ISSN: 2977-6139

Research Article

Open Access Journal of Pediatrics Research

Splenomegaly: Clinical Profile, and Spectrum of Etiologies among Yemeni Children. A Two-Years Study in Al Kuwait Hospital, Sana'a-Yemen

Abdulrahman Alhadi[1*], Majedah Abdulrahman Radman Ali[2], Mohammed Abduh Ali Aqlan[3] and Ali Ahmed Al-Zaazaai[4]

[1]*Associate Professor of Pediatrics Member of Scientific Council of Pediatrics, Yemen*

[2]*Senior Pediatric Specialist Al-Kuwait university hospital - Sana'a, Yemen*

[3]*Pediatric consultant, Al-Kuwait university hospital - Sana'a, Yemen*

[4]*M.Sc., Clinical Pharmacy of Wenzhou Medical University, China*

[*]**Corresponding author**

Abdulrahman Alhadi, Associate Professor of Pediatrics Member of Scientific Council of Pediatrics, Yemen.

Received: December 03, 2025; **Accepted:** December 08, 2025; **Published:** December 15, 2025

ABSTRACT

Background: The spleen is the largest lymphoid tissue with a unique structure that provides an environment for direct contact between blood and immune system. It is vulnerable for enlargement (splenomegaly) beyond normal limits. Splenomegaly is an important sign in pediatrics. Many pathological processes may affect the spleen in children. In most cases it is the result of a systemic disease. Identification of etiology is mandatory for proper management of splenomegaly in children.

Objective: To determine clinical profile, and spectrum of etiologies of splenomegaly among children attending to Al-Kuwait University Hospital in Sana'a-Yemen.

Methods and Settings: It was a retrospective descriptive study collected data of children with splenomegaly over a period of two years (from January 2020 to December 2021). A questionnaire was used to capture data which included demographic data of child (age, gender, resident area, father's job, family income), data related to characteristics of splenomegaly (degree of splenomegaly, associated hepatomegaly, associated lymphadenopathy, associated anemia, and associated hypersplenism), data related to clinical manifestations, and data related to etiology of splenomegaly.

Results: The study has included 200 children presented with splenomegaly. Number of males was slightly higher than females (53.5% vs 46.5%). The age ranged between 1 years and 15 years with most of the cases (43.5%) in the age group between 6 and 10 years. Most of cases (60%) were coming from rural areas, and most of them (74%) presented with moderately enlarged spleen. An associated hepatomegaly, lymphadenopathy, anemia, hypersplenism were observed in rate of 58.5%, 23%, 79%, and 16% respectively. Results of this study revealed that the most frequent clinical manifestations were fever, pallor, weakness, and abdominal distention in rates of 86.5%, 78%, 60%, and 48% respectively. Followed by jaundice, weight loss, and abdominal pain in rates of 33.5%, 27.5%, and 24% respectively. Other less common symptoms were dyspnea, edema, and bleeding in rates of 22.5%, 18%, and 13.5% respectively. Regarding etiological diagnosis, the most frequent etiologies observed in this study were hematological (27% caused by hemolytic anemias, 9% caused by lymphomas, and 2% caused by leukemias), infective (malaria represented 19%, visceral leishmania represented 6%, enteric fever represented 5%, and septicemia represented 4%), storage disease (glycogen storage disease in 3.5%, and mucopolysaccharidosis in 2.5%), congestive blood flow (portal hypertension in 2.5%, and congestive heart failure in 1.5%), and connective tissue disease represented 3.5%. Unknown diagnosis was documented for 10% of cases. No significant association was found between etiology and gender or age.

Conclusions

Splenomegaly is an important sign in pediatrics. The underlying etiologies observed in this study were hematologic (38%), infectious (34%), storage disease (6%), congestive (4%), connective tissue disease (3.5%), miscellaneous (4.5%), and unknown etiology (10%). Most cases seen in the age group under 10 years, and most of cases presented with moderate degree of splenomegaly. A greater degree of suspicion in these cases and proper laboratory workup and early referral to specialized centers is mandatory and can improve the outcome significantly.

Keywords: Splenomegaly, Hepatomegaly, Hemolytic Anemia, Malaria, Leishmania, Infective Disease, Pediatrics, Yemen

Citation: Abdulrahman Alhadi, Majedah Abdulrahman Radman Ali, Mohammed Abduh Ali Aqlan, Ali Ahmed Al-Zaazaai. Splenomegaly: Clinical Profile, and Spectrum of Etiologies among Yemeni Children. A Two-Years Study in Al Kuwait Hospital, Sana'a-Yemen. Open Access J Ped Res. 2025. 2(4): 1-11.
DOI: doi.org/10.61440/OAJPR.2025.v2.32

List of Abbreviations

AIDS	:	Acquired immune deficiency syndrome
CT	:	Computed tomography
HIV	:	Human immunodeficiency virus
JRA	:	Juvenile rheumatoid arthritis
MRI	:	Magnetic resonance imaging
POEMS	:	Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin abnormalities
RBCs	:	Red blood cells
SCA	:	Sickle cell anemia
SD	:	Standard division
SLE	:	Systemic lupus erythematosus
SPSS	:	Statistical Package for the Social Sciences
US	:	Ultrasonography
VL	:	Visceral leishmaniasis
WHO	:	World Health Organization

Chapter 1: Introduction

Background

Spleen is the largest lymphoid tissue in the body. Anatomy of the spleen provides a uniquely close contact between its immunologic tissues and blood [1].

