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# Prevalence and Outcome of Cholelithiasis in Children with Sickle Cell Disease at King Saud Medical City, Saudi Arabia

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**Abstract:**

**BACKGROUND:** Sickle cell disease (SCD) is one of the common hereditary blood diseases in Saudi Arabia. The hepatobiliary system is one of the common organs to be affected either directly from the sickling process or indirectly as a result of chronic hemolysis and multiple blood transfusions. Cholelithiasis is one of the common complications of sickle cell anemia.

**OBJECTIVES:** To assess the prevalence of cholelithiasis in children with SCD treated at King Saud Medical City (KSMC); Pediatric Hospital in Saudi Arabia and describe the outcome, management, and clinical profile of children with SCD and cholelithiasis.

**MATERIALS AND METHODS:** This is a retrospective descriptive study conducted at a single tertiary health care center, KSMC, Pediatric Hospital, Riyadh from 2012 to 2019 on 277 patients aged <14 years. Medical records of all pediatric patients with SCD included in the study were identified and reviewed.

**RESULTS:** From total of 277 patients, 87 (31.4%) had cholelithiasis. Forty three (49.4%) of them were female and 44 (50.6%) were male. From 87 patients who developed cholelithiasis, 15 patients aged <5 years old, 50 aged (5–10 years), and 22 aged >10 years. According to the genotype of sickle cell (SS), the occurrence of cholelithiasis were (75.9% in SS, 23% in S/BETA 0 and 1.1% in S/BETA+). The majority were symptomatic (59.8%) compared to asymptomatic (40.2%) and 26 patients (29.9%) were complicated. In our study, we found that complications for the gallstones were acute calcular cholecystitis, chronic cholecystitis, direct hyperbilirubinemia, transaminitis, and acute pancreatitis.

**CONCLUSION:** The prevalence of cholelithiasis in our study was significant. The large majority of patients were symptomatic. Cholecystectomy must be strongly recommended in symptomatic patients.

**Keywords:**

Cholelithiasis, gallstones, hepatobiliary, sickle cell disease

## Introduction

Sickle cell disease (SCD) is a group of inherited diseases (including sickle cell anemia (SCA), HbSC, and HbSβ-thalassemia) characterized by mutations in chromosome 11 in the gene encoding the hemoglobin subunit β. Hemoglobin (Hb) is a tetrameric protein composed of different combinations of globin subunits; each globin subunit is associated with the cofactor heme, which can carry a molecule of oxygen.[1] The replacement of glutamic acid by a valine residue at position 6 in the β-globin polypeptide chain characterizes the abnormal Hb of SCD.[2] SCD is a common hereditary blood disease in Saudi Arabia with a high prevalence in the community and it is more common in the eastern and southern regions of the country.[3]

The most clinical manifestation of SCD is anemia due to chronic hemolysis. The

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hepatobiliary system is one of the common organs to be affected either directly from the sickling process or indirectly as a result of chronic hemolysis and multiple blood transfusions. Cholelithiasis is one of the common complications of SCA. These are usually pigment stones that result from chronic hemolysis leading to increased bilirubin production.[4] The occurrence of gallstones is one of the most important manifestations of SCD in the digestive tract.[5-8]

Cholelithiasis mostly occurs after the age of 5 and is directly related to the severity of SCD and to the intensity of hemolysis. Cholelithiasis can be detected even in under 5-year-old children, but it is more common in adolescents and adults with SCA. The prevalence of cholelithiasis is high in patients with SCD and increases progressively with age. Its frequency is variable, ranging from 5% to 55%, with a reported prevalence of 50% in young adults.[9-15] In a previous large prospective study done in Saudi Arabia included 305 children aged from 1 to 18 years with SCA, gallstones were demonstrated in 60 children with a prevalence of 19.7%. This increased from 8.7% in those <10 years of age to 36% in those 15–18 years of age.[4,9] Some studies showed that patients with Hb SS disease were at higher risk for the development of cholelithiasis compared to other Hb genotype.[13,15]

