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A retrospective review of children with gallstone: Single-center experience from Central Anatolia

BILIARY

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Original Article

ABSTRACT

Background/Aims: To evaluate children with gallstone in respect to demographic features, type of presentation, predisposing risk factors, laboratory features, complications, and outcome.

Materials and Methods: Overall, 124 children with sonographically diagnosed gallstone were stratified into group 1 (symptomatic) and group 2 (asymptomatic). The data on demographic features, predisposing risk factors, laboratory features, complications, and outcome were collected from medical charts and compared by using convenient statistical methods.

Results: There were 76 (61%) children in group 1. Females were significantly older than males at the time of diagnosis (p=0.001). After adjusting for age and sex, asymptomatic presentation was associated with hemolytic anemia (r=346, <0.001) and being an oncologic patient (r=248, p=0.006). No risk factor was specifically associated with having a symptomatic presentation. Sixteen children (12.9%) developed complications: 14 (18.4%) in group 1 and 2 (4.2%) in group 2 (p=0.027). Gallstone resolution was detected in 20 (29.4%) and 10 children (23.3%) in groups 1 and 2, respectively (p=0.477). Resolution was observed in 43.8% of children with ceftriaxone-associated gallstone. The rate of resolution with ursodeoxycholic acid (UDCA) was similar to that observed with expectant management. Gallstone resolution was evident in 9 infants (50.0%) and was significantly higher than children over 2 years of age (21 out of 106 children, 19.8%) (p=0.006). The most important factor associated with gallstone resolution was to be an infant (<2 years of age) at the time of diagnosis (OR: 3.1; 95% CI: 1.1-8.8; p=0.034).

Conclusion: Ceftriaxone-associated gallstones are most likely to resolve but do not always undergo spontaneous resolution. UDCA treatment seems to be ineffective. Young age is a favorable factor for gallstone resolution. The rate of complications in children with asymptomatic presentation is considerably low. Thus, clinical follow-up rather than surgical intervention is suggested in children with asymptomatic presentation and in infants.

Keywords: Children, gallstone, complication, risk factors

INTRODUCTION

Gallstones were considered to be uncommon in infants and children but have been increasingly diagnosed in recent years. It is probably due to improved detection from the widespread use of diagnostic ultrasonography (US) in children and/or a genuine increase in the incidence of cholelithiasis from recognized predisposing factors, such as total parenteral nutrition (TPN), obesity, and prematurity, etc. (1-5). Although the exact prevalence of gallstones in children is not known, studies have shown an overall prevalence of 0.13% to 1.9% in children (1,6,7).

The increased use of sonography in the diagnosis and monitoring of gastrointestinal and genitourinary pathologies has led to increased detection of asymptomatic gallbladder calculi. For asymptomatic adults, expectant management with periodical clinical and

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sonographic controls is recommended (8). In children, the data on the natural history of asymptomatic gallstones are limited, and small series suggest conservative management for those without symptoms (6,9). Ursodeoxycholic acid (UDCA) as a nonsurgical approach has been rarely studied in children and found to be ineffective (10-12).

In the present study, we aimed to comprehensively review children with gallstone in respect to demographic features, type of presentation, predisposing risk factors, laboratory features, complications, and outcome. This study is also important as the first comprehensive report from Central Anatolia.

MATERIALS AND METHODS

The medical records of children diagnosed with gallstone sonographically from January 2005 to September 2010 were reviewed retrospectively. Conventional hepatic US was performed by radiologists using a GE Logiq S6 (General Electric, USA) with convex transducers (Frequency bandwidth 3.5 MHz). Gallstone was defined as echogenic foci in the gallbladder or bile ducts that produced posterior acoustic shadowing. Patients with nonshadowing intraluminal material that reprents sludge or sludge balls were excluded.