The spleen plays an important role in cellular and immune response to infection and inflammation. It also has a phagocytic role and acts as a filter for circulating microorganisms, old and deformed red cells, and other antigens [2].

Enlarged spleen is a frequent and important clinical sign [1]. Splenomegaly is simply defined as presence of palpable spleen below left costal margin [3].

Spleen in infant and children is involved in variety of pathological process. Some of these processes cause isolated splenomegaly where others involve spleen as a part of systemic illness [4].

Enlargement of spleen may result from increase in its vascular space (congestive splenomegaly, liver disease), hematologic disorders (hemolytic anemia), inflammation (infection, collagen disease), infiltration (primary or secondary neoplasm), storage disorders etc [4,5].

Splenic enlargement in newborns is often due to congenital infection like rubella, toxoplasmosis and cytomegalovirus. Non-infectious cause of neonatal Splenomegaly is erythroblastosis fetalis [6].

Splenomegaly is usually accompanied by hepatomegaly and other signs and symptoms of systemic illnesses. On some occasions, it may be the only finding [7]. Hepatosplenomegaly is a common finding in infants and children with various etiological factors [8].

Splenic Function

The spleen is a hematopoietic organ, which, at various times during intrauterine and/or extrauterine life, is capable of supporting elements of the erythroid, myeloid, megakaryocytic, lymphoid, and monocyte-macrophage (ie, reticuloendothelial) systems. In certain disease states (eg, beta thalassemia major, primary myelofibrosis), it may become the site of extramedullary hematopoiesis and contain developing erythroid, myeloid, and megakaryocytic precursors [9].

The white pulp of the spleen is a major part (up to 25%) of the lymphoid tissue in the body. Like lymph nodes, it has germinal centers where early B-lymphocytes predominate, along with plasma cells. T-lymphocytes are the major population around periarteriolar sheaths. When antigens are present in the circulation, the spleen plays a key role in providing an environment for the immunologic response. Thus, in the absence of the spleen, antibody production may be significantly diminished. As an example, when pneumococcal vaccine is given intramuscularly to asplenic individuals, the IgG and IgM antibody titers are less than those noted in normal individuals [10]. Likewise, the titers of pneumococcal antibodies decline more rapidly in asplenic patients [11].

The largest component of the spleen is the red cell mass known as the “red pulp.” It consists of the red blood cells surrounding endothelial cords of Billroth and interdigitating splenic sinusoids, which are lined with macrophages. The high concentration of red cells in these arterioles and sinusoids explains how relatively mild degrees of hypoxia can cause transformation of sickle cells to the irreversibly hardened variety and promote infarction in this organ (autosplenectomy) [12].

In the splenic sinusoids, which course through white and red pulp, macrophages line the vascular spaces. These macrophages are important parts of the immune system in presenting antigens to lymphocytes in the white pulp as well as in destroying antibody-coated bacteria or hematopoietic cells. When red cells squeeze through these sinusoids, the surrounding macrophages are able to remove senescent red cells, destroy erythrocytes with abnormal membranes, and remove red cell inclusions such as nuclear remnants. As a result, when the spleen is absent, many of these abnormal red cells may circulate, along with red cells containing nuclear remnants (ie, Howell-Jolly bodies) [13,14].

Spleen size

The spleen is felt in 30% of normal newborns and up to 10% of one year olds. It may also be felt in 1% of normal older children and adolescents. An enlarged spleen may not be palpable until it is 2-3 times its normal size. Reasons for feeling a normal spleen include an unusual position and being pushed down by hyperexpanded lungs. During the examination of the spleen, the child should be in the supine position or on their right side. It is important to start low in the abdomen to prevent missing a massively enlarged organ. Asking the patient to take a deep breath may be helpful. The presence of an enlarged spleen may be confirmed by ultrasound, computerized tomography, or radionucleotide studies [15].

The spleen weighs 11 g at birth, 55 g at six years of age, and 125 g (range 100 to 250 g) at puberty [16].

It is palpable below the left costal margin in nearly one-third of neonates, 10 percent of normal children, and more than 2 percent of normal 19-year-olds. However, a splenic edge felt more than 2 cm below the ribs definitely is an abnormal finding [17].

The size of a normal spleen is dependent on the age (size) of the child. Tables of normal splenic size based on age and weight are available in the literature (Table 1). Splenic size is judged by its length on ultrasound (US), extending from the dome of the spleen to its inferior tip. The normal spleen does not extend beyond the lower margin of the left kidney. Splenic length is readily assessed with US. A splenic measurement of greater than 1.25 times the length of the left kidney indicates splenomegaly [4].

Table 1: Normal Splenic Size in Children

Age	Upper limit of normal splenic length (cm)
3 m	6.0
3-6 m	6.5
6-12 m	7.0
1-2 y	8.0
2-4 y	9.0
4-6 y	9.5
6-8 y	10.0
8-10 y	11.0
10-12y	11.5
>12 y	12

Source: Hilmes & Strouse, 2007 [4].

