 (27.37%) were obese. There was no difference in BMI between patients grouped by diagnosis ($p > 0.05$). Complete data are presented in Tab. 4.

Laboratory tests

Among the numerous laboratory test results analysed, the most frequently abnormally elevated parameters were gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin. Moreover, lipid metabolism disorders, including hypercholesterolemia and hypertriglyceridemia, were found in 7/106 (6.6%) and 9/106 (8.49%) patients, respectively. No disturbances in calcium and phosphate metabolism were observed in the study group. Detailed results of laboratory tests are presented in Tab. 5.

Imaging tests

All the patients underwent abdominal ultrasonography, which revealed gallstones in 87.7% of cases. The most common findings in ultrasound were features of cholecystitis, fluid in the abdomen/pleural cavity, and features of acute pancreatitis. In all patients with gallbladder deposits on ultrasound, cholecystostomy confirmed the presence of gallbladder stones. In inconclusive cases, magnetic resonance cholangiopancreatography (MRCP) was performed. Cholangio-MRI examination was conducted in 28 patients (26.4%). Interestingly, gallstones in the bile ducts were observed in MRI, but not in ultrasound, in 8/22

Parameter	Value range	Median	Total number of patients with abnormal results
GGT [U/L]	8.0–1,098.0	94	59/106 (55.66%)
AST [U/L]	10.0–955.0	62	56/106 (52.83%)
ALT [U/L]	7.0–798.0	57	53/106 (50%)
Total bilirubin [µmol/L]	0.41–781.9	15.3	49/106 (46.23%)
Direct bilirubin [µmol/L]	0.7–390.9	4.1	40/106 (37.74%)
CRP [mg/L]	0.2–181.6	3.25	26/106 (24.53%)
Amylase [U/L]	3.0–7773.0	42	16/106 (15.09%)
WBC [10^3/µL]	3.55–23.86	8	16/106 (15.09%)

ALT – alanine transaminase; **AST** – asparagine transaminase; **CRP** – C-reactive protein; **GGT** – gamma-glutamyl transpeptidase; **WBC** – white blood count.

Tab. 5. Basic laboratory test results of the examined patients

DOI: 10.15557/PiMR.2024.0063

Type of examination	Findings	Total
Ultrasound	Gallstones	93/106 (87.7%)
	Features of cholecystitis	17/106 (16%)
	Fluid in abdominal/pleural cavity	13/106 (12.26%)
	Features of acute pancreatitis	6/106 (5.66%)
	Hydrocele	4/106 (3.77%)
	Hepatomegaly	4/106 (3.77%)
	Features of cholangitis	2/106 (1.89%)
MRI	Gallstones	22/28 (78.57%)
	Features of cholecystitis	5/28 (17.86%)
	Features of acute pancreatitis	4/28 (14.29%)
	Features of cholangitis	2/28 (7.14%)
	Fluid in abdominal/pleural cavity	2/28 (7.14%)
	Hydrocele	1/28 (3.57%)

MRI – magnetic resonance imaging.

Tab. 6. Findings from the imaging tests (ultrasound and MRI)

(36.6%) patients with choledocholithiasis. The predominant findings in MRI were features of cholecystitis and signs of acute pancreatitis. Other findings or complications detected during imaging examinations are presented in Tab. 6.

Treatment

A total of 18 ERCPs were performed on 106 patients (16.9%). Among this group, there were 17 (94.44%) biliary sphincterotomies. Stone extraction was performed in 9/18 (50%) patients, while in the other half of cases (9/18 patients), the procedure revealed spontaneous stone extraction. Stents were used for biliary drainage in 2/18 (11.11%) patients. The remainder of the clinical group was treated symptomatically. All patients with symptomatic cholecystolithiasis, choledocholithiasis, and biliary pancreatitis were urgently referred for cholecystectomy (76/106, 71.7%). To date, only 40/76 (52.63%) qualified patients have undergone cholecystectomy, all with a laparoscopic approach. There were only 2/40 (5%) complications of cholecystectomy in the study group. The first complication was postoperative stricture of the bile ducts, which occurred in one of the youngest patients (10 months old) in the study group. The stricture was removed during laparoscopic surgery. The second complication was iatrogenic damage to the bile ducts – the clip had covered the common hepatic duct. During laparoscopic reoperation, the clip was removed from the common hepatic duct, and a Kehr's drain was placed.