Demographic information, medical history, predisposing factors, presenting symptoms, imaging findings, and complications were noted in all of the children. Patients were divided into group 1 (symptomatic) and group 2 (asymptomatic), based on symptomatology at the time of initial diagnosis. Patients with any symptom potentially related to gallstones were deemed "symptomatic." The remaining ones with no symptoms or symptoms that were not related to gallstone, such as left or right lower quadrant pain, or having a confirmed cause for symptoms (eg, urinary tract infection, invagination) were included in the "symptomatic" group. The groups were analyzed in respect to demographic features, distribution of risk factors, laboratory findings, complications, management, and outcome. Complications were assessed, based on clinical and imaging findings. In children not requiring cholecystectomy at initial presentation, follow-up data were recorded. based on clinical and sonographic findings. The patients who did not undergo surgery were followed by 3 monthly clinical and ultrasound assessments for 6 to 12 months. If they remained asymptomatic, they were only further followed with clinical and/or sonographic assessments every 6-12 months or if symptoms developed.

In those patients who underwent cholecystectomy, operative and pathology reports were reviewed and were then correlated with clinical and sonographic findings.

The study was performed in accordance with the Declaration of Helsinki (13) and approved by the local ethical committee. Informed consent of all subjects was taken from the parents.

Statistical analysis

Analyses were performed using SPSS v.15.0 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to describe the sample. Numerical variables are expressed as median (range). Categorical variables are shown as number and percentage. Variables were compared using Mann-Whitney U-test, chi-square (χ^2) test, and Fisher exact test. Spearman test was used to evaluate the association of risk factors with being symptomatic or asymptomatic. Logistic regression was used to quantify the impact of each predictor on the probability of stone resolution. All of the tests were 2-sided, and P values <0.05 were considered statistically significant.

RESULTS

The medical records of children diagnosed with gallstone from January 2005 to September 2010 were reviewed retrospectively. A total of 124 children included 63 (51%) females and 61 (49%) males. There were 55 (44.4%) children over the age of 10 years, 51 (41.1%) children between 2-10 years, and 18 (14.5%) children below 2 years of age. Overall, there was no significant difference in the sex distribution (p=0.928). On the other hand, 36 (65%) out of 55 children who were 10 years of age or older were female—significantly greater than the number of males (p=0.004). The median age was 9.0 years (0.08-18.0) overall: 10.5 years (0.08-18.0) in females and 7.0 years (0.25-16) in males. Females were significantly older than males at the time of diagnosis (p=0.001).

There were 76 (61%) children in group 1 and 48 (39%) in group 2. The median age of children was 9.0 years (0.08-17.0) in group 1 and 8.5 years (0.25-18.0) in group 2 (p=0.122). There was no significant difference between median ages. There were 39 (51%) females and 37 (49%) males in group 1. The complaints or symptoms reported by patients or parents were abdominal pain in 62 patients (81.5%), vomiting in 44 (57.9%), fever in 11 (14.5%), irritability in 11 (14.5%), jaundice in 5 (6.6%), weight loss in 1 (1.3%), and pale stools in 1 (1.3%). There were 48 [24 females (50%)] children in group 2. There was no significant difference in the sex distribution between groups 1 and 2 (p=0.483). Indications of ultrasound in group 2 were screening in patients at risk for gallstone formation in 13 (27.1%), investigation or follow-up of known renal pathology in 11 (23%), investigation of liver pathology in 7 (14.6%), oncology in 5 (10%), investigation or follow-up of confirmed bowel pathology in 3 (6%), metabolic disease in 3 (6%), search for congenital anomaly in 2 (4%), and miscellaneous in 4 (8.3%).