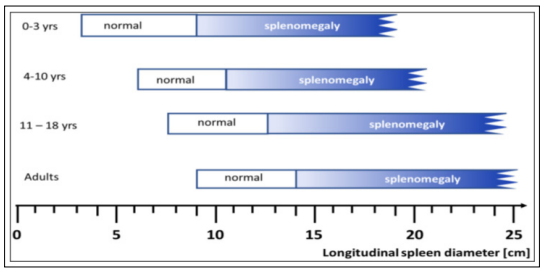

Figure 1: Range of spleen size assessed by ultrasound examination according to age [18].

Physical examination of the spleen

Numerous studies have shown wide interobserver variability in the ability to appreciate an enlarged spleen, which generally is not associated with the level of clinical experience [19]. The most frequent errors made in palpation of the spleen involve incomplete relaxation of the abdominal musculature of the patient and the musculature of the examiner's hand. Effectiveness in palpating the spleen can be maximized by paying attention to the following:

- With the patient supine, allow the patient to feel the examining hand on the abdomen and to become adjusted to its presence before pressing down. Do not suddenly increase pressure during palpation, as an enlarged spleen may be quite tender (particularly if it has enlarged quickly) and the patient may be reluctant to allow the examination to continue.
- Make sure that the patient is relaxed, with arms at the sides of the abdomen. If the arms are raised, this may stiffen the abdominal musculature and make examination more difficult.
- Relaxation of the patient can be improved if the legs and neck are slightly flexed. Relaxation of the examiner can be improved by being comfortably seated in a chair alongside the patient's bed or examining table, with the examiner on the patient's right side, the right hand doing the palpation and the left hand underneath and supporting the patient's left lower rib cage [17]. A spleen that is only minimally enlarged will be quite movable with respiration and may be palpable only at the end of inspiration. Using a light touch, with the skin depressed under the left costal margin, one can feel a minimally enlarged spleen as a rounded edge with the consistency of normal liver, which slips under the examiner's fingers at the end of inspiration and back on expiration. A normal spleen is soft and non-tender [17].

In more extreme cases, the enlarged spleen extends across the midline and may even be palpable in the right upper quadrant. The presence of a notch or indentation on the medial splenic edge is a further indication that the mass is spleen and not the left kidney or a pancreatic pseudocyst [17]. The presence of exquisite splenic tenderness suggests the presence of infarction or perisplenitis in such massively enlarged spleens [17].

Epidemiology of splenomegaly

The incidence of splenomegaly is strongly dependent on the geographical location reflecting the etiology as causes may vary with diseases prevalent in a given area. In Asia and Africa, tropical splenomegaly due to malaria, sickle cell disease or schistosomiasis is very common. Concerning the underlying causes of splenomegaly differences between developing and developed countries are quite obvious. Even between hospitals from different regions in the same country, the causes of splenomegaly can vary. The spleen size may be influenced by variation between individuals and by different ethnicities and interfering genetic or infectious factors. In Western world countries, the underlying diseases in all age groups causing splenomegaly are, in the order of decreasing frequency: hematological diseases, hepatic disease, infections, congestive or inflammatory diseases, and metabolic storage diseases. In pediatric patients within the group of hematological disorders, the most common diagnoses associated with splenomegaly at diagnosis are acute leukemia, lymphoma, hemolytic anemia, chronic myeloid leukemia, and juvenile myelomonocytic leukemia [18].

Pathogenesis and etiology of splenomegaly

General mechanisms of splenic enlargement are proliferation of lymphoid tissue. infiltration by neoplastic cells or lipid-laden macrophages, extramedullary hematopoiesis, increase of phagocytic cells, and obstruction of vascular drainage leading to congestion [2].

There is a wide spectrum of causes of splenomegaly, which includes: infectious mononucleosis, systemic infection (tuberculosis, infective endocarditis, malaria, HIV, cat scratch disease, babesiosis), hematologic malignancy (acute lymphoblastic leukemia, acute myelogenous leukemia), lymphoproliferative diseases (lymphoma, Langerhans cell histiocytosis, hematophagocytic lymphohistiocytosis, autoimmune lymphoproliferative syndrome, Castleman disease and POEMS syndrome), hemolytic anemias (RBC membrane defects, RBC enzyme defects, hemoglobinopathies,

autoimmune hemolytic anemia, other acquired hemolytic anemias), liver disease (biliary atresia, viral hepatitis, Wilson disease, galactosemia, primary sclerosing cholangitis, alpha-1-antitrypsin deficiency, alagille syndrome, cystic fibrosis), portal vein thrombosis, autoimmune disease (SLE, JRA), primary immunodeficiency (common variable immunodeficiency), storage disorders (Gaucher disease, Niemann-pick disease, mucopolysaccharidosis, other lysosomal storage disorders), space-occupying lesions (hemangioma, hamartoma, cysts, intracapsular hematoma caused by trauma) [12].