Some patients with gallstones report abdominal pain, whereas others might be asymptomatic. Gallstone migration can block the common bile duct leading to acute abdomen. Because of the potential complications and severity of this condition, early diagnosis is very important. Ultrasonography has become a reliable noninvasive method for investigating the biliary tract. Cholecystectomy is indicated for symptomatic patients, but controversy still exists regarding the appropriate treatment for asymptomatic patients with cholelithiasis.[16] Recommendation of elective cholecystectomy for sickle cell (SS) patients with asymptomatic gall stones is increasing because of lower mortality and fewer surgical complications compared to emergency surgery or procedure after an acute cholecystitis episode and to prevent potential complications of biliary colics, acute cholecystitis, and choledocholithiasis which leads to major risks, discomfort, and longer hospital stay.[17-20]

The purpose of this study is to determine the frequency of cholelithiasis in children with SCD treated at King Saud Medical City (KSMC); Pediatric Hospital in Saudi Arabia, and to describe the follow-up and outcome after the diagnosis of cholelithiasis. Furthermore, this study aims to evaluate the profile of patients with SCD and cholelithiasis.

## Materials and Methods

### Study design and duration

This is a retrospective descriptive study conducted at a single tertiary health care center, KSMC, Pediatric Hospital, Riyadh from 2012 to 2019.

### Population

Pediatric SCD patients at KSMC – Riyadh – Saudi Arabia.

### Study participants

The study was conducted by reviewing the medical records of 520 patients diagnosed with SCD. The clinical charts were requested from the medical reports department and reviewed. Also, imaging and laboratory workup was reviewed through the hospitals' electronic system. Demographic data (age, gender, SCD type) and history of comorbid conditions, and ultrasound diagnosis of cholelithiasis were reviewed retrospectively.

### Inclusion and exclusion criteria

Pediatric patients <14 years of age with a diagnosis of SCD were included in the study. However, patients aged ≥14 years of age, SS trait, no abdominal ultrasound studies were excluded from our study.

### Statistical analysis

Data analysis was performed using IBM SPSS, version 20.0 (IBM Corp., Armonk, NY, USA). The Chi-square test was used to determine the association of qualitative variables (sex, type of SCD, and Hb electrophoresis type). A $P < 0.05$ was considered to indicate statistical significance.

Baseline characteristics of SCA children with cholelithiasis was compared with those with SCA and without cholelithiasis using the Chi-square test and Fisher's Exact tests for categorical variables and two-sided Student's *t*-test for continuous variables.

The *t*-test and crosstabs analysis were used to determine the significance of the occurrence of cholelithiasis in children with SCA. $P < 0.05$ are considered significant.

### Ethical considerations

This study was ethically approved by the institutional review board at the Department of Pediatric Hematology/Oncology– Pediatric Hospital, KSMC. Appropriate ethics policies and regulations were followed in the study. The medical records were reviewed for all included patients, without disclosure of patient identification.

## Results

A total of 520 patients with SCD screened, 243 were

excluded (11 due to insufficient information and 232 because no ultrasound done) while 277 were included, 127 were female (45.8%) and 150 were male (54.2%). Classification of SCD patients in the study according to genotype were 192 (69.3%) homozygous SS, 79 (28.5%) sickle Beta 0, 5 (1.8%) sickle Beta + thalassemia and only one patient (0.4%) was SC [Table 1].

In this study, the prevalence of cholelithiasis observed was 31.4%. The mean age for diagnosing cholelithiasis was 8 ± 3.3 years. The youngest age with a diagnosis of gallstones was 1 year 11 months in 1 patient. Sludge only developed in 36 patients (13%) and in 18 of them resolved spontaneously.

Data in Table 2 show the demographic and clinical factors in patients with and without cholelithiasis. There were no significant differences in frequency of cholelithiasis between males and females (29.3% and 33.8%, respectively; $P = 0.419$) and between SS, S/BETA+, S/BETA0 and SC (34.4%, 20%, 25.3%, and 0%, respectively, $P > 0.05$).

