Al-Mukhtar Journal of Sciences 40 (2): 83-92, 2025
Doi: https://doi.org/10.54172/

Research Article **Open Access**

Prevalence and Risk Factors of Cholelithiasis among Children with Hereditary Hemolytic Anemia: A Single Center Experience Benghazi, Libya

Asma Albarasi[1], Hana Saied Abdulali[2], Amal A. Elfakhri[3] and Hala Ammar[4*]

[1] Department of Pediatrics, Faculty of medicine, University of Benghazi, Libya.

[2] Department of Pediatrics, Faculty of Medicine Almarj, Benghazi university, Libya.

[3] Department of Family and Community Medicine, Faculty of Medicine, University of Benghazi, Libya.

***Corresponding author:** drhalammar@gmail.com, Department of Pediatrics, Faculty of Medicine, University of Benghazi, Libya.

Received:
26 June 2025

Accepted:
16 October 2025

Publish online:
31 December 2025

Abstract

Cholelithiasis is increasingly recognized in pediatric hereditary hemolytic anemias (HHAs), with limited data on its frequency and risk factors in Libyan children. This study aimed to assess cholelithiasis prevalence and risk factors in children with HHAs at Benghazi Medical Center. A cross-sectional study of 100 children (4 months-16 years) with HHAs was conducted (2009–2024). Data included age, HHA type, family history, transfusion frequency, and ultrasonography-confirmed gallstones. Mean age at HHA diagnosis was 3.1 ± 3.8 years. Gallstones were detected in 36% of cases, most commonly at age 7 (range: 1.5–15 years). Three children developed cholelithiasis before age 2. Severe hemolysis and frequent transfusions significantly increased gallstone risk. Gallstones are prevalent in Libyan children with HHAs, particularly sickle cell anemia and hereditary spherocytosis, with early onset in some cases. We recommend annual ultrasound screening for early detection, especially in severely affected and frequently transfused patients, and exploring transfusion-sparing therapies.

Keywords: Gallbladder Stones, Cholelithiasis, Hereditary Hemolytic Anemias, Blood Transfusion

INTRODUCTION

Introduction

Gallbladder stones (GBS), once considered rare in pediatric populations, have demonstrated a significant rise in prevalence in recent years (Chamorro et al., 2020; Murphy et al., 2016). The etiology of GBS in children is multifactorial, with chronic hemolytic diseases representing the most common underlying cause (Enayet et al., 2020; Karavdić, 2022). Additional risk factors include chronic cholestasis, liver cirrhosis, cystic fibrosis, prematurity, prolonged ceftriaxone use, total parenteral nutrition, ileal diseases, cancer therapy, familial predisposition, obesity, and congenital gallbladder anomalies (Enayet et al., 2020; Karavdić, 2022).

Among hereditary hemolytic anemias (HHAs), GBS is a frequent comorbidity, accounting for approximately 20–40% of pediatric gallstone cases (Enayet et al., 2020; Karavdić, 2022). The pathogenesis involves chronic hemolysis, which increases bilirubin excretion and precipitation in the

gallbladder, promoting stone formation (Vitek & Carey, 2012). Furthermore, repeated blood transfusions may exacerbate hemolysis and iron deposition, further contributing to cholelithiasis (Acqua et al., 2015). Pigment stones are the predominant type in HHA, often leading to complications such as biliary colic and cholecystitis (Vitek & Carey, 2012; Mishra & Tiwari, 2013)

MATERIALS AND METHODS

Participants and Design

This cross-sectional study included 100 children with confirmed HHA attending the hematology unit at Benghazi Medical Center between December 2009 and November 2024. Participants were recruited from eastern Libya.

Data Collection

Medical records were reviewed for demographic and clinical variables, including:

- Sex and age at HHA diagnosis.
- Type of HHA (e.g., sickle cell anemia, hereditary spherocytosis).
- Family history of hemolytic disorders.
- Gallbladder stone detection via abdominal ultrasonography.
- Frequency of blood transfusions (defined as ≥3 transfusions since the diagnosis of HHA).