In children, splenomegaly most commonly is the result of an exuberant response of the immune system to infections by many different agents, disorders of immune regulation, or abnormal destruction of red blood cells. However, infiltration with neoplastic or storage disease cells, abnormal splenic blood flow as in portal hypertension, and space-occupying lesions also must be considered [17]. In children with hereditary spherocytosis, sickle cell anemia (SCA), thalassemia, infections, or malignant diseases, serial assessment of splenic size is important in order to define the need for, or the response to, appropriate therapeutic interventions. As an example, in the child with SCA, a rapidly enlarging spleen with a falling hematocrit suggests the presence of a splenic sequestration crisis, which is a medical emergency associated with a mortality rate as high as 10 to 15 percent [12].

Causes of a massively enlarged spleen

A spleen is considered to be massively enlarged if its lower pole is within the pelvis or if it crosses the midline. Only a few diseases cause this degree of splenic enlargement. These include the following disorders, each of which is discussed elsewhere on the appropriate topic reviews: [12].

- Leukemia (lymphoid or myeloid, usually chronic, as in chronic myeloid leukemia)
- Thalassemia major
- Lymphoma, usually the more indolent variants
- Langerhans cell histiocytosis
- Autoimmune lymphoproliferative syndrome (Canale Smith syndrome) [20]
- Castleman disease [12]
- Gaucher disease [22]
- AIDS with Mycobacterium avium complex [23]
- Kala-azar [24]
- Hyperreactive malarial splenomegaly syndrome, also called tropical splenomegaly syndrome [25]
- Hemophagocytic lymphohistiocytosis/familial erythro-phagocytic lymphohistiocytosis [21,26,27].

Among infective etiologies, leishmania represents an important one due difficulty in its treatment [28]. Leishmaniasis covers a wide spectrum of diseases from cutaneous lesions to fatal visceral leishmaniasis (VL), caused by various species of leishmania parasite. The clinical manifestation of the disease has 3 forms, namely cutaneous, mucocutaneous, and visceral [29]. VL (kala-azar) is caused by different species of leishmania such as donovani, Chagas, and infantum, each with a certain geographical distribution [30]. This disease is spread by the bite of infected sandflies, with a body length of 2 to 3 mm, that feed from humans and animals. The reservoirs of this disease, which is transmitted by different species of sandflies, include dogs and canines (fox and jackal).

Transmission through the bite of an infected rodent, organ transplant, accidental inoculation among laboratory staff, congenital transmission, and blood transfusion are among rare cases.[31,32] Acute leishmania is the most common type of leishmania among children, specifically children aged 2 months to 2 years. The incubation period of the disease lasts from several weeks to several months. Diagnosis of VL in infancy may be delayed due to the long incubation period and nonspecific initial symptoms [33].

Regarding malaria, it is the most common vector-borne disease in Yemen, with an annual incidence of about 900,000 cases and approximately 60% of the total population considered to be at risk of the disease. Plasmodium falciparum accounts for 95% of the cases [34]. According to WHO report of 2020, Yemen takes the second place after Sudan in the incidence of malaria Eastern Mediterranean Region [34]. Yemen is now the only country in the Arabian Peninsula that remains plagued with malaria, with considerable mortality and morbidity. Unfortunately, the country has been unstable for many years, suffering from civil wars, a deteriorating economic and health status [35-38].

Evaluation of the child with unexplained splenomegaly

The history may provide valuable clues as to the possible cause of splenomegaly. In children with a recent viral syndrome including fever, pharyngitis, and malaise, one would naturally include common viral infections (eg, infectious mononucleosis, cytomegalovirus, hepatitis) as an etiology [39,40]

In the patient with systemic complaints such as fever, night sweats, malaise, and/or weight loss, an enlarged spleen may reflect activity of a systemic disease, such as lymphoma, AIDS, systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis, malaria, tuberculosis, or hematologic disorders (eg, acute or chronic leukemias), that may already have been diagnosed. In such cases, the spleen may revert to normal size when the underlying disease is brought under control with appropriate therapy [17].

The problem often confronting the examining physician is that the child presents with splenomegaly for which no prior diagnosed or evident condition can be considered responsible. A reasonable and standard approach to such patients begins with an accurate history (including recent travel information), physical examination, complete blood count with white blood cell differential and platelet count, liver function studies, urinalysis, and chest x-ray [17].

Testing for the presence of antibodies to Epstein-Barr virus, cytomegalovirus, parvovirus, HIV-1, or reduced acid beta-glucosidase activity in white blood cells in Gaucher disease should be considered when no other causes for splenomegaly are apparent [22].

The complete blood count and white blood cell differential, along with a careful examination of the peripheral smear, often are of utmost importance in determining the cause of an enlarged spleen. The peripheral smear may yield sufficient clues to suggest an immediate diagnosis [41].

An alternative approach is to biopsy tissue depending upon the clinical suspicion. Thus, if infection is suspected, a lymph

node or bone marrow biopsy may be indicated, or a liver biopsy if liver disease is suspected [23]. Without a specific organ or tissue to biopsy, a reasonable approach would be performance of a bone marrow aspiration with biopsy and culture. Conditions such as lipid storage diseases, disseminated mycobacterial or granulomatous disease, hemophagocytic syndrome, and occult tumors may be diagnosed in this way [17].

So, when a child is found to have hepatosplenomegaly all the other signs and symptoms should be taken in to account in order to narrow the diagnosis and do necessary work up in that line. So, clinical findings like jaundice, anemia, lymphadenopathy, pyrexia, ascites, arthritis, rashes, nephromegaly, cardiomegaly, malabsorption, mental retardation, seizure etc. should be carefully examined in order to suspect the etiology [42].

