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Ultrasonographically Detected Gallbladder Disease in Transfusion-Dependent Beta-Thalassemia: Correlation with Iron Overload and Transfusion Burden

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Abstract

Objective: To determine the prevalence of USG-detected gallbladder disease in patients suffering from transfusion dependant thalassemia.
Methodology: In this descriptive, cross-sectional study 106 consecutive patients, of beta thalassaemia major, were studied at Pakistan Railways hospital over a period of six months from October 2024 to February 2025. Abdominal ultrasonography was performed to evaluate the underlying gallbladder disease.
Results: Out of 106 patients with transfusion dependant thalassemia 51 (48%) were males and 55 (51.9%) were females. 17 (16.04%) patients were less than 10 years, 53 (50.00%) were between 10 and 20 years and 36 (33.96%) were older than 20 years. 38 (36.85%) patients had gall bladder disease detected on ultrasonography. 4 (3.77%) patients already had cholecystectomy for symptomatic gall stones, 16 (15.1%) had gall stones and 18 (16.98%) had sludge in gall bladder. Amongst the patients with gall bladder disease 6 (15.79%) were less than 10 years, 16 (42.1%) were between 10 and 20 years, 14 (36.84%) between 20 and 30 years and 2 (5.26%) were above 30 years of age. 28 (73.68%) patients with gallbladder disease had received more than two transfusion every month, while 10 (26.31%) had received two or less transfusions per month with p-value> 0.02. Among the patients with gallbladder disease, 33 (86.8%) had serum ferritin levels above 2500 ng/ml, while 5 (14.3%) had levels below this threshold, p-value<0.01.
Conclusion; Gall bladder disease is a common complication in transfusion dependant thalassemics in Pakistan, therefore, ultra-sonographic evaluation should be considered early and continued at regular intervals to avoid serious complications. High serum ferritin and increased transfusions frequency had a significant association with cholelithiasis and gall bladder sludge
Key words: Thalassemia, gall bladder disease, gall bladder stones, ultrasound.

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Introduction

Transfusion dependant thalassemia poses a significant public health challenge in Pakistan, as 5,000-9,000 children are born with this condition every year. [1,2] These patients need lifelong treatment with regular transfusion of red blood cells and iron chelation.[3, 4] Such treatment prolongs life spanbut is not available to most of the patients in low and middle income countries like Pakistan. In the absence of high quality treatment these patients continue to have numerous complications like cardiomyopathy, chronic liver disease, disorders of growth and puberty, endocrinopathies, alloimmunisation, hypersplenism, osteoporosis and gall stones.[5]

The formation of gallstones in TM is primarily attributed to the chronic state of haemolysis, which increases the bilirubin load from heme catabolism, leading to the formation of calcium bilirubinate pigment stones. Several factors such as ineffective erythropoiesis, potential gallbladder dysmotility, and hepatic siderosis secondary to iron overload may further contribute to this pathology.[5,16,17] Hepatitis C virus infection, a common complication in thalassemia, is another known factor for development of gall stone.[6] While often asymptomatic, cholelithiasis can lead to significant morbidity, including biliary colic, acute cholecystitis, and pancreatitis, potentially requiring surgical intervention.[7] Timely diagnosis, therefore, can save patients from these complications.

Ultrasonography (USG) stands as a valuable non-invasive tool for detecting these gallbladder abnormalities.[8] Despite the known risks, comprehensive local data on

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the prevalence and determinants of USG-detected gallbladder disease from Pakistani thalassaemics are limited. International studiesshow variable prevalence rates, ranging from 0% to over 54%, influenced by age, ethnicity, transfusion history, and splenectomy status.[9,10] This study was therefore conductedto determine the prevalence of USG-detected gallbladder disease in patients suffering from transfusion dependant thalassemia in Pakistan.