Inclusion and Exclusion Criteria

Included: Children with confirmed HHA who underwent ultrasonography.
Excluded: Patients with GBS unrelated to HHA.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics (Version 25). Descriptive statistics summarized demographic and clinical characteristics (frequencies, percentages, mean ± SD). The chi-square test evaluated associations between age groups (<6 vs ≥6 years) and GBS prevalence. Binary logistic regression identified risk factors for GBS (*p* < .05 significance threshold).

RESULTS

The study included 100 children with Hereditary Hemolytic Anemia (HHA), ranging in age from 4 months to 16 years. The mean age at diagnosis of HHA is 3.1 years ± 3.8 years (Median: 1.5 years) (Table 1).

Table (1). Age at diagnosis of Hemolytic anemia

Statistic	Value
N	100
Missing	0
Mean Age	3.08
Standard deviation	3.78
Median Age	1.5
Age Range	0.4 - 16 years

The sex of the sample contains 100 patients; there were 63 males (63%) and 37 females (37%), showing a slight male predominance (Figure 1)

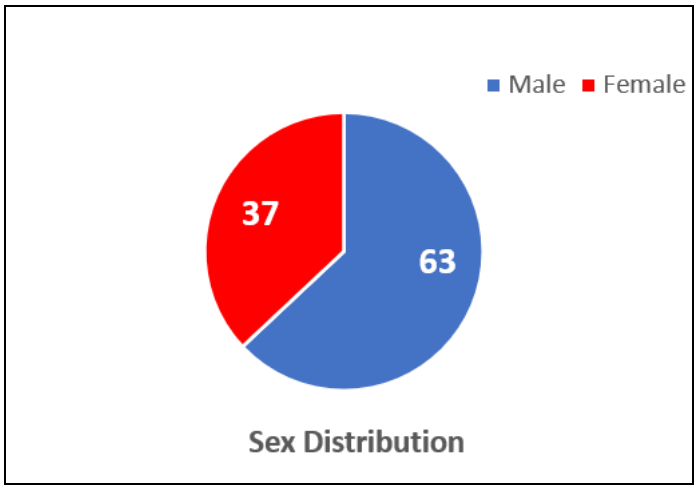

Figure (1). Sex distribution of the study population

The type of Hemolytic anemias comprises the following:

Sickle Cell Anemia (n = 35, 35.0%), Hereditary Spherocytosis (n = 23, 23.0%), Glucose 6 Phosphate Dehydrogenase Deficiency (n = 19, 19.0%), Sickle Thalassemia (n = 6, 6.0%), Thalassemia Major (n = 6, 6.0%), Sickle Trait (n = 5, 5.0%), Alpha Thalassemia (n = 2, 2.0%), Pyruvate Kinase Deficiency (n = 2, 2.0%), Sickle C (n = 1, 1.0%), and Thalassemia Trait (n = 1, 1.0%). (Figure 2)