Objectives

General objective

To determine clinical profile, and spectrum of etiologies of splenomegaly among children attending to Al-Kuwait University Hospital in Sana'a-Yemen.

Specific objectives

1. To explore demographic characteristics of the studied cases (age, gender, resident area, father's job, and family income).
2. To determine characteristics related to splenomegaly (degree of splenomegaly, associated hepatomegaly, associated lymphadenopathy, associated anemia, and associated hypersplenism).
3. To find out clinical manifestations of cases with splenomegaly.
4. To determine possible diagnostic etiologies of splenomegaly.
5. To test correlation between etiology of splenomegaly and age.
6. To test correlation between etiology of splenomegaly and gender.

Chapter 2: Methods And Materials

Study design

Hospital-based retrospective descriptive study.

Study duration

The study has been conducted over two years; from January 2020 to December 2021.

Sample size

Two-hundred children with splenomegaly were included in this study.

Inclusion criteria

Clinically diagnosed children with splenomegaly of both gender in the age group under 15 years were included in this study.

Exclusion criteria

Children in neonatal periods, or more than 15 years in age were excluded from this study. Cases with incomplete data were excluded as well.

Data collection

Data were collected from pediatrics department at Al-Kuwait Hospital. A questionnaire was used to collect data which included demographic data of child (age, gender, resident area, father's job, family income), data related to characteristics of splenomegaly (degree of splenomegaly, associated hepatomegaly, associated lymphadenopathy, associated anemia, and associated hypersplenism), data related to clinical manifestations, and data related to etiology of splenomegaly.

The diagnosis of splenomegaly major was made by clinical examination and confirmed by ultrasonography. Splenomegaly is classified in to three grades based on its length as mild (1-3cms), moderate (4-7cms) and massive (more than 7cms). Then laboratory investigations were asked according to the case to determine the etiology.

Data Analysis

After being collected, data were coded and processed using the Statistical Package for Social Sciences (SPSS) version 23. Data were displayed in table and graphs, and summarized as counts, percentages, and means. Chi square was used to find association between age; gender and etiology. The test was considered to be significant when p value less than 0.05.

Ethical consideration

Before starting in data collection, permission was obtained from the hospital authorities. All data were dealt confidentially and no indicative personal information -like names- was disseminated.

Limitations

Incomplete data for some cases was the main limitation.

Being a study at a resource limited governmental hospital, it was expected that not all investigations were done for every patient as recommended by doctors and this would hinder the results on etiology

Chapter 3: Results

Distribution of the studied cases according to gender

In present study, out of 200 splenomegaly cases, the disease is slightly higher in males (53.5% males, vs 46.5% females).

Distribution of the studied cases according to age

The mean age of splenomegaly cases was 7.5±3.3 years (range: 1 – 15 years). The age group from 1 to 5 years represented 39%, the age group from 6 to 10 years represented 43.5%, and the age group from 11 to 15 years represented only 17.5%.

Table 2: Distribution of the studied cases according to age

Age categories	Count	Percent
From 1 to 5 years	78	39.0%
From 6 to 10 years	87	43.5%
From 11 to 15 years	35	17.5%
Total	200	100%

Mean ± SD = 7.5 ± 3.3 years, range: 1 – 15 years.

Distribution of the studied cases according to resident area

In present study, most of cases (60%) were coming from rural areas. This may indicate that rural areas have poor healthcare services; so people seek healthcare in main cities like Sana'a.

Distribution of patients according to occupation of father

A considerable proportion of fathers (37.5%) are jobless. Manual workers represented 27.5%, employee represented 26%, and professional workers represented 9%.

Table 3: Distribution of patients according to occupation of father

Occupation of father	Number	Percent
Manual worker	55	27.5%
Employee	52	26.0%
Professional	18	9.0%
Jobless	75	37.5%
Total	200	100%

Distribution of cases according to family income

Most of cases (71.5%) are children of families that have an unsatisfactory income. The minority of them (28.5%) are belonged to families that have a satisfactory income.

Degree of splenomegaly

Most of cases (74%) have a moderately enlarged spleen. Mild degree of splenomegaly is found in 10% of cases, while cases with massive splenomegaly represented only 16%.

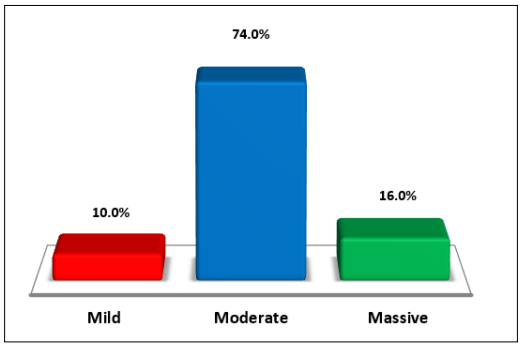

Figure 2: Degree of splenomegaly

Associated hepatomegaly

Cases with enlarged liver (hepatosplenomegaly) represented 58.5%. Splenomegaly is frequently associated with hepatomegaly because they are usually affected by the same pathology