The frequency of cholelithiasis was significantly associated with patients' age, ranging between 16.1% in patients aged <5 years to 35.2% in those aged 5–10 years and up to 54.2% in patients aged >10 years ($P < 0.001$). Furthermore, there was a high frequency of cholelithiasis among patients taking hydroxyurea (44.1%) which was statistically significant ($P = 0.018$).

As shown in Table 3, retics, alanine transaminase (ALT) and total bilirubin (12.06 ± 4.25, 25.53 ± 7.25, 48.97 ± 24.28, respectively) were significantly higher among the group of patients with cholelithiasis compared to those without cholelithiasis (8.93 ± 3.56, 22.88 ± 7.45, 28.51 ± 13.66, respectively) with $P \leq 0.001$. Otherwise, no statistically significant differences were observed between the two groups regarding Hgb, white blood cell (WBC), platelet (PLT), aspartate transaminase (AST), and Hgb F ($P > 0.05$).

Of 87 patients having gallstones, 52 patients (59.8%) were symptomatic and 35 (40.2%) were asymptomatic. The most common symptom observed was abdominal pain. Complications occurred in 26 patients (29.9%) [Table 4].

In our study, we found that complications for the gallstones were acute calcular cholecystitis, chronic cholecystitis, direct hyperbilirubinemia, transaminitis, and acute pancreatitis [Table 4].

In 7 patients among the 87 with cholelithiasis, gallstones resolved spontaneously (8.04%). Cholecystectomy was done in 42 patients (48.3%). Elective surgery was done in 38 and 4 did emergency surgery [Table 5]. Among patients who underwent cholecystectomy, 31 (73.8%) patients were symptomatic and 11 (26.2%) were asymptomatic (with $P = 0.018$), this is statistically significant [Table 6]. The mean length of stay in the hospital was around 7 ± 4.5 days.

**Table 1: Frequency of sickle cell disease according to gender and genotype**

| | Frequency (%) |
|---|---|
| Gender | |
| Female | 127 (45.8) |
| Male | 150 (54.2) |
| Sickle cell genotype | |
| SS | 192 (69.3) |
| S/beta0 | 79 (28.5) |
| S/beta+ | 5 (1.8) |
| SC | 1 (0.4) |
| Total | 277 (100) |

**Table 2: Demographic and clinical factors in patients with and without cholelithiasis**

| Factors | With cholelithiasis (*n*=87; 31.4%), *n* (%) | Without cholelithiasis (*n*=190; 68.6%), *n* (%) | Test of significant ($\chi^2$) | *P* |
|---|---|---|---|---|
| Gender | | | | |
| Female | 43 (33.8) | 84 (66.2) | 0.654 | 0.419 |
| Male | 44 (29.3) | 106 (70.7) | | |
| Age (years) | | | | |
| <5 | 15 (16.1) | 78 (83.9) | 19.606* | <0.001* |
| 5-10 | 50 (35.2) | 92 (64.8) | | |
| >10 | 22 (52.4) | 20 (47.6) | | |
| SC genotype | | | | |
| SS | 66 (34.4) | 126 (65.6) | 2.557 | 0.11 |
| S/beta+ | 1 (20) | 4 (80) | 0.308 | >0.99 |
| S/beta0 | 20 (25.3) | 59 (74.7) | 1.904 | 0.16 |
| SC | 0 | 1 (100) | 0.460 | >0.99 |
| Use of hydroxyurea | | | | |
| Yes | 26 (44.1) | 33 (55.9) | 5.577* | 0.018* |
| No | 61 (28) | 157 (72) | | |

*Statistically significant at $P \leq 0.05$. $\chi^2$=Chi square test, *P*=*P* value for comparing between the studied groups