Methodology

This descriptive cross-sectional study was conducted at Pakistan Railways Hospital over a six-month period from October 2024 to February 2025. The hospital provides services to patients with transfusion-dependent thalassemia who are referred from various centers in Punjab, Kashmir, and Khyber Pakhtunkhwa provinces.

A total of 106 consecutive patients were recruited from the outpatient department (OPD). Inclusion criteria were: confirmed diagnosis of β-thalassemia major, age greater than 5 years, and regular red blood cell transfusions. Exclusion criteria: pre-existing hepatobiliary disease unrelated to thalassemia.

Data were collected after obtaining ethical approval from the Institutional Review Board. Informed consent was obtained from the parents or legal guardians of each participant, and from the patient if he or she was 18 years or older. Recorded variables included weight (kg), height (cm), age at diagnosis (months), age at first transfusion (months), pre-transfusion hemoglobin (g/dl), frequency of transfusion, duration and type of iron chelation therapy, and splenectomy status.

Abdominal ultrasonography was performed by an experienced radiologist using a high-resolution Mindray (China) 2022 model ultrasound machine with a 3.5–5 MHz curvilinear transducer. Patients were instructed to fast for at least 4–6 hours prior to examination. The gallbladder was assessed for:

Cholelithiasis – defined as mobile echogenic foci with posterior acoustic shadowing.

Sludge – defined as echogenic material without acoustic shadowing that layers in the dependent portion of the gallbladder.

Additional parameters recorded included gallbladder wall thickness (mm), presence of sludge (Yes/No), polyp (Yes/No), cholelithiasis (Yes/No), details of stones (number, size, posterior acoustic shadowing), common bile duct (CBD) diameter (mm), portal vein diameter (mm), liver span (cm), spleen size (cm) or splenectomy status, liver echotexture, and pancreatic appearance. Data were entered and analyzed using SPSS version 25.0.

Results

Out of 106 patients with transfusion-dependent thalassemia, 48% were males and 51.9% females. The age distribution, ethnic background, and transfusion frequency are presented in Table I. Liver size, spleen size, and splenectomy status are summarized in Table II.

38 (36.85%) patients had gall bladder disease detected on ultrasonography. 4 (3.77%) patients already had cholecystectomy for symptomatic gall stones, 16 (15.1%) had gall stones and 18 (16.98%) had sludge in gall bladder.32 (84.21%) out of 38 patients who had gall bladder disease had already had splenectomy or massive enlargement of spleen whereas only 1 (2.63%) had normal size of spleen.

Table I: Characteristics of Patients. (N=106)

Ethnic Origin	N(%)
Punjabi	65 (61.32%)
Pakhtoon	30 (28.30%)
Kashmiri	11 (10.37%)
Age Group	
< 10 years	17(16.04%)
10–20 years	53(50.00%)
> 20 years	36(33.96%)
Gender	
Male	51(48.1%)
Female	55(51.9%)
Transfusion History	
Once/month	16 (15.09%)
Twice/month	38(35.85%)
Thrice/month	40(37.74%)
Four times/month	12(11.32%)
Blood Groups	
A +ve	12(11.3%)
B +ve	36 (33.96%)
O +ve	40 (37.74%)
AB +ve	8(7.54%)
A –ve	2(1.88%)
B –ve	3(2.83%)
O –ve	3(2.83%)
AB –ve	2(1.88%)

Amongst the patients with gall bladder disease 6 (15.79%) were less than 10 years, 16 (42.1%) were between 10 and 20 years, 14 (36.84%) between 20 and 30 years and 2 (5.26%) were above 30 years of age.