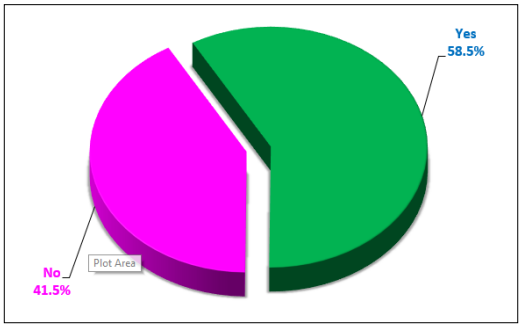

Figure 3: Associated hepatomegaly

Associated lymphadenopathy

The majority (77%) of the studied cases have no associated lymphadenopathy. Only 46 cases (23%) presented with associated enlarged lymph nodes.

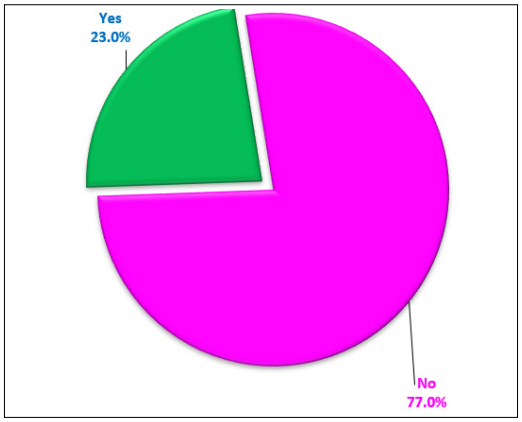

Figure 4: Associated lymphadenopathy

Associated anemia

The majority (79%) of the studied cases have an associated anemia. The anemia in these cases may result from hemolysis or infiltrative disorders to the bone marrow.

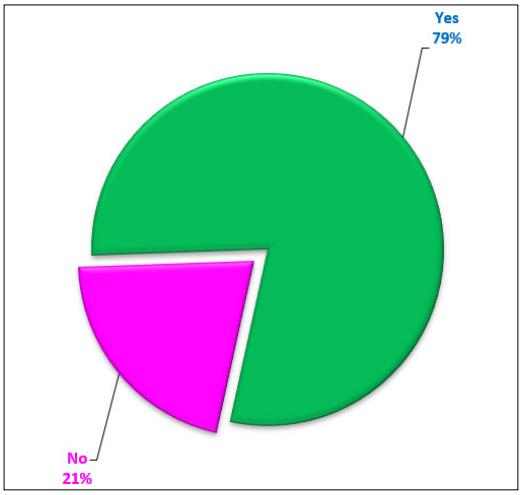

Figure 5: Associated anemia

Associated hypersplenism

Hypersplenism was documented for 16% of cases. Cytopenias (neutropenia, anemia, and/or thrombocytopenia) may be present, as these formed elements can be trapped in an enlarged spleen, giving the nonspecific picture termed “hypersplenism.”

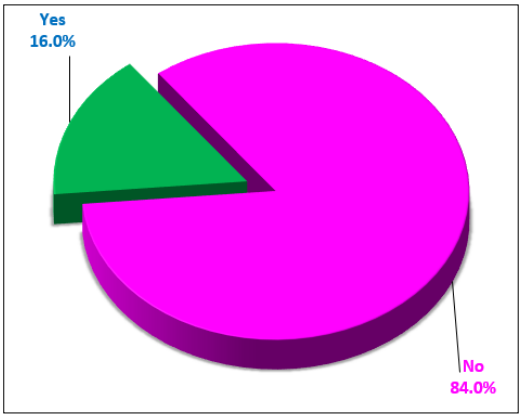

Figure 6: Associated hypersplenism

Clinical manifestations of the studied cases

Figure below shows the most frequent clinical manifestations among cases were fever, pallor, weakness, and abdominal distention in rates of 86.5%, 78%, 60%, and 48% respectively. Followed by jaundice, weight loss, and abdominal pain in rates of 33.5%, 27.5%, and 24% respectively. Other less common symptoms were dyspnea, edema, and bleeding in rates of 22.5%, 18%, and 13.5% respectively.

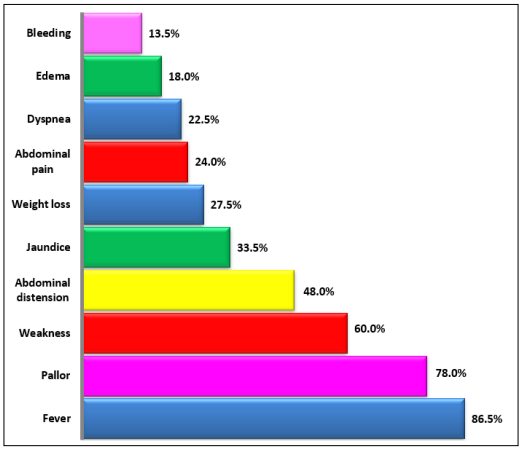

Figure 7: Clinical manifestations of the studied cases

Etiologies of splenomegaly

Hematological and infective disorders are the most frequent etiologies which represented 38% and 34% respectively. Other causes include storage disease, congestive causes, connective tissue disease in rates of 6%, 4%, and 3.5% respectively. Miscellaneous and idiopathic cases represented 4.5% and 10% respectively.