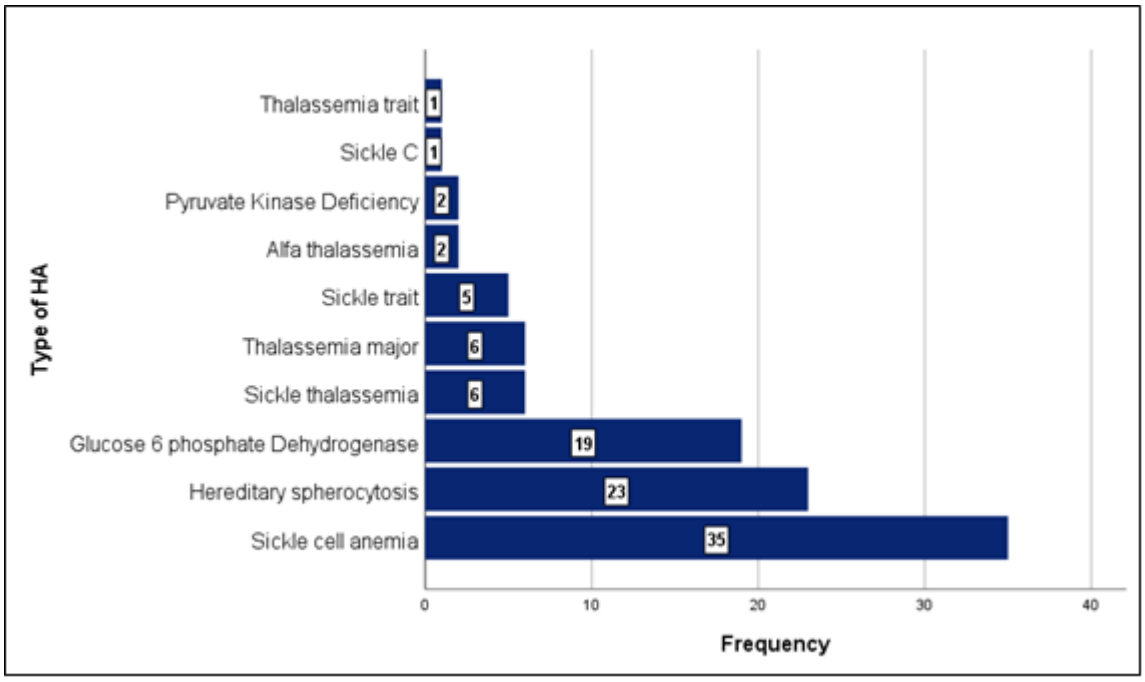

Figure (2): Types of hemolytic anemias

Hemolytic Anemia and Gallbladder Stone:

Diagnosis of gallbladder stone was detected in 36 patients (36%).

The mean age at diagnosis was 7.6 ± 3.95 years (range: 1,5 -15 years).

The majority of cases occurred between the ages of 6 and 9 years. Three patients developed GBS before the age of 3, including one at 1,5 years (Table 2 and Table 3). There was no statistically sig-

nificant association between age group (<6 years > 6 years) and the presence of gallbladder stone (x^2 0.14 P value 0.71; Table 4, Figure 3).

Characteristics of HA cases having GBS

Table (2). Age Distribution of GBS Onset

Descriptive Statistics	N	Minimum	Maximum	Mean	Std. Deviation
Age at GBS	36	1.50	15.00	7.6361	3.95418

Table (3). Age interval Distribution of GBS

Age Interval (in years)	Frequency (n)	Percentage (%)
0–<3	4	11,11
3–< 6	8	22,22
6–< 9	12	33,33
9–< 12	3	8,33
12–< 15	8	22,22
15+	1	2,78
No GBS	64	-

Table (4). Association between Age and GBS

Predictor of GBS		GBS		Total	Test and Significance
		Yes	No		
Age	< 6 years	12 (38.7%)	19 (61.3%)	31(100%)	$\chi^2 = 0.14$
	≥ 6 years	24 (34.8%)	45 (65.2%)	69 (100%)	p. value = 0.71

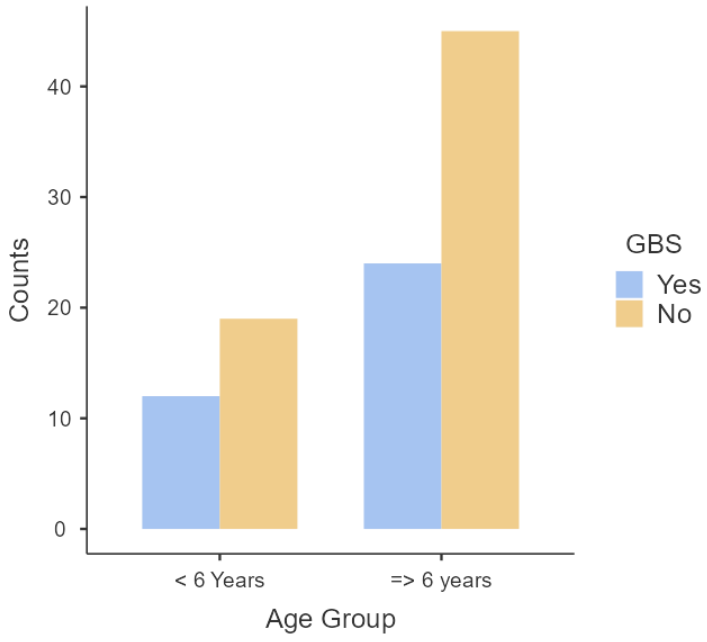

Figure (3). Graphical Representation of Age and GBS Relation

Sex and Gallbladder Stones:

Among the 36 patients, 21(58,3%) were males and 15(41.7%) were females, indicating non-significant male predominance (Table5)