**Table 3: Laboratory data in patients with and without cholelithiasis**

| Laboratory parameters | With cholelithiasis (*n*=87) | Without cholelithiasis (*n*=190) | Test of significant | *P* |
|---|---|---|---|---|
| Hgb (g/dl) | | | | |
| Minimum-maximum | 6.60-10.40 | 6.20-11.70 | *t*=0.304 | 0.761 |
| Mean±SD | 8.23±0.81 | 8.20±0.83 | | |
| Median (IQR) | 8.20 (7.6-8.8) | 8.15 (7.6-8.7) | | |
| Retics (%) | | | | |
| Minimum-maximum | 2.0-22.0 | 1.30-18.70 | *t*=5.977* | <0.001* |
| Mean±SD | 12.06±4.25 | 8.93±3.56 | | |
| Median (IQR) | 12.0 (9.2-14.8) | 8.50 (6.2-11.0) | | |
| WBCs | | | | |
| Minimum-maximum | 5.80-22.0 | 5.30-25.10 | *t*=0.413 | 0.680 |
| Mean±SD | 12.53±3.38 | 12.70±3.18 | | |
| Median (IQR) | 12.80 (10.3-14.5) | 12.60 (10.5-15.0) | | |
| Platelets | | | | |
| Minimum-maximum | 130.0-620.0 | 150.0-665.0 | *t*=1.489 | 0.138 |
| Mean±SD | 358.7±113.4 | 380.0±109.6 | | |
| Median (IQR) | 350.0 (270.0-445.0) | 369.5 (304.0-447.0) | | |
| AST (U/L) | | | | |
| Minimum-maximum | 22.30-80.0 | 16.0-90.0 | U=7202.50 | 0.086 |
| Mean±SD | 40.60±9.17 | 39.10±10.44 | | |
| Median (IQR) | 40.0 (33.6-47.0) | 37.0 (33.0-43.0) | | |
| ALT (U/L) | | | | |
| Minimum-maximum | 10.0-45.0 | 9.30-65.0 | U=6232.00* | 0.001* |
| Mean±SD | 25.53±7.25 | 22.88±7.45 | | |
| Median (IQR) | 25.0 (20.0-30.5) | 21.0 (18.0-27.0) | | |
| Total bilirubin (umol/L) | | | | |
| Minimum-maximum | 13.20-150.0 | 9.60-97.0 | U=3445.50* | <0.001* |
| Mean±SD | 48.97±24.28 | 28.51±13.66 | | |
| Median (IQR) | 41.0 (30.4-62.9) | 25.0 (19.5-34.0) | | |
| Hgb F (%) | | | | |
| Minimum-maximum | 0.0-27.90 | 0.0-28.50 | U=7659.0 | 0.327 |
| Mean±SD | 11.0±6.53 | 11.98±7.03 | | |
| Median (IQR) | 9.90 (5.5-14.5) | 11.25 (6.0-16.7) | | |

*Statistically significant at $P \leq 0.05$. *t*: Student *t*-test, U: Mann-Whitney test, *P*: *P* value for comparing between the studied groups, IQR=Inter quartile range; SD=Standard deviation; Hgb=Hemoglobin; WBC=White blood cell; AST=Aspartate transaminase; ALT=Alanine transaminase; Hgb F=Fetal hemoglobin

**Table 4: Cholelithiasis in relation to frequency of symptoms and complications**

| Symptoms at diagnosis | Frequency (%) |
|---|---|
| Symptomatic | 52 (59.8) |
| Asymptomatic | 35 (40.2) |
| Total | 87 (100) |
| Symptoms | |
| Abdominal pain | 50 |
| Jaundice | 19 |
| Fever | 3 |
| Vomiting | 11 |
| Nausea | 5 |
| Complications | |
| Yes | 26 (29.9) |
| No | 61 (70.1) |
| Type of complication | |
| Acute calcular cholecystitis | 10 |
| Chronic cholecystitis | 6 |
| Direct hyperbilirubinemia (obstructive jaundice) | 16 |
| Transaminitis | 2 |
| Acute pancreatitis | 1 |