Complications

Overall, 35/106 (33%) children presented with 48 complications of cholelithiasis. Cholecystitis was the most common complication, followed by acute pancreatitis and cholangitis. There were only two complications, both acute pancreatitis, in the outpatient clinic group (2/45, 4.44%), compared to the hospital group with 33 complications (33/61, 54.1%). Detailed information about the complications is presented in Fig. 1.

Risk factors

The leading risk factors for cholelithiasis in the study group were comorbidities, including endocrinological, haematological, and oncological diseases, present in 40.57% of patients. The second most common risk factor was excessive body weight, observed in 37.74% of patients. Positive family

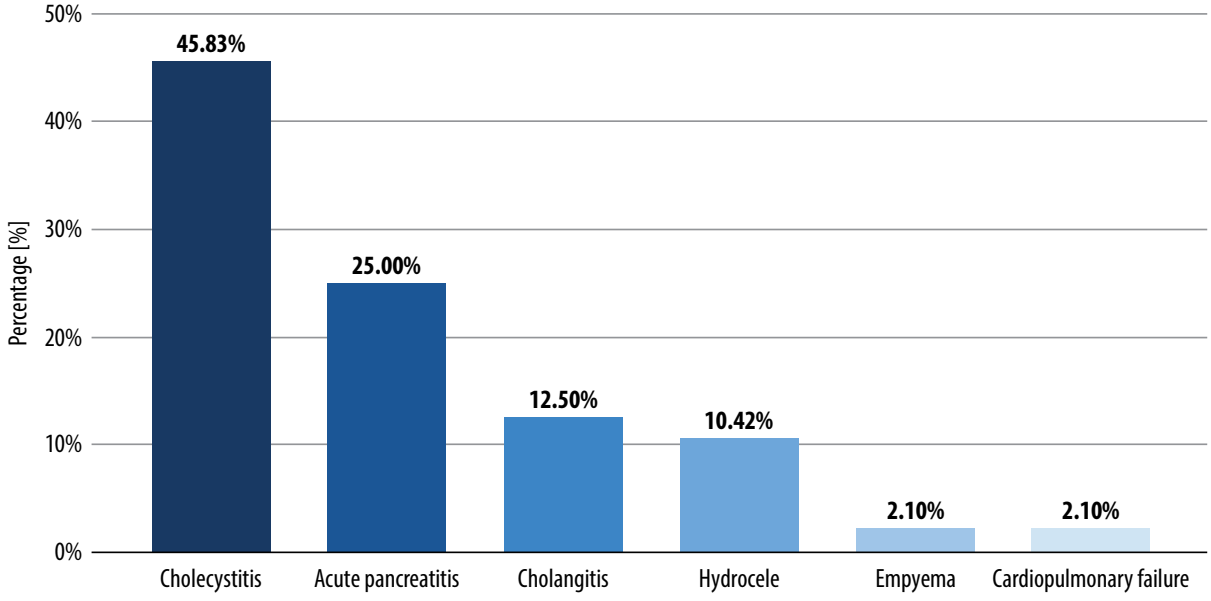

Fig. 1. Complications of cholelithiasis in the study group

 DOI: 10.15557/PiMR.2024.0063

Risk factor		Number of patients (%)
Comorbidities		**43/106 (40.57%)**
Overweight and obesity		**40/106 (37.74%)**
Family history of cholelithiasis		**16/106 (15.09%)**
Psychotropic drugs		**13/106 (12.26%)**
Significant perinatal history	**Total** Prematurity NEC	**12/106 (11.32%)** 12/106 (11.32%) 4/106 (3.77%)
Endocrinological disorders	**Total** Hypothyroidism PCOS Hypopituitarism	**12/106 (11.32%)** 9/106 (8.49%) 2/106 (1.89%) 1/106 (0.94%)
Other medications	**Total** Ceftriaxone Spironolactone Furosemide	**12/106 (11.32%)** 5/106 (4.72%) 4/106 (3.77%) 3/106 (2.83%)
Lipid metabolism disorders	**Total** Hypertriglyceridemia Hypercholesterolemia Abetalipoproteinemia	**12/106 (11.32%)** 9/106 (8.49%) 7/106 (6.6%) 1/106 (0.94%)
Liver diseases	**Total** NASH PSC PFIC	**7/106 (6.6%)** 4/106 (3.77%) 2/106 (1.89%) 1/106 (0.94%)
History of parenteral nutrition		**6/106 (5.66%)**
Rapid weight loss		**6/106 (5.66%)**
Defect of gallbladder and biliary tract		**5/106 (4.72%)**
Haemolytic anaemia		**5/106 (4.72%)**
Trisomy 21		**4/106 (3.77%)**
Oncological diseases		**3/106 (2.83%)**

NASH – non-alcoholic steatohepatitis; **NEC** – necrotising enterocolitis; **PCOS** – polycystic ovary syndrome; **PFIC** – progressive familial intrahepatic cholestasis; **PSC** – primary sclerosing cholangitis.