The risk factors predisposing patients to gallstone formation are displayed in Table 1 and Figure 1. Overall, 54 (43.5%) children had no identifiable risk factor and were categorized as idiopathic. There were statistically more children in idiopathic category in group 1 (52.6%) than in group 2 (29.2%) (p=0.010). At least 1 risk factor was found in 70 (56.5%) patients overall. Group 2 was associated with hemolytic anemia (r=336,

Table 1. Risk factors predisposing gallstone formation

	Group 1 (n=76) n (%)	Group 2 (n=48) n (%)	Total (n=124) n (%)	P*
Idiopathic	40 (52.6)	14 (29.2)	54 (43.5)	0.010
Familiarity	13 (17.1)	7 (14.6)	20 (16.1)	0.710
Hemolytic anemia	3 (3.9)	13 (27.1)	16 (12.9)	<0.001
Cephalosporin	9 (11.8)	7 (14.6)	16 (12.9)	0.657
Oncologic patient	-	4 (8.3)	4 (3.2)	0.021
Obesity	7 (9.2)	3 (6.3)	10 (8.1)	0.739
Trisomy	-	3 (6.3)	3 (2.4)	0.056
Surgery (abdominal, cardiac)	4 (5.3)	1 (2.1)	5 (4.0)	0.648
Miscellaneous**	10 (13.2)	10 (20.8)	20 (16.2)	0.258

*Chi-Square
**Diüretic use, total parenteral nutrition, sepsis, prematurity, chronic liver disease, dehydration (either isolated or together with one or more of other risk factors)

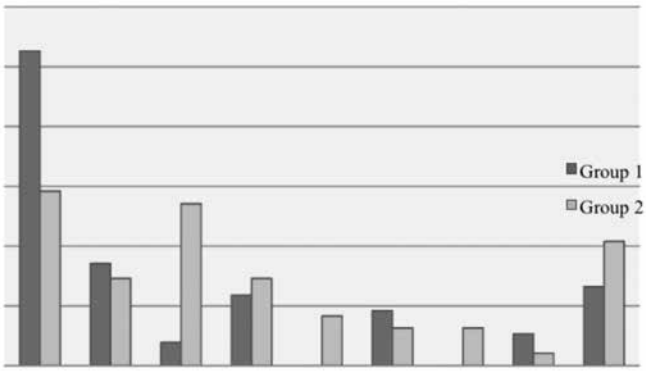

Figure 1. Risk factors predisposing gallstone formation (%).

-<0.001), being an oncologic patient (r=230, p=0.010), and being an infant (r=190, p=0.035) at the time of diagnosis. After adjusting for age and sex, group 2 was associated with hemolytic anemia (r=346, <0.001) and being an oncologic patient (r=248, p=0.006). No risk factor was specifically associated with having a symptomatic presentation.

Laboratory

Overall, alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), and bilirubin levels were elevated in 25 (20.3%), 30 (30.1%), and 21 (17.1%) patients, respectively. Overall, there was leukocytosis in 24 (19.5%) and leukopenia in 7 (5.7%) children. Anemia was detected in 25 (20.3%) patients. There were more patients in group 2 whose bilirubin levels were higher than the upper limit of normal (P=0.066), and median total bilirubin level was significantly higher than in group 1 (p=0.029). In group 2, anemia was more frequent (p=0.136), and the median Hb value of children was significantly lower (p=0.034). The other laboratory measures of group 1 and 2, including liver enzymes, direct bilirubin levels, and leukocyte count, were similar (Table 2).

Complications

Of the 124 children, 16 (12.9%) developed complications: 14 (18.4%) in group 1 and 2 (4.2%) in group 2 (p=0.027). Complications in group 1 were as follows: cholecystitis in 10, choledocholithiasis in 2, pancreatitis in 1, and choledocholithiasis plus pancreatitis in 1. Four children with cholecystitis, 1 child with choledocholithiasis, and 1 with choledocholithiasis plus pancreatitis underwent cholecystectomy. One patient with choledocholithiasis spontaneously passed the stone. The remaining 7 children were followed conservatively with bowel rest, IV hydration, and antibiotics. In group 2, patient with choledocholithiasis underwent cholecystectomy, whereas the one with cholecystitis was managed conservatively.