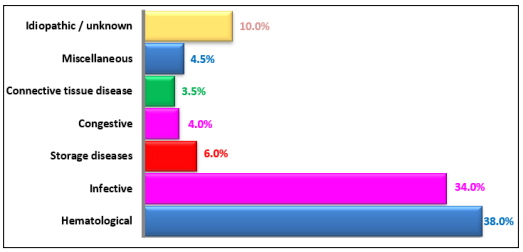

Figure 8: Etiologies of splenomegaly

Specific causes of splenomegaly among the studied cases

Among 38% of hematological disorders, 27% caused by hemolytic anemias, 9% caused by lymphomas, and 2% caused by leukemias.

Among 34% of infective disorders, malaria represented 19%, visceral leishmania represented 6%, enteric fever represented 5%, and septicemia represented 4%.

Among 6% of storage disease, glycogen storage disease represented 3.5%, and mucopolysaccharidosis represented 2.5%.

Among 4% of congestive blood flow, portal hypertension represented 2.5%, and congestive heart failure represented 1.5%.

Table 4: Specific causes of splenomegaly among the studied cases

Etiology of splenomegaly	Count	Percent
Hematological	76	38.0%
Hemolytic diseases	54	27.0%
Lymphoma	18	9.0%
Leukemia	4	2.0%
Infective	68	34.0%
Malaria	38	19.0%
Visceral leishmania	12	6.0%
Enteric fever	10	5.0%
Septicemia	8	4.0%
Storage diseases	12	6.0%
Glycogen storage disease	7	3.5%
Mucopolysaccharidosis	5	2.5%
Congestive	8	4.0%
Portal hypertension	5	2.5%
Congestive heart failure	3	1.5%
Connective tissue disease	7	3.5%
Miscellaneous	9	4.5%
Idiopathic / unknown	20	10.0%

Correlation between etiology of splenomegaly and age

As shown in the table below, there is no special pattern of etiology distribution of splenomegaly among different age groups (p value >0.05).

Table 5: Correlation between etiology of splenomegaly and age

Etiology of splenomegaly	From 1 to 5 years		From 6 to 10 years		From 11 to 15 years	
	Count	Percent	Count	Percent	Count	Percent
Hemolytic diseases	30	(38.5%)	37	(42.5%)	9	(25.7%)
Infective	25	(32.1%)	29	(33.3%)	14	(40.0%)
Storage diseases	4	(5.1%)	7	(8.0%)	1	(2.9%)
Congestive	6	(7.7%)	0	(0.0%)	2	(5.7%)
Connective tissue disease	2	(2.6%)	3	(3.4%)	2	(5.7%)
Miscellaneous	4	(5.1%)	3	(3.4%)	2	(5.7%)
Idiopathic / unknown	7	(9.0%)	8	(9.2%)	5	(14.3%)
Total	78	(100.0%)	87	(100.0%)	35	(100.0%)

P value = 0.456

Correlation between etiology of splenomegaly and gender
As shown in the table below, there is no special pattern of etiology distribution of splenomegaly according to gender (p value >0.05).

Table 6: Correlation between etiology of splenomegaly and gender

Etiology of splenomegaly	Males		Females	
	Count	Percent	Count	Percent
Hemolytic diseases	40	(37.4%)	36	(38.7%)
Infective	39	(36.4%)	29	(31.2%)
Storage diseases	9	(8.4%)	3	(3.2%)
Congestive	2	(1.9%)	6	(6.5%)
Connective tissue disease	3	(2.8%)	4	(4.3%)
Miscellaneous	2	(1.9%)	7	(7.5%)
Idiopathic / unknown	12	(11.2%)	8	(8.6%)
Total	107	(100.0%)	93	(100.0%)

P value = 0.149

Chapter 4: Discussion
Splenomegaly is a frequent and important sign in clinical practice. It is prominent among infants and children. The most important is its possible association with serious disorders including hematological malignancies to which no age group is exempted [43].

The aim of this study was to determine clinical profile, and spectrum of etiologies of splenomegaly among children attending to Al-Kuwait Hospital in Sana'a.

In present study, out of 200 splenomegaly cases, the disease is slightly higher in males (53.5% males, vs 46.5% females). This result is consistent with result in a study by Champatiray et al., who found that males (58.7%) outnumbered females (41.3%) [43]. Similarly, Rajender and Batruni reported males predominance (64%) [44].

In current study, the mean age of splenomegaly cases was 7.5±3.3 years (range: 1 – 15 years). The age group from 1 to 5 years represented 39%, the age group from 6 to 10 years represented 43.5%, and the age group from 11 to 15 years represented only 17.5%. These findings are consistent with findings by Champatiray et al., who found that children from one year to 5 years' age group constituted 45.3% followed by 6 years to 10 years and 11 years to 14 years' age group which comprised 41.3% and 13.3% respectively.[42] Similar findings also reported by Somaiah et al [45].

In present study, most of cases (60%) were coming from rural areas. This may indicate that rural areas have poor healthcare services; so people seek healthcare in main cities like Sana'a. In addition, rural areas are more to be endemic for infectious disease like leishmania and malaria. This finding is consistent with finding by Al-Mekhlafi et al who reported that and residing in a rural area was significantly associated with malarial infection [46].