Tab. 7. Analysed risk factors for cholelithiasis in the study group

history, prematurity, and use of certain medications were found to be other important risk factors.

Depending on the age of diagnosis, for patients with gallstones before the age of 2 years, the dominant risk factors were prematurity (7/25) and congenital disorders (8/25), such as anatomical defects of the gallbladder and bile ducts, congenital heart defects, trisomy 21, or serious infections (7/25). In the population of children diagnosed after the age of 10 years, the dominant risk factor was obesity or overweight, observed in 28/54 patients.

In addition, the study found that another significant risk factor, not typically associated with cholelithiasis in children, may be psychiatric medications. The use of these drugs was reported in 13/106 (12.26%) patients. The drugs belonged to the following groups: atypical antipsychotics (6/13), hydroxyzine (6/13), selective serotonin reuptake inhibitors (SSRIs) (3/13), classic antipsychotics (2/13), and benzodiazepines (1/13). Considering potential confounding factors in this study, 8/13 patients taking psychiatric medications were overweight or obese, and 5/13 patients had other comorbidities.

No disorders of calcium and phosphate metabolism were observed in the study group. Detailed data on identified risk factors are presented in Tab. 7.

DISCUSSION

Prevalence of cholelithiasis

The prevalence of cholelithiasis in children is increasing, likely due to the higher number of patients with comorbidities such as obesity and wider access to imaging tests[2,6,40]. The global prevalence of cholelithiasis in children ranges from 0.15 to 0.22%, but some sources indicate that the number of patients is underestimated and could reach as high as 2%, or even 6% in obese children[13,22].

Risk factors

According to our study results, comorbidities and excessive body weight represent the most frequently observed risk factors for paediatric cholelithiasis. However, the predisposing factors vary significantly depending on age. Prematurity and its complications, congenital disorders, and infections predominate in younger children, while in older children, the metabolic consequences of obesity have an increasing impact. This study aligns with the finding that excessive body weight is a significant risk factor for cholelithiasis[2,6,8,31]. In a Polish perspective study, children with cholelithiasis were more frequently overweight (35.6% vs. 18.4%,) and obese (12.2% vs. 6.7%) than controls[40]. This study shows a higher percentage of obese children, compared to the range of 7% to 21% presented in previous studies[2,3,6,12–14,28,32,33]. The higher rate of obesity in this study may be explained by the increasing prevalence of obesity in the Polish paediatric population. Considering the data on the increasing incidence of obesity and overweight in children, cholelithiasis may become a significant paediatric problem in the coming years[40]. The promotion of a healthy lifestyle should focus on the prevention of cholelithiasis in children.

Other studies confirm that comorbidities are among the leading risk factors, although this may vary depending on the study population. Overall, haemolytic diseases were the most frequent, but in this Polish group, the most common disorders were endocrine diseases, while in the Korean study, it was hepatitis[4,16,19]. Similarly, certain drugs (furosemide, antiepileptic drugs, octreotide, ceftriaxone) may contribute to cholelithiasis in up to 25% of children[3]. Among these, ceftriaxone is the most common risk factor for gallstones, especially in younger children and those treated over prolonged periods with high doses due to bacterial meningitis. In most cases, gallstones resolve after discontinuation of drugs[3,41]. Despite the numerous known risk factors, the unknown aetiology of cholelithiasis still accounts for more than half of cases in the paediatric population[3,14,28].