Cholecystectomy was required in 20 patients. Of them, 13 (17.1%) were in group 1 and 7 (12.5%) were in group 2 (p=0.710). Only 3 out of 13 children in group 1 had risk factors: hereditary spherocytosis (HS) in 1 and obesity in 2. Cholecystectomy was performed in 7 patients at initial presentation and in 6 at the follow-up due to complications. Six patients out of in group 2 had risk factors: HS in 4 and idiopathic hemolytic anemia in 2. Cholecystectomy was performed in 5 during elective splenectomy and in 2 due to complications at follow-up.

Follow-up

Of the 69 patients in group 1 who were not operated on at the initial presentation, clinical and sonographic follow-up was available in 68 (98.6%). The median follow-up time was 24 months (range, 2-45 months). Gallstone was resolved in 20 (29.4%) in a median of 3 months (range, 1-6 months). In group 2, 43 (89.6%) patients had clinical and sonographic follow-up. The median follow-up time was 33 months (range, 5-69 months). Gallstone was resolved in 10 (23.3%). Time to gallstone resolution was a median of 3 months (2-12 months). There was no significant difference between groups 1 and 2 in respect to gallstone resolution (p=0.477).

Ursodeoxycholic acid was used in 51 (41.1%) children overall. Of them, 33 (48.5%) children were in group 1, and 18 (41.9%) were in group 2 (p=0.514). Gallstone resolution was observed in 15 (29.4%) children who were given UDCA and in 15 (25.0%) children who were not (p=0.602). The median ages of children with and without gallstone resolution were 7.25 (0.25-17.00) and 9.00 (0-18.00) (p=0.487). Gallstone resolution was associated with being an infant (<2 years of age) at the time of diagnosis (Spearman, p=0.016, r=0.228) (Table 3). UDCA treatment, etiology, and age were evaluated as factors that may possibly have an effect on gallstone resolution by logistic regression analysis. The only factor was young age [to be infant (<2 years of age)] at the time of diagnosis (OR, 3.1; 95% CI: 1.1-8.8; p=0.034).

There were only 18 infants in the study group. Of them, 7 (38.9%) were in group 1. The complaints or symptoms reported by parents were irritability in all (100%), fever in 3 (42.9%),

vomiting in 3 (42.9%), weight loss in 1 (14.3%), and acholic gaita in 1 (14.3%). The risk factors in the symptomatic group were ceftriaxone use in 1 (14.3%), sepsis in 1(14.3), prematurity plus ceftriaxone use in 1 (14.3%), and dehydration plus ceftriaxone use in 1 (14.3%). There was ceftriaxone use in 3 (42.9%) patients overall. The risk factors in the asymptomatic group were multiple, and the most frequent ones were ceftriaxone use in 4 (36.4%), prematurity in 3 (25.0%), and trisomies in 3 (25.0%). The remaining risk factors were TPN, diuretics, and short bowel syndrome. None required cholecystectomy either during initial presentation or at follow-up. Clinical and sonographic follow-up was available for all infants. Gallstones disappeared in 9 (50.0%) patients overall. Gallstone resolution was observed at a median of 3 months (1-6 months). The rate of spontaneous resolution in infants was significantly higher than in children over 2 years of age (21 out of 106 children, 19.8%) (p=0.006).

Table 2. Laboratory features of symptomatic and asymptomatic children with gallstone

	Group 1 (n=76) n (%)	Group 2 (n=48) n (%)	P*
ALT	19 (8-542)	21 (8-140)	0.748
GGT	15 (8-667)	14 (8-346)	0.807
Total bilirubin	0.5 (0.2-5.3)	0.7 (0.2-11.8)	0.029
Direct bilirubin	0.1 (0.05-3.0)	0.1 (0.1-0.7)	0.288
Leukocyte	8000 (2900-27,000)	7725 (3100-16,900)	0.314
Hb	12.7 (7.9-17.1)	12.2 (7.3-15.1)	0.034

*Chi-Square
ALT: alanine aminotransferase; GGT: gamma-glutamyl transpeptidase; Hb: hemoglobin