Table II: Hepatosplenomegaly. (N=106)	
Hepatomegaly	
Normal or ≤ 2 cm	4 (3.77%)
2 – 5 cm	37 (34.90%)
>5 cm	65 (61.32%)
Splenomegaly	
Splenectomy	24(22.64%)
More than 6 cm	65 (61.32%)
Less than 6 cm	17 (16.03%)

Gallbladder disease was significantly more prevalent in patients receiving more than two blood transfusions per month (n-28, 73.68%) compared to those receiving two or fewer transfusions per month (n-10, 26.31%) with *p-value<0.02*. Only five (4.71%) patients were compliant to iron chelation treatment with either desferrioxamine infusion or oral Deferiprone /Deferasirox. 101 (95.28%) patients were noncompliant with serum ferritin levels above 2500 ng/ml in 79 (74.52%) and above 1000 ng/ml in 22 (20.75%) patients. Among the patients with gallbladder disease, 33 (86.8%) had serum ferritin levels above 2500 ng/ml, while 5 (14.3%) had levels below this threshold, *p-value<0.01*. (Table III)

Table III: Comparison of gall bladder disease with frequency of transfusion and ferritin levels.		
	Gall Bladder Disease (Stones & Sludge)	p-value
Transfusion frequency		*<0.02**
1-2/month	10 (26.31%)	
More than 2 /month	28 (73.68%)	
Ferritin Levels		*<0.01**
<2500 ng/ml	05 (14.3%)	
>2500 ng/ml	33 (86.8%)	

Discussion

Chronic illnesses particularly with severe disease are likely to develop complications which are more common if quality treatment is not available to majority of patients. Identification of these complications provides the evidence for measures to prevent and timely intervene. Non-invasive, simple and readily available techniques like ultrasonography are useful for the evaluation of the gall bladder disease which require minimal cooperation of the patient and are particularly suitable for studying children.

Our study provides important insights into the burden of gallbladder abnormalities in Pakistani patients with transfusion dependant thalassemia. We found that 38 (35.85%) patients had gall bladder disease; 20 (18.86%) had gall stones and 18 (16.985) had sludge in gall bladder. These findings are significant and fall within the range reported in international studies (0-54%), including those from neighbouring countries.[10-14] This variability often reflects differences in patient age, transfusion and chelation practices, and genetic backgrounds.

The prevalence of cholelithiasis significantly increased with age. Amongst the patients with gall bladder disease only 6 (15.79%) were less than 10 years, 32 (84.21%) were more than 10 years of age. The strong positive correlation between older age and cholelithiasis is consistent with the understanding that gallstone formation is a chronic process, with risk accumulating over years of persistent hemolysis and iron loading.[12].

The significantly higher prevalence of cholelithiasis in splenectomized patients (84.2%) is a critical finding, and is reported in earlier studies.[11,14] Splenectomy, by removing a primary site of red cell destruction and increasing the lifespan of abnormal erythrocytes, leads to an augmented bilirubin load presented to the liver, thereby predisposing to pigment stone formation. This highlights the need for careful pre-splenectomy gallbladder assessment.

The association of cholelithiasis with a higher transfusion frequency and elevated serum ferritin levelspoints towards the role of increased rate of haemolysis (necessitating more transfusions) and iron overload.[18, 20] Chronic iron deposition in the liver can impair hepatobiliary function, and increased haemolysis directly elevates bilirubin production, both contributing to the formation of gall stones.[16,17,19]

Strengths and Limitations: This study is one of the few from Pakistan to evaluate USG-detected gallbladder abnormalities. Nevertheless, inclusion of patients from a hospital setting may not be a true representation of the overall state of patients in a community.

Implications: Our findings advocate for the integration of routine USG screening for gallbladder abnormalities into the standard care protocols for children with TM in Pakistan, especially for older children and those post-splenectomy. Early detection can allow for prophylactic

advice, monitoring for symptoms, and timely intervention, potentially preventing more severe complications.

Conclusion

Gall bladder disease is a common complication in transfusion dependant thalassemics in Pakistan, therefore, ultra-sonographic evaluation should be considered early and continued at regular intervals to avoid serious complications. High serum ferritin and increased transfusions frequency had a significant association with cholelithiasis and gall bladder sludge

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