DOI: 10.15557/PiMR.2024.0063

Psychiatric drugs as a potential risk factor for cholelithiasis

During the analysis of the study group, it was observed that drugs typically associated with cholelithiasis were rarely present when considered individually by drug groups. However, many children used psychiatric medications (atypical antipsychotics, hydroxyzine, SSRIs, classic antipsychotics, benzodiazepines), which are not typically linked to cholelithiasis. The data on the influence of psychiatric medications in the pathophysiology of cholelithiasis are limited, especially in the paediatric population. One study showed that ultrasound examinations revealed gallstones in 25% of psychiatric patients. It also found that the presence of gallstones correlated with the duration of neuroleptic use, implying that long-term neuroleptic treatment may be an important factor in the increased risk of cholelithiasis[42]. However, in the case of this study, overlapping factors were not mentioned. Despite the extensive knowledge about cholelithiasis, future research should focus on examining new risk factors, including the use of psychiatric medications.

Variable course depending on the age of patients

This study indicates that older children are more frequently diagnosed with cholelithiasis, but the wide age range in the study group suggests that the disease can occur at any age, from infancy to adolescence.

Moreover, our observation that asymptomatic courses are more characteristic for younger age groups and complicated courses are more frequent in older children is consistent with the findings reported by other authors. Tuna Kirsaclioglu et al. showed that the mean age of patients with complicated cholelithiasis (12 years) was significantly higher than others (8 years), and Sarrami et al. reported that children older than 12 years presented a higher rate of choledocholithiasis and acute pancreatitis[3,12,13,18,25]. This disproportion may be explained by the early detection of gallstones in young asymptomatic patients due to the widespread use of ultrasonography in children with burdened pregnancy, childbirth history, or other related comorbidities[3]. Furthermore, the literature reports that obesity also increases the risk of cholelithiasis-related complications[32], which may explain the higher rates of complications in adolescents. Moreover, Losa et al. found in their multivariate regression model that children over the age of 10 years were more likely to develop complications, while children under 2 years had a higher rate of spontaneous resolution of cholelithiasis[43], which is similar to our observations. Tannuri et al. observed that 25.1% of children presented with complications as the first sign of cholelithiasis[4]. Overall, it should be noted that the rates of complications seem to be higher in children than in adults[25].

According to this study, the occurrence of complications correlates with the age of the children and age-related predisposing factors, which in younger children lead to early detection of gallstones via ultrasound, while adolescents are typically diagnosed when complications occur. Early detection of cholelithiasis, even in asymptomatic paediatric patients, may be significant in the differential diagnosis of abdominal pain. It may contribute to shortening the diagnostic process in cases of biliary colic or complications and be crucial for older, obese children, in whom complications occur more frequently.

Diagnostics and treatment

Abdominal ultrasound is the examination of choice for cholelithiasis but has certain limitations. This study aligns with the findings that, in cases of suspected choledocholithiasis, normal ultrasound results have insufficient sensitivity and may be falsely reassuring. Similar to our results, Isherwood et al. reported that 30/71 patients (42.25%) with choledocholithiasis and normal ultrasound results showed findings on MRCP[44,45]. In contrast, Stock et al. reported that only 7% of children with choledocholithiasis had false-negative ultrasound results, suggesting that MRI provides little additional information in children with a normal ultrasound image of the common bile duct, except in patients with pancreatitis or persistent symptoms[46]. Therefore, when choledocholithiasis is suspected, ultrasound may be insufficient, and diagnostics should be always extended if clinical symptoms worsen. ERCP is crucial in the treatment of choledocholithiasis, serving as both a sensitive diagnostic tool and a therapeutic option, even in paediatric cases. Complications like pancreatitis and cholangitis in children from ERCP are similar to adults, occurring at a frequency of 0–10%[47,48].

In paediatric patients, common bile duct exploration (LCBDE) has emerged as a secure and effective approach for managing both choledocholithiasis and cholelithiasis concurrently, without the need for papillotomy or fluoroscopy. LCBDE is a reliable and efficient option when performed by a proficient surgeon and shortens the hospital stay[49–51]. However, LCBDE is a relatively new method, poorly available for paediatrics in some countries, including Poland. Interestingly, a multicentre, retrospective cohort study by Rauh et al. revealed that, in cases of paediatric choledocholithiasis, upfront laparoscopic cholecystectomy, followed by intraoperative cholangiogram and possible transcystic LCBDE, is associated with fewer ERCPs, shorter hospital stays, and fewer complications than the traditional approach (ERCP followed by laparoscopic cholecystectomy)[52]. More research is needed to promote this method and compare its effectiveness with the more available approach of ERCP, especially in countries with poor availability of this method, like Poland.