Table 3. Investigation of correlation between gallstone resolution and possible factors

	r	P*
Gender	-0.105	0.271
Symptomatic versus asymptomatic	0.068	0.481
Presence of risk factor	0.027	0.775
Family history	-0.160	0.092
Ursodeoxycholic acid treatment	0.050	0.606
Age group (infant vs >2 years of age)	0.228	0.016

*Spearman

DISCUSSION

Children with gallbladder disease, especially cholelithiasis, may be either symptomatic or asymptomatic. Unlike adults having an asymptomatic disease over 80% (14,15), children are less likely to present with asymptomatic presentation, ranging between 17%-50% (6,12,16). In the present study, the frequency of asymptomatic disease was concordant with the current literature by comprising 38.7% of the entire study population. The higher frequency of asymptomatic disease in adults may be partially explained by droup out of symptomatic patients by time. Likewise, nonspecific abdominal symptoms, especially in younger children, may be falsely attributed to gallstones, so that more children could have been factitiously classified in the symptomatic group. Inversely, symptoms may have been underestimated by adult patients and caused a reporting bias.

Boys and girls are equally affected in early childhood, but as in adults, most previous studies reported a female predominance in pediatric gallbladder disease starting from puberty (6, 16-18). In the study by Wesdrop et al. (6), a female predominance was noted only after the age of 14 years. Bogue et al. (16) reported equal gender frequency overall. Female gender then increased to 55% above the age of 12 years, although there was no significant difference in sex distribution. In the present study, we found equal sex distribution overall. Above the age of 10 years, on the other hand, females were predominant (p=0.004). As in adults, this corresponds with the time at which cholesterol saturation in bile increases partly due to the secondary effects of estrogens, preceding the development of cholesterol-related gallstones (19).

Cholelithiasis is reported to have a bimodal distribution in childhood, a small peak in infancy, and a steady increase starting from early adolescence onwards (20). Studies in the literature documented that most gallstones in childhood are detected in the second decade (5,6,16). In the study by Wesdrop et al. (6), the mean age at diagnosis was 10.5 years, and two-thirds of patients were over the age of 10 years. Bogue et al. (16) reported that 52% of cases were over the age of 10 years at the time of diagnosis. The mean age was 9.4 years; children in the asymptomatic group had a mean age of 8.2 years, which was younger than the mean age (10.2 years) of the symptomatic group. In the present study, most children (44.4%) at the time of diagnosis were older than 10 years. The median age at diagnosis was 9.0 years (0.08-18.0) overall, which was somewhat concordant with the current literature (6,16,2,21). Similar to what was reported by Bogue et al. (16), the asymptomatic group was younger than the symptomatic group at diagnosis, although not significantly (p=0.122). The younger age of asymptomatic children at diagnosis is not surprising, since most children at risk are already under close surveillance and may have a chance to be diagnosed early while yet asymptomatic. However, the data on this issue are lacking.

We did not identify any risk factor in 54 (43.5%) children overall. In the literature, the idiopathic category was reported between 23.2%-52.5% (6,12,16). The risk factors in children are diverse and may vary according to age, geographic localization, ethnicity, referral status, and facilities of centers. The hemolytic anemias are the leading risk factor in Mediterranean countries, where the incidence of hereditary hemolytic anemias is high (12,16). In centers with a large pediatric cardiac surgical practice (16), cardiac bypass, which is thought to cause gallstone