## Discussion

The frequency of gallstones in patients with SCD varies according to different studies.[3,5-7,9,21-25] The selection of distinct populations, different age ranges may explain some differences. In the present study, the prevalence of cholelithiasis was 31.4% with a mean age of 8 ± 3.3 years. A similar prevalence was reported in a study in KSA by Al-Salem *et al*. who reported a 35.5% prevalence of cholelithiasis.[9] A slightly lower frequency was reported in two studies, one in Jamaica by Walker *et al*. (23.8%) and the other one in Medina, Saudi Arabia by Alhawsawi *et al*. (27.5%).[7,21] In Nigeria, a low prevalence of cholelithiasis of 6% in patients under 15 years was reported by Akinyanju and Ladapo.[26] In 226 children aged 5–13 who were tested by abdominal ultrasound, Webb *et al*. reported a 13% prevalence of cholelithiasis.[27] In another study in Sudan by Attalla the overall prevalence of cholelithiasis was 11.5% and it increased with age.[28]

In other studies, a significantly higher rate has been reported where adolescent and adult age groups were considered.[11,13] A study in the UK, in the HbSS group and in the HbSC group, respectively, Bond *et al*. have recorded a prevalence of 58% and 17% of cholelithiasis who were investigated by ultrasound in 95 patients 10–65 years old.[11] Among Brazilian participants in a study by Gumiero *et al*., the prevalence of cholelithiasis was 45%.[13]

The results in this study showed that age is considered a significant risk factor for gallstones among patients with SCA and in patients aged 5 years or older the incidence of such complication increases significantly. This trend was also observed in other studies when they were categorized into age groups.[11-14,21,28] Alhawsawi *et al*. reported that the frequency of cholelithiasis was significantly associated with patients' age; proportions ranged between 11.5% in patients aged <6 years, to 24.4% in those aged 6 to <12 years, and up to 40.8% in patients aged 12 years or older ($P$ = 0.018).[21] Similar results were reflected in a study conducted by Attalla who demonstrated the proportion of patients with gallstones was 0.7% in those <5 years old, 13% in those aged 5–10 years, and 33% in patients aged 10–16 years.[28]

In regard to gender as risk factor for cholelithiasis in the present study, there were no significant differences in frequency of cholelithiasis between males and females (29.3% and 33.8%, respectively; $P$ = 0.419). Similar findings were observed in other studies.[13,21,28]

An increased frequency of cholelithiasis was reported among patients with SS as compared with patients who had S/BETA; these differences were not statistically significant ($P$ > 0.05). Similar results were reported by Alhawsawi *et al*.[21] However, the Brazilian study by Gumiero *et al*. reported a significantly higher prevalence of cholelithiasis in patients with SS than in those with SC or S/BETA disease ($P$ = 0.0044).[13]

**Table 5: Type of cholecystectomy**

| Cholecystectomy | Frequency (%) |
|---|---|
| Elective | 38 (90.5) |
| Emergency | 4 (9.5) |
| Type of cholecystectomy | |
| Laparoscopic | 40 (95.2) |
| Open | 2 (4.8) |

In the present study, we found retics, ALT and total bilirubin significant risk factors for cholelithiasis with significant differences between patients who developed gallstones and those who did not. Otherwise, no statistically significant differences were observed between the two groups regarding Hgb, WBC, PLT, AST, and Hgb F. Sarnaik reported a higher mean bilirubin concentration in patients with gallstones.[12] Webb *et al*. reported that children with gallstones had significantly lower total Hb and higher bilirubin concentrations.[27] Alhawsawi *et al*. found no significant difference between patients who developed gallstones and those who did not with respect to WBCs, PLTs, total Hb, and Hb A, A2, and F levels.[21] Attalla reported that total Hb, reticulocyte %, and total bilirubin showed no significant differences between patients with and without gallstones.[28] Kamdem *et al*. reported that Hb F, reticulocyte count, and lactate dehydrogenase significantly increased the risk for cholelithiasis.[29]

Our study demonstrated a significant difference in the frequency of cholelithiasis between patients who used hydroxyurea (44.1%) and those who did not (28%) with $P$ = 0.018. Martins *et al*. and Alhawsawi *et al*. reported no significant correlation between the intake of hydroxyurea and the formation of gallstones.[21,30] However, the findings are not conclusive on this point because the study has the limitation of not having been able to check the patients' adherence to the use of hydroxyurea. It was also not possible to identify whether patients had already had gallstones before the use of this medicine.