Table (5). Sex Disparity of GBS occurring

Sex	Frequency	Percent
Male	21	58.3
Female	15	41.7
Total	36	100.0

Type of hemolytic anemias and GBS:

Sickle Cell Anemia had the highest number of cases (35), with 13 diagnosed with GBS and 22 without, followed by Hereditary Spherocytosis, 23 cases, of which 12 had GBS. Other anemias similar to Glucose-6-Phosphate Dehydrogenase Deficiency, Thalassemia, and Pyruvate Kinase Deficiency, and sickle trait had fewer cases, with mixed GBS associations. (Table 6)

Table (6). Type of hemolytic anemia according to GBS diagnosis

	GBS		TOTAL
Type of H anemia	Yes (n,%)	No (no,%)	
Sickle Cell Anemia	13 (36)	22	35
Hereditary spherocytosis	12 (33.3)	11	23
Glucose 6 Phosphate Dehydrogenase	4 (11.1)	15	19
Sickle thalassemia	2 (5,6)	4	6
Sickle trait	1 (2.8)	4	5
Sickle C	0	1	1
Thalassemia major	2 (5.6)	4	6
Thalassemia trait	0	1	1
Alfa thalassemia	0	2	2
Pyruvate Kinase Deficiency	2 (5.6)	0	2
TOTAL	36(36%)	64 (64%)	100

Key risk factors of GBS:

Analysis: A binary logistic regression model, Coefficients - Diagnosis of GBS (Table 7)

1. Intercept: (Estimate: -1.6358) This is the baseline log odds for the diagnosis of GBS being "No" when all predictors are at their reference levels. This value is not statistically significant ($p = 0.175$).
2. Sex: (Estimate: -0.0945) This indicates that the odds of being diagnosed with GBS are slightly lower for males compared to females, but this effect is not statistically significant ($p = 0.845$).
3. Type of HA: (Estimate: -0.0760). This suggests that the odds of being diagnosed with GBS decrease slightly with different types of Hemolytic Anemia, but this is not statistically significant ($p = 0.300$).
4. Blood Transfusion: (Estimate: 1.8159). This shows a significant positive association with the diagnosis of GBS ($p = 0.001$). The odds of being diagnosed with GBS are much higher if the patient has had a blood transfusion.

5. Family History of HA: (Estimate: 0.2328). This indicates a small increase in the odds of being diagnosed with GBS if there is a family history of Hemolytic Anemia. However, this is not statistically significant (p = 0.690).

6. Age at Diagnosis of HA: (Estimate: -0.1150). This suggests that older age at diagnosis of Hemolytic Anemia slightly decreases the odds of being diagnosed with GBS, and is close to statistical significance (p = 0.078).

Key risk factors of GBS

Table (7). logistic regression model Coefficients - Diagnosis of GBS

Predictor	Estimate	SE	Z	P
Intercept	-1.636	1.2063	-1.356	0.175
Sex	-0.0945	0.4819	-0.196	0.845
Type of HA	-0.0760	0.0732	-1.037	0.300
Blood transfusion	1.8159	0.5603	3.241	0.001**
Family history of HA	0.2328	0.5841	0.399	0.690
Age at diagnosis of HA	-0.1150	0.0652	-1.762	0.078

Notes:
Estimates represent the log odds of "Diagnosis of GBS = No" vs. "Diagnosis of GBS = Yes"
Highly significant results (P-value < 0.05).

DISCUSSION

To date, no article has summarized the frequency and risk factors of cholelithiasis in Libyan children with inherited hemolytic anemia. The current study demonstrates a high prevalence of gallbladder stones (GBS) (36%) among children with hereditary hemolytic anemia (HHA) in Libya, substantially higher than the 12% prevalence reported in Egyptian children (Enayet et al., 2020). This discrepancy may reflect regional differences in disease severity, diagnostic practices, or genetic factors

In our study, the most common types of HHA were sickle cell anemia (35%), hereditary spherocytosis (23%), and Glucose 6 Phosphate Dehydrogenase deficiency(19%), the frequency of cholelithiasis was 36.1%, 33.3%, 11.1% respectively, but we found the difference between the type of hemolytic anemia and gallbladder stone formation was not statistically significant, while Mohammed et al. (2023) have identified the type of hemolytic anemia, particularly sickle cell anemia and thalassemia major, as predictors of gallbladder stone formation.