formation by acute hemolysis, may be an important risk factor. Besides, family history of gallstones; hepatobiliary disease, including Wilson disease, cystic fibrosis, and progressive familial intrahepatic cholestasis; TPN, particularly in the presence of ileal disease or ileal resection; systemic infections and antibiotics, especially cephalosporins; and obesity were reported as other important risk factors (3-6,12,16,22). In the present series, family history, hemolytic anemia, ceftriaxone use, and obesity are most important risk factors overall and take place within the general distribution of risk factors (6,12,23). Family history of gallstone is an important factor but rarely assessed. It was reported in 7 (8.5%) out of 82 children in the study by Wesdrop et al. (6). In an Italian study (12), on the other hand, family history was striking and documented in 28.2% of patients. In the present series, 20 (16.1%) patients had a family history of gallstones, which was a single risk factor in 11 (8.8%). The remaining 9 patients had additional risk factors: hemolytic anemia in 7 and ceftriaxone use in 1 and being an oncologic patient in 1, respectively. Hepatobiliary disease, TPN, bowel disease or resection, and surgery were less frequently encountered risk factors in our series, partly due to the referral status of our center. Our center is one of the large centers in Turkey and deals with premature and risky infants that have congenital heart disease requiring diuretic therapy and major cardiac operation; need TPN for prematurity, intolerance, or bowel resection; and suffer from sepsis requiring antibiotic therapy. But, these risk factors above other than antibiotics were rarely observed in our series. The reason(s) of this low prevalence is obscure. TPN is a well-recognized risk factor for gallstone formation, especially in children with associated ileal disease or resection. The incidence of gallstone formation in children requiring TPN for 3 months or more was reported as high as 43% (3). In our center, the low prevalence of children requiring long-term TPN either due to medical problems, such as prematurity, sepsis, small bowel disease, or surgery, such as bowel resection, may be one of the reasons.

According to the presence of symptoms at presentation, patients were divided into 2 groups: group 1 symptomatic and group 2 asymptomatic. Idiopathic cases in the symptomatic group were much higher in number than the asymptomatic group (64.5% versus 33.3% respectively, $p<0.001$). The most frequent risk factors in the symptomatic group were family history in 13 (17.1%), ceftriaxone use in 9 (11.8%), obesity in 7 (9.2%), and surgery (abdominal, cardiac) in 4 (5.3%). Hemolytic anemia, family history, and ceftriaxone use were the most frequent risk factors in the asymptomatic group. Patients with hemolytic anemia and oncologic disease were significantly associated with having an asymptomatic presentation. No risk factor was found to be associated with symptomatic presentation. Hemolytic anemia was associated with symptomatic presentation in the study by Bogue et al. (16). It is difficult to explain this contrast. However, our findings are meaningful. Since children at risk, such as ones with hemolytic anemia, are already under close follow-up, it should not be surprising that they were diagnosed early while yet asymptomatic. Nonetheless, the data on this issue are limited, and we need further studies of a large sample size.

Overall, ALT, GGT, and bilirubin levels were found to be elevated in 25 (20.3%), 30 (30.1%), and 21 (17.1%) patients, respectively. Both the frequency of patients with abnormal transaminase and GGT levels and their corresponding median values of groups 1 and 2 were similar. Wesdrop et al. (6) found elevated transaminase and GGT levels in nearly one-half of patients with biliary colic. Interestingly, laboratory investigations revealed no abnormality in the cases with complicated gallstones. In the present study, elevated hepatic transaminase and GGT levels were seen in 21.3% and 20.0% of symptomatic children, respectively. There were more patients in the asymptomatic group whose bilirubin levels were higher than the upper limit of normal ($p=0.066$), and median total bilirubin level was significantly higher than group 1 ($p=0.029$). It was thought to be due to the higher number of patients with hemolytic anemia in group 2. Anemia was detected in 25 (20.3%) patients. In group 2, anemia was more frequent ($p=0.136$), and the median Hb value of children was significantly lower ($P=0.034$). There are two possible reasons: 1) Most of the patients with hemolytic anemia were allocated in the asymptomatic group, and 2) Hb may have been factitiously elevated in symptomatic patients who are possibly dehydrated due to fever, vomiting, or inadequate oral intake. The other laboratory measures of groups 1 and 2, including liver enzymes, direct bilirubin levels, and leukocyte count, were similar (Table 2). Low Hb and high bilirubin levels may suggest asymptomatic presentation. But, this can only be said for our series and can not be generalized to the general cholelithiasis population. In general, laboratory testing does not help to differentiate symptomatic from asymptomatic disease and even may cause confusion in deciding surgery. Nevertheless, it should be integrated with a history suggesting biliary disease and physical examination and imaging findings.