This study showed that the majority of cases with cholelithiasis were symptomatic (59.8%) and (40.2%) were asymptomatic. The most common symptom was abdominal pain. Cholecystectomy was done in 42 patients, laparoscopic in 40 (90.2%), and only 2 (4.8%) underwent open cholecystectomy with no major perioperative complications. We also noticed that cholecystectomy was associated with increasing age, 73.8% at age 10 years and above. Similar findings were observed in a study by Suell *et al*. that found 71% symptomatic and 29% asymptomatic with abdominal pain as the most common symptom (59%) and 65% underwent cholecystectomy.[18]

In a study by Gumiero *et al*. 55 children of a total of 101 with SCD and cholelithiasis underwent cholecystectomy, 44 were symptomatic (80%). About 50% of patients

**Table 6: Relation between cholecystectomy and symptomatic versus asymptomatic patients with cholelithiasis**

| Cholecystectomy | Symptomatic ($n$=52), $n$ (%) | Asymptomatic ($n$=35), $n$ (%) | $\chi^2$ | $P$ |
|---|---|---|---|---|
| Yes | 31 (73.8) | 11 (26.2) | 5.579* | 0.018* |
| No | 21 (46.7) | 24 (53.3) | | |
| Total | 52 | 35 | | |

*Statistically significant at $P \leq 0.05$. $P$=$P$ value for comparing between the studied groups, $\chi^2$=Chi square test

with gallstones were asymptomatic, most of them did not undergo surgery and did not present complications during a 7-year follow-up period.[13] Attalla reported none of the 30 patients included in the study were symptomatic at the time of diagnosis of cholelithiasis. One patient became symptomatic during follow-up. He underwent cholecystectomy with no postoperative complications.[28]

Walker *et al*. followed up patients for 25 years and found a large number of asymptomatic patients and a low 7% proportion of surgical indications.[7]

Other studies have concluded that proceeding with elective surgery in the asymptomatic patient may avoid complications and the need for emergency surgery.[31,32] Elective laparoscopic cholecystectomy was performed on 16 asymptomatic children with no major complications reported. No transfusions were necessary postoperatively and the mean postoperative stay was 3 days.[19]

The National Heart, Lung, and Blood Institute of the United States recommended, from evidence-based management of SCD, that asymptomatic gallstones should be treated with watchful waiting in children and adults. In those who develop symptoms specific to gallstones, cholecystectomy should be performed with the laparoscopic approach being preferred if surgically feasible and available.[16]

Appropriate treatment for asymptomatic patients with cholelithiasis is still controversial. Prospective studies to establish optimal management and the best timing to indicate surgery, in asymptomatic patients, through ultrasound screening for SCD and gallstones patients are needed.

## Conclusion

In the present study, our results showed an increased prevalence of cholelithiasis (31.4%) in pediatric patients with SCD and the incidence increasing with age, typically rising after the age of 5 years. Hepatobiliary complications in patients with SCD are frequent that may keep increasing with the patient's age. Cholecystitis and obstructive jaundice were the most common complications among the group of patients observed. Regular clinical follow-ups, abdominal ultrasound studies are strongly recommended to help in the early detection of cholelithiasis and prevention of its complications.

Cholecystectomy must be strongly considered in symptomatic patients. In asymptomatic patients, conservative management seems to be the safe choice. Further studies are recommended to establish the age at which to start screening and to assess the course of asymptomatic gallstones.

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## Conflicts of interest

There are no conflicts of interest.

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