LIMITATIONS

This study has several limitations that should be acknowledged. The quality of the results is influenced by the retrospective design and the limited sample size due to the

 DOI: 10.15557/PiMR.2024.0063

recruitment of patients from a single research centre. Some variables may lack some details, such as family history, past medical history, and previously taken medications, because of potential lacks in medical databases. It was impossible to determine disease relapse, as some patients either relocated or continued chronic treatment in other centres or outpatient clinics. Another possible limitation may be selection bias. Due to the highly specialised nature of our centre, a significantly higher proportion of patients were children with complicated cholelithiasis, choledocholithiasis, and acute pancreatitis, compared to what might be encountered in other centres. In this study, the issue of cholelithiasis is mostly presented from the perspective of paediatricians and paediatric gastroenterologists, so detailed surgical data are limited. The data on risk factors for cholelithiasis in children in this study should be interpreted as preliminary, due to the absence of a control group and the inclusion of confounding factors.

CONCLUSIONS

In the paediatric population, an increasing incidence of cholelithiasis is being observed, even among the youngest patients. Undoubtedly, the pathogenesis of cholelithiasis is influenced by co-occurring diseases, medications, and obesity. The use of psychiatric drugs should be considered as a possible risk factor for cholelithiasis in children. Further research is needed to explore the effects of psychiatric medications on the development of cholelithiasis. A helpful approach would be to separate a study group of children from psychiatric clinics who are taking psychiatric drugs, perform ultrasound examinations to detect cholelithiasis, and compare the results with those of children without psychiatric disorders. The differential diagnosis of abdominal pain in the paediatric population should always include cholecystolithiasis and choledocholithiasis. In diagnosing choledocholithiasis, ultrasound examination may have insufficient sensitivity. Therefore, it is necessary to extend the diagnosis to include MRI examination in patients presenting with cholestasis symptoms. This may contribute to shortening the diagnostic process and prove crucial in older, obese children, in whom complications occur more often.

Ethical approval and consent to participate

According to the decision of the Bioethics Committee of the Medical University of Silesia in Katowice (BNW/NWN/0052/KB/3/24), the study does not meet the criteria of a medical experiment and, therefore, does not require bioethical approval. All procedures performed in the study were in accordance with the ethical standards set by the institutional research committee and the 1964 Declaration of Helsinki with its subsequent amendments. Consent to participate was not required due to the retrospective nature of the study.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study: MN, SW. Collection, recording and/or compilation of data: MN, ZO, PŁ, JT, SW. Analysis and interpretation of data: MN, ZO, PŁ, JT, DB, SW. Writing of manuscript: MN, ZO, OŁ, JT, DB, SW. Critical review of manuscript: UGC, TK, SW. Final approval of manuscript: MN, ZO, PŁ JT, UGC, TK, SW.