In the present study, 35% of study population were sickle cell anemias, 13 (36.1%) of the children with cholelithiasis had sickle cell anemia, giving a general prevalence as 37.1% (13/35) among SCA patients, this finding is higher than previous study done in Benghazi city (Beayoul & Matoug, 2009) and is high as comparable with Arabic report that done at KSA and another in Assiut [31.4%, 38.1%] (Almudaibigh et al., 2021; Mohammed et al., 2023) and higher than reports from sub-Saharan Africa (Inah & Ekanem, 2019; Mohammed et al., 2021). The youngest SCA patient with GBS in our study (4 years) was comparable to Egyptian findings but older than Sudanese reports (2.5 years; Attalla et al., 2013)

Gallbladder stone occurrence in sickle cell trait is less documented compared to sickle cell anemia. Cholelithiasis is a rare complication of sickle cell trait, and there is insufficient evidence to suggest an independent association with cholelithiasis. However, specific data is limited; in the current study, we found a case of a 7-year-old child with sickle cell trait who developed gallbladder stones (Hussein et al., 2015).

Despite hereditary spherocytosis being known to be common in northern European and Western European populations, our study showed a significant number of cases in the study population (23%). Twelve cases (33.3%) of gallbladder stones were attributed to hereditary spherocytosis, resulting in a prevalence of 52.17% (12/23) among children diagnosed with hereditary spherocytosis. This finding is higher compared to other studies reporting 26% and 30.8% (Gungor et al., 2018; Das et al., 2014), and comparable to research by Tamary et al. (2003), which reported a 41% prevalence in children and young adults.

Strikingly, gallstones formed as early as 18 months in our study, whereas other studies reported older ages of onset (Hussein et al., 2015; Gungor et al., 2018; Das et al., 2014).

Although thalassemia prevalence is highest in Mediterranean and Middle Eastern regions, our study found a small number of cases (5.6%), which may be attributed to genetic or ethnic factors. We found that the prevalence of gallbladder stones was significant (33.3%, 2/6), consistent with previous reports (Mohammed et al., 2023; Hussein et al., 2015; Lotfi et al., 2009).

Glucose-6-phosphate dehydrogenase (G6PD) deficiency, a common RBC enzyme deficiency, constituted 19% of our study group. Of these, 4/36 (11.1%) developed gallbladder stones, with an overall prevalence of 21% (4/19) among G6PD-deficient patients, as previously reported by Kilic et al. (2021).

Pyruvate kinase deficiency is a rare disease. In our study, twins had the condition, both of whom developed gallbladder stones, accounting for 5.6% of our cholelithiasis cases. This compares with the 20% prevalence reported by Ghonat et al. (2021) in pediatric cases.

Several studies have reported that the risk of gallbladder stone (GBS) formation increases with age, which is likely due to the cumulative effects of chronic hemolysis and prolonged bilirubin production (Adeniyi et al., 2022; Alhawaswi et al., 2019). However, our findings did not demonstrate a significant association between increasing age and GBS development, as reported by Mohammed et al. (2023). One possible physiological explanation is the early onset of severe hemolysis that required multiple blood transfusions in many of our patients, which led to high bilirubin levels and pigment stone formation even at younger ages. This suggests that the intensity and duration of hemolysis, rather than chronological age alone, may be the critical determinant of stone formation.

We found three children developed GBS during the first two years of life, the youngest being 1.5 years old, which represents a rare occurrence (Hussein et al., 2015; Gungor et al., 2018; Das et al., 2014).

Our study revealed no significant association between age at diagnosis of inherited hemolytic anemia and GBS formation. This may be attributed to the fact that age at diagnosis does not necessarily reflect the cumulative impact of hemolysis or disease severity. The pathogenesis of cholelithiasis in hereditary hemolytic anemia (HHA) appears more strongly influenced by chronic hemolysis, bilirubin overload, and treatment-related factors, such as blood transfusions. Moreover, variability in age

at diagnosis could result from differences in parental awareness or disease presentation rather than the true onset of hemolysis. This suggests that age at diagnosis of hemolytic anemia may not provide a reliable estimate of hemolytic stress duration, weakening its utility as a predictive factor for GBS development (Mohammed et al., 2023).