Major problems and complications observed in patients with gallstone are acute and chronic cholecystitis, ascending cholangitis, common bile duct stones and choledocholithiasis, and pancreatitis. The frequency of complications varied in the published literature. Some of the studies found pancreatitis as the most frequent complication reported in 8%-12% of patients (24,25). Others reported that cholecystitis and choledocholithiasis are more common, and even sometimes, cholecystitis may be surpassed by choledocholithiasis, observed in 8.9%-18.0% of patients (2,16). Cholecystitis was more common and reported in 10.1% of symptomatic children, whereas it was observed in only 1 out of 194 asymptomatic children (16). In the present series, complications were documented in 16 (12.9%) patients overall. Of them, 14 complications (18.4%) were seen in the symptomatic group. Cholecystitis was the most common complication and seen in 10 (13.2%) out of 76 symptomatic children. Choledocholithiasis and pancreatitis were less frequent and seen in 3 (3.9%) and 2 (2.6%) children, respectively.

In the present study, the overall complication rate was lower than previous reports and concordant with a latter study by Bogue et al. (16). In general, the former studies reported complication rates of surgically treated children that were mostly symptomatic. The present study, on the other hand, included both symptomatic and asymptomatic children, as in the study by Bogue et al. (16). Given the rare occurrence of complications in asymptomatic patients, we considered that the relative low rate of complications in the present study is not surprising.

The data on gallstone resolution with expectant therapy with or without UDCA are limited. When surgical patients are excluded, the rate of gallstone resolution was documented in 29 (21.8%) out of 133 children who have clinical and sonographic follow-up (16). Gallstone resolution was higher in the symptomatic group (29%) compared to asymptomatic group (19%). In the study by Della Corte et al. (12), gallstone resolution was documented in only 5 (3.3%) out of 151 children. Of them, 117 were under UDCA therapy. None of the 34 children with expectant treatment cleared their gallstones. The authors stated that UDCA therapy was ineffective in the dissolution of gallstone. In the present study, gallstone resolution was observed in 30 (27.0%) out of 111 children who had clinical and laboratory follow-up when surgically treated patients at initial presentation were excluded. Gallstone was resolved in 20 (29.4%) children in the symptomatic group and 10 (23.3%) children in the asymptomatic group. As in the study by Bogue et al. (16), there were more patients with gallstone resolution in the symptomatic group, but the difference was statistically insignificant (p=0.477). Ursodeoxycholic acid was used in 51 (41.1%) children overall. Gallstone resolution was observed in 15 (29.4%) children who were given ursodeoxycholic acid and 15 (25.0%) children who were not (p=0.602). UDCA therapy seems to be ineffective in gallstone resolution.

We evaluated the relationship between gallstone resolution and etiology. Patients with ceftriaxone-associated gallstones were found more likely to undergo spontaneous resolution. The antibiotic ceftriaxone, which is concentrated in the bile after excretion, causes a reversible pseudolithiasis that can be seen in 17% to 40% of patients receiving the antibiotic after at least 4 days of treatment (6,22,26). Araz et al. (26) showed spontaneous resolution of ceftriaxone-associated stones in all 7 patients within 1 month of cessation of ceftriaxone. In another study (22), pseudolithiasis was demonstrated in 16 (10%) out of 156 patients, and all underwent spontaneous resolution within 30 days. In contrast, gallstone resolution was not observed in all patients but detected in 7 (43.8%) out of 16 children with ceftriaxone use (p=0.05) in the present study. The reason is not clear. Gallstone resolution was observed in only 1 (6.3%) child with hemolytic anemia. It is not clear why gallstone resolution is less likely in children with hemolytic anemia. Some reasonable but speculative explanations are: 1) Gallstones in hemolytic anemias are most likely to be black pigment stones. In black pigment stones, pigments form cross-linked polymers that are insoluble in all solvents (27). 2) Ongoing hemolysis can be assumed to be a continuous stimulating factor for gallstone formation. This issue should be discussed further. UDCA treatment, etiology, and age were evaluated as factors that may possibly have effects on gallstone resolution by logistic regression analysis. The only factor was young age [to be infant (<2 years of age)] at the time of diagnosis (OR: 3.1; 95% CI: 1.1-8.8; p=0.034). The only factor that was associated with gallstone resolution was also younger age in the study of Bogue et al. (16).