References

1. Jeanty C, Derderian SC, Courtier J et al.: Clinical management of infantile cholelithiasis. J Pediatr Surg 2015; 50: 2289–2292.
2. Fradin K, Racine AD, Belamarich PF: Obesity and symptomatic cholelithiasis in childhood: epidemiologic and case-control evidence for a strong relation. J Pediatr Gastroenterol Nutr 2014; 58: 102–106.
3. Tuna Kirsaclioglu C, Çuhacı Çakır B, Bayram G et al.: Risk factors, complications and outcome of cholelithiasis in children: a retrospective, single-centre review. J Paediatr Child Health 2016; 52: 944–949.
4. Tannuri ACA, Leal AJG, Velhote MCP et al.: Management of gallstone disease in children: a new protocol based on the experience of a single center. J Pediatr Surg 2012; 47: 2033–2038.
5. Biner B, Oner N, Celtik C et al.: Ceftriaxone-associated biliary pseudolithiasis in children. J Clin Ultrasound 2006; 34: 217–222.
6. Svensson J, Makin E: Gallstone disease in children. Semin Pediatr Surg 2012; 21: 255–265.
7. Huang JS, Barlow SE, Quiros-Tejeira RE et al.: Childhood obesity for pediatric gastroenterologists. J Pediatr Gastroenterol Nutr 2013; 56: 99–109.
8. Koebnick C, Smith N, Black MH et al.: Pediatric obesity and gallstone disease. J Pediatr Gastroenterol Nutr 2012; 55: 328–333.
9. Kaechele V, Wabitsch M, Thiere D et al.: Prevalence of gallbladder stone disease in obese children and adolescents: influence of the degree of obesity, sex, and pubertal development. J Pediatr Gastroenterol Nutr 2006; 42: 66–70.
10. Argiriov Y, Dani M, Tsironis C et al.: Cholecystectomy for complicated gallbladder and common biliary duct stones: current surgical management. Front Surg 2020; 7: 42.
11. Adeniyi OF, Akinsete AM, Odeghe EA et al.: Cholelithiasis in children and adolescents with sickle cell disease: experience in a resource-limited setting. Ann Afr Med 2022; 21: 58–64.
12. Bhaumik K. Asymptomatic cholelithiasis in children: management dilemma. J Indian Assoc Pediatr Surg 2021; 26: 228–233.
13. Lia E, Amri K: Cholelithiasis in children: a characteristic study. Med J Malaysia 2022; 77: 59–61.
14. Della Corte C, Falchetti D, Nebbia G et al.: Management of cholelithiasis in Italian children: a national multicenter study. World J Gastroenterol 2008; 14: 1383–1388.
15. Alvarenga LR, Sandy NS, Gomez GS et al.: Symptomatic cholelithiasis as the presentation of pediatric primary sclerosing cholangitis – case series and literature review. Arq Gastroenterol 2021; 58: 227–233.
16. Frybova B, Drabek J, Lochmannova J et al.: Cholelithiasis and choledocholithiasis in children; risk factors for development. PLoS One 2018; 13: e0196475.
17. Kang JY, Ellis C, Majeed A et al.: Gallstones – an increasing problem: a study of hospital admissions in England between 1989/1990 and 1999/2000. Aliment Pharmacol Ther 2003; 17: 561–569.
18. Kiuru E, Kokki H, Juvonen P et al.: The impact of age and sex adjusted body mass index (ISO-BMI) in obese versus non-obese