The frequency of cholelithiasis was slightly higher among males (58.3%); however, this difference was not statistically significant in our study, consistent with other reports (Mohammed et al., 2023; Alhawaswi et al., 2019).

Family history of hereditary hemolytic anemias did not necessarily increase gallstone risk in our study, potentially due to individual variations in disease severity and genetic defects, consistent with findings from Assiut (Mohammed et al., 2023)

We found that patients who received multiple blood transfusions had a statistically significant increased risk of developing cholelithiasis ($p = 0.001$), consistent with previous studies (Mohammed et al., 2023; Acqua et al., 2015; Ghonat et al., 2021; Alhawaswi et al., 2019). Severe hemolysis contributes to GBS development as patients require transfusions, and iron overload may further increase the likelihood of gallstone formation (Mishra & Tiwari, 2013; Mohammed et al., 2023; Attalla et al., 2013)

CONCLUSION

1. High frequency of gallbladder stones: 36% of children with inherited hemolytic anemia developed gallbladder stones.
2. Variation in the prevalence of gallbladder stones among different types of inherited hemolytic anemia, which are commonly seen in sickle cell anemias and hereditary spherocytosis.
3. Early onset of gallbladder stones was detected in children as young as 1.5 years old.
4- Multiple blood transfusions were identified as a significant risk factor for gallbladder stone development

Recommendations:
1. Early and regular abdominal ultrasonography screening for gallbladder stones is recommended for children with inherited hemolytic anemia.
2. Close monitoring of patients requiring multiple blood transfusions is necessary to prevent gallbladder stone development, and consider alternative treatments to reduce transfusion requirements.
3. Further research is needed to understand the relationship between hemolysis severity and gallbladder cholelithiasis

Limitations:
The single-center design may limit generalizability. The cross-sectional nature precludes causal inferences, and detailed bilirubin/iron studies were unavailable. Future multicenter longitudinal studies with biochemical monitoring would strengthen these findings.

ACKNOWLEDGEMENT

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

ETHICS

The study was a retrospective study that did not need patient consent.

Duality of interest: We don't have any duality of interest associated with this manuscript.

Author contributions: 1.2.3.4. Developed the theoretical formalism, performed the analytic calculations, and performed the numerical simulations. 1 and 4 authors contributed to the final version of the manuscript. 4. supervised the project.

Funding: The authors received no funding.

REFERENCES

Abdullah, U., Jassim, H. M., Baig, A. A., Khorsheed, R. M., Al-Khayat, A., Sulong, A., . . . Yassin, W. A. (2015). Gallstones in patients with inherited hemolytic diseases. *Int J Pharm Pharm Sci, 7*(7), 9-15.

Adeniyi, O. F., Akinsete, A. M., Odeghe, E. A., Olowoyeye, O. A., Okeke, O. F., Seyi-Olajide, J. O., & Akinsulie, A. (2022). Cholelithiasis in children and adolescents with sickle cell disease: experience in a resource-limited setting. *Annals of African Medicine, 21*(1), 58-64.

Alhawsawi, Z. M., Alshenqeti, A. M., Alqarafi, A. M., Alhussayen, L. K., & Turkistani, W. A. (2019). Cholelithiasis in patients with paediatric sickle cell anaemia in a Saudi hospital. *Journal of Taibah University Medical Sciences, 14*(2), 187-192.

Almudaibigh, A. H., Alkasim, F. A., & Ghareeb, E. F. (2021). Prevalence and outcome of cholelithiasis in children with sickle cell disease at King Saud Medical City, Saudi Arabia. *Journal of applied Hematology, 12*(4), 203-209.

Amina Mohamed, B., & Idris, M. (2009). Childhood haemoglobinopathies in Benghazi.

Attalla, B., Karrar, Z., Ibnouf, G., Mohamed, A., Abdelwahab, O., Nasir, E., & Seed, M. (2013). Outcome of cholelithiasis in Sudanese children with Sickle Cell Anaemia (SCA) after 13 years follow-up. *African health sciences, 13*(1), 154-159.