Gallstone resolution was observed in 34.0% of children under the 2 years of age, whereas it was evident in 16.3% of patients above the age of 1 year (12). Observation and expectant management in asymptomatic infants (28) and conservative management with higher threshold for surgery (23) may be used, because most of these patients will undergo spontaneous resolution of stones. In the present study, most of the children below 2 years of age were asymptomatic (61.1%); only 1 (5.6%) developed a complication and was managed conservatively, and 50.0% of them underwent spontaneous resolution compared to only 24.4% of patients above the age of 2 years (p=0.029). It is not clear why the rate of stone resolution is lower in older children. In infants, the risk factors are multiple, such as ceftriaxone use, sepsis, TPN, diuretic, prematurity, etc., and are not usually permanent problems. So, the disappearance or removal of risk factors for stone formation may be assumed to be a reason for the high rate of stone resolution in this age group. Familial predisposition, chronic hemolytic anemia, ceftriaxone use, and obesity are the main risk factors in older children. Chronicity of or higher chance of having a repeated or cumulative exposure (for example, cephalosporins) to these risk factors may cause a somewhat continuous stimulation for stone formation and presumably result in a lower chance of stone resolution in this age group. This issue needs to be further discussed and clarified by large sample-size and long-term studies.

The limitations of the present study are several. Firstly, the retrospective and cross-sectional nature of the study allows only association rather than causation when we talk about the relation of gallstones with risk factors, demographic and laboratory features, and the relation of gallstone resolution with demographic factors, etiology, and type of management. Secondly, the sample size of the present study is lower than some recent studies, although the statistical power of the study is 100%. Given the diverse and multiple risk factors for gallstone formation, low sample size may decrease the strength of the conclusion regarding the distribution of risk factors and their relation with gallstone formation. Thirdly, the median follow-up time, which is 24 months (range, 2-45 months) in the symptomatic group and 33 months (range, 5-69 months) in the asymptomatic group, is within the range reported in the literature (6,12,16), but it is still short to make firm statements on, for example, the rate of complication and gallstone resolution. Finally, we could not determine any risk factors in nearly one-half of pa-

tients whose GGT values were not elevated in the majority. In those cases, it might be reasonable to make a genetic analysis for progressive familial intrahepatic cholestasis - a chronic liver disease that is associated with increased risk of gallstone formation (29,30). Indeed, none of the children had any stigmata or laboratory findings of chronic liver disease during initial presentation and at follow-up.

Although there are several studies, only a few, including the present study, compared asymptomatic patients with symptomatic ones regarding the risk factors, clinical and laboratory features, clinical course, and complications. We propose that the distribution of risk factors changes according to geographic localization, facilities, and reference status of centers. Laboratory values do not help in differentiating symptomatic children from asymptomatic ones. UDCA does not seem to be effective in gallstone resolution. But, further studies are needed to evaluate its efficacy in certain subgroups, such as in children with cholesterol gallstones.

The most important factor associated with gallstone resolution was young age. Ceftriaxone-associated gallstones are most likely to resolve but do not always undergo spontaneous resolution. Thus, both clinical and sonographic follow-up is prudent in these patients. We suggest clinical follow-up rather than surgical intervention in children with asymptomatic presentation owing to the considerably low complication rate and in infants whose gallstones are most likely to resolve.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital**.**

Informed Consent: Written informed consent was obtained from patients' parents who participated in this study.

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