children and adolescents with cholecystectomy. In Vivo 2014; 28: 615–619.
19. Lee YJ, Park YS, Park JH: Cholecystectomy is feasible in children with small-sized or large numbers of gallstones and in those with persistent symptoms despite medical treatment. Pediatr Gastroenterol Hepatol Nutr 2020; 23: 430–438.
20. Bosley ME, Zamora IJ, Neff LP: Choledocholithiasis – a new clinical pathway. Transl Gastroenterol Hepatol 2021; 6: 35.
21. Toscano E, Trivellini V, Andria G: Cholelithiasis in Down's syndrome. Arch Dis Child 2001; 85: 242–243.
22. Nunes MM, Medeiros CCM, Silva LR: Cholelithiasis in obese adolescents treated at an outpatient clinic. J Pediatr (Rio J) 2014; 90: 203–208.
23. Almeida RQ, Gerardi Filho VA, Dias JLF et al.: Laparoscopic cholecystectomy for symptomatic cholelithiasis in children and adolescents: analysis of 50 cases from a single institution. Acta Cirúrgica Bras 2024; 39: e394124.
24. Poffenberger CM, Gausche-Hill M, Ngai S et al.: Cholelithiasis and its complications in children and adolescents: update and case discussion. Pediatr Emerg Care 2012; 28: 68–78.
25. Sarrami M, Ridley W, Nightingale S et al.: Adolescent gallstones – need for early intervention in symptomatic idiopathic gallstones. Pediatr Surg Int 2019; 35: 569–574.
26. Goldman DA: Gallbladder, gallstones, and diseases of the gallbladder in children. Pediatr Rev 2020; 41: 623–629.
27. Loria P, Lonardo A, Lombardini S et al.: Gallstone disease in non-alcoholic fatty liver: prevalence and associated factors. J Gastroenterol Hepatol 2005; 20: 1176–1184.
28. Agrawal V, Tiwari A, Sharma D et al.: Etiology-based decision-making protocol for pediatric cholelithiasis. Indian Pediatr 2021; 58: 729–732.
29. Di Ciaula A, Portincasa P: Recent advances in understanding and managing cholesterol gallstones. F1000Res 2018; 7: F1000 Faculty Rev-1529.
30. Pogorelić Z, Aralica M, Jukić M et al.: Gallbladder disease in children: a 20-year single-center experience. Indian Pediatr 2019; 56: 384–386.
31. Demidowicz G, Lasota N, Trąbka N et al.: Cholelithiasis – current knowledge about one of the most common diseases of the digestive system. J Educ Heal Sport 2023; 38: 258–276.
32. Bonfrate L, Wang DQH, Garruti G et al.: Obesity and the risk and prognosis of gallstone disease and pancreatitis. Best Pract Res Clin Gastroenterol 2014; 28: 623–635.
33. Diez S, Müller H, Weiss C et al.: Cholelithiasis and cholecystitis in children and adolescents: does this increasing diagnosis require a common guideline for pediatricians and pediatric surgeons? BMC Gastroenterol 2021; 21: 186.
34. Jaruvongvanich V, Sanguankeo A, Upala S: Significant association between gallstone disease and nonalcoholic fatty liver disease: a systematic review and meta-analysis. Dig Dis Sci 2016; 61: 2389–2396.
35. Hemminki K, Hemminki O, Försti A et al.: Familial risks for gallstones in the population of Sweden. BMJ Open Gastroenterol 2017; 4: e000188.
36. Gökçe S, Yıldırım M, Erdoğan D: A retrospective review of children with gallstone: single-center experience from Central Anatolia. Turk J Gastroenterol 2014; 25: 46–53.
37. Huang D, Joo H, Song N et al.: Association between gallstones and the risk of biliary tract cancer: a systematic review and meta-analysis. Epidemiol Health 2021; 43: e2021011.
38. Shabanzadeh DM, Holmboe SA, Sørensen LT et al.: Are incident gallstones associated to sex-dependent changes with age? A cohort study. Andrology 2017; 5: 931–938.
39. Kan M, Shi HY, Han B et al.: Prediction of unbound ceftriaxone concentration in children: simple bioanalysis method and basic mathematical equation. Antimicrob Agents Chemother 2020; 65: e00779-20.
40. Krawczyk M, Kułaga Z, Niewiadomska O et al.: Are children with gallstone disease more overweight? Results of a matched case-control analysis. Clin Res Hepatol Gastroenterol 2023; 47: 102204.
41. Louta A, Kanellopoulou A, Alexopoulou Prounia L et al.: Ceftriaxone administration associated with lithiasis in children: guilty or not? A systematic review. J Pers Med 2023; 13: 671.
42. Fukuzako H, Hashiguchi T, Nomaguchi M et al.: Ultrasonography detected a higher incidence of gallstones in psychiatric inpatients. Acta Psychiatr Scand 1991; 84: 83–85.
43. Losa A, Silva G, Mosca S et al.: Pediatric gallstone disease – management difficulties in clinical practice. Gastroenterol Hepatol 2024: 502228.
44. Isherwood J, Garcea G, Williams R et al.: Serology and ultrasound for diagnosis of choledocholithiasis. Ann R Coll Surg Engl 2014; 96: 224–228.
45. Capparelli MA, D Alessandro PD, Questa HA et al.: Development of a risk score for choledocholithiasis in pediatric patients. Pediatr Surg Int 2021; 37: 1393–1399.
46. Stock MR, Fine RO, Rivas Y et al.: Magnetic resonance imaging following the demonstration of a normal common bile duct on ultrasound in children with suspected choledocholithiasis: what is the benefit? Pediatr Radiol 2022; 53: 358–366.
47. European Association for the Study of the Liver (EASL). Electronic address: easloffice@easloffice.eu. EASL Clinical Practice Guidelines on the prevention, diagnosis and treatment of gallstones. J Hepatol 2016; 65: 146–181.
48. Felux J, Sturm E, Busch A et al.: ERCP in infants, children and adolescents is feasible and safe: results from a tertiary care center. United Eur Gastroenterol J 2017; 5: 1024–1029.
49. Bosley ME, Ganapathy AS, Sanin GD et al.: Reclaiming the management of common duct stones in acute care surgery. J Trauma Acute Care Surg 2023; 95: 524–528.
50. Pavlidis ET, Pavlidis TE: Current management of concomitant cholelithiasis and common bile duct stones. World J Gastrointest Surg 2023; 15: 169–176.
51. Pogorelić Z, Lovrić M, Jukić M et al.: The laparoscopic cholecystectomy and common bile duct exploration: a single-step treatment of pediatric cholelithiasis and choledocholithiasis. Children 2022; 9: 1583.
52. Rauh J, Dantes G, Wallace M et al.: Transcystic laparoscopic common bile duct exploration for pediatric patients with choledocholithiasis: a multi-center study. J Pediatr Surg 2023; 59: 389–392.