Chamorro, C., Arteaga, P., Paredes, C., Bravo, N. C., Giraldo, C., Betancourt, G. C., . . . Torres, C. (2020). Cholelithiasis and associated complications in pediatric patients. *Cir. Pediatr, 33*, 172-176.

Chonat, S., Eber, S. W., Holzhauer, S., Kollmar, N., Morton, D. H., Glader, B., . . . Sharma, M. (2021). Pyruvate kinase deficiency in children. *Pediatric blood & cancer, 68*(9), e29148.

Das, A., Bansal, D., Das, R., Trehan, A., & Marwaha, R. (2014). Hereditary spherocytosis in children: profile and post-splenectomy outcome. *Indian pediatrics, 51*(2), 139-141.

Enayet, A., Afifi, R., Mogahed, E., El-Raziky, M., & Abdellatif, M. (2020). Gallstones in Egyptian infants and children: risk factors, complications and outcome: a single center experience. *Egyptian Liver Journal, 10*(1), 31.

Gumiero, A. P. d. S., Bellomo-Brandão, M. A., & Costa-Pinto, E. A. L. d. (2008). Gallstones in children with sickle cell disease followed up at a Brazilian hematology center. *Arquivos de gastroenterologia, 45*, 313-318.

Güngör, A., Yaralı, N., Fettah, A., Ok-Bozkaya, İ., Özbek, N., & Kara, A. (2018). Hereditary spherocytosis: Retrospective evaluation of 65 children. *The Turkish journal of pediatrics, 60*(3), 264-269.

Inah, G. B., & Ekanem, E. E. (2019). Sonographic diagnosis and clinical correlates of gallbladder stones in patients with sickle cell disease in Calabar, Nigeria. *Open access Macedonian journal of medical sciences, 7*(1), 68.

Karavdic, K. (2023). The Specific features of pediatric cholelityhiasis. A Literature review. *South-East European Endo-Surgery Journal, 1*(2), 50-69.

Kılıç, M. A., Özdemir, G. N., Tahtakesen, T. N., Uysalol, E. P., Bayram, C., Ayçiçek, A., & Aydoğan, G. (2021). Glucose 6 phosphate dehydrogenase deficiency: A single-center experience. *Turkish Archives of Pediatrics, 56*(3), 245.

L'Acqua, C., Bandyopadhyay, S., Francis, R. O., McMahon, D. J., Nellis, M., Sheth, S., . . . Hod, E. A. (2015). Red blood cell transfusion is associated with increased hemolysis and an acute phase response in a subset of critically ill children. *American journal of hematology, 90*(10), 915-920.

Lotfi1ABF, M., Keramati1ABCDEF, P., Assadsangabi1ABE, R., Nabavizadeh1AEF, S. A., & Karimi2AB, M. (2009). Ultrasonographic Assessment of the prevalence of cholelithiasis and biliary sludge in β-thalassemia patients in Iran. *Med Sci Monit, 15*(8), 402.

Mishra, A. K., & Tiwari, A. (2013). Iron overload in Beta thalassaemia major and intermedia patients. *Maedica, 8*(4), 328.

Mohamed, S. O., Ibrahim, O. A., Mohammad, D. A., & Ali, A. H. (2021). Correlates of gallbladder stones among patients with sickle cell disease: A meta-analysis. *JGH Open, 5*(9), 997-1003.

Mohammed, S., Moez, A. L., & Galal, S. M. (2023). Gallbladder status among children with chronic hemolytic anemia attending Assiut University Children's Hospital. *Journal of Current Medical Research and Practice, 8*(1), 39-42.

Murphy, P. B., Vogt, K. N., Winick-Ng, J., McClure, J. A., Welk, B., & Jones, S. A. (2016). The increasing incidence of gallbladder disease in children: A 20 year perspective. *Journal of Pediatric Surgery, 51*(5), 748-752.

Tamary, H., Aviner, S., Freud, E., Miskin, H., Krasnov, T., Schwarz, M., & Yaniv, I. (2003). High incidence of early cholelithiasis detected by ultrasonography in children and young adults with hereditary spherocytosis. *Journal of pediatric hematology/oncology, 25*(12), 952-954.

Vítek, L., & Carey, M. C. (2012). New pathophysiological concepts underlying pathogenesis of pigment gallstones. *Clinics and research in hepatology and gastroenterology, 36*(2), 122-129.