A considerable proportion of fathers (37.5%) are jobless. Manual workers represented 27.5%, employee represented 26%, and professional workers represented 9%. This result is consistent with other studies [46]. Jobless fathers in this study represented 37.5% which is high comparing to 14.85% mentioned in a previous report, and is reflecting worse economic situation as a result of continuous armed conflict and siege [47].

Most of cases (71.5%) in this study are children of families that have an unsatisfactory income. The minority of them (28.5%) are belonged to families that have a satisfactory income. This result is consistent with other studies [46]. This economic status is not different from general economic status for Yemeni population in which most of population lives under poverty line [48-50]. Similar findings were reported in other developing countries [42,45].

Most of cases (74%) in this study have a moderately enlarged spleen. Mild degree of splenomegaly is found in 10% of cases, while cases with massive splenomegaly represented only 16%. These findings are consistent with findings by Rajender &Patruni who observed that 8% of cases had mild degree of splenomegaly, and 72% had moderate degree, and 20% had massive degree of splenomegaly [44].

In current study, cases with enlarged liver (hepatosplenomegaly) represented 58.5%. The rate is close to 62% associated hepatomegaly reported by Rajender and Batruni [44]. Splenomegaly is frequently associated with hepatomegaly because they are usually affected by the same pathology [18].

The majority (77%) of the studied cases have no associated lymphadenopathy. Only 46 cases (23%) presented with associated enlarged lymph nodes. This rate of lymphadenopathy is lower than 28% reported by Rajender and Batruni [44].

Results showed that the majority (79%) of the studied cases have an associated anemia. The anemia in these cases may result from hemolysis or infiltrative disorders to the bone marrow. Associated anemia also noted in nearly half (48%) of cases studied by Rajender and Batruni [44].

Results of this study showed that the most frequent clinical manifestations among cases were fever, pallor, weakness, and abdominal distention in rates of 86.5%, 78%, 60%, and 48% respectively. Followed by jaundice, weight loss, and abdominal pain in rates of 33.5%, 27.5%, and 24% respectively. Other less common symptoms were dyspnea, edema, and bleeding in rates of 22.5%, 18%, and 13.5% respectively.

Similarly, Champatiray et al., found that the most common presenting features was anemia (79.3%) followed by fever (78%), jaundice (38.7%), abdominal pain (22.7%), abdominal distension (37.3%), lymphadenopathy (12.6%), edema (26%), bleeding (16.7%), and dyspnea (22.7%) [42]. Somaiah et al., found that the most clinical presentations were anemia (80.7%) followed by fever (66.7%), jaundice (37.3%), abdominal pain (30.7%), abdominal distension (18%), lymphadenopathy (20%), and dyspnea edema (8%) [45].

Similar manifestations but in different rates reported by Bricks et al., who reported that the most frequent manifestations were fever (43.8%), pallor (29.2%), weight loss (23.6%), jaundice (15.7%), abdominal pain (14.6%), lymphadenopathy (10.1%), vomiting (9.0%), urinary (9.0%), diarrhea (7.9%), and purpura (4.5%) [51].

Hematological and infective disorders are the most frequent etiologies which represented 38% and 34% respectively. Other causes include storage disease, congestive causes, and connective tissue disease in rates of 6%, 4%, and 3.5% respectively. Miscellaneous and idiopathic cases represented 4.5% and 10% respectively.

The most common causes for an enlarged spleen vary from country to country, according to prevailing incidences of infection and genetic disorders. As an example, in a study of 22 children with splenomegaly from Pakistan, causes included beta thalassemia (55%), hematologic malignancy (18%), hemolytic anemia other than thalassemia (14%), storage disorders (9%), and congenital sideroblastic anemia (4%) [43].

A study conducted in India reported that the most frequent causes of hepatosplenomegaly were infectious (50%) followed by hematological (36%) and congestive (6%) causes Bricks et al., found that the major etiologies for splenomegaly were hematologic disorders, infection, metabolic, neoplastic, and congestive in rates of 78.7%, 47%, 8%, 5.6%, and 3.3% respectively [51]. Similarly, Rajender and Batruni found that the commonest etiologies of splenomegaly cases were infectious (44%) followed by hematologic disorders (36%), neoplastic (6%), and congestive causes (4%) [54].

In a study by Emelie et al hematological diseases were the underlying causal diagnosis in 39%; hepatic diseases in 18%, infectious disease in 10%, other diseases in 8%, and 25% of patients with splenomegaly remained without a causal diagnosis [42].

The incidence of the cause of splenomegaly is subjected to geographical variation. Studies that have been conducted in western countries 1996-1999 have showed a large variation in the distribution of the underlying diagnosis. Hematological diseases have been reported to account for 16-66%, hepatic diseases for 9-41%, infectious diseases for 9-36%, inflammatory or congestive diseases for 4-10%, primary splenic causes for 1-6%, and 1-2% remain idiopathic [52]. However, it can be roughly estimated that in western countries, myeloproliferative disorders; hemolytic anemia; leukemia; and malignant lymphomas account most of the cases [53]. In tropical countries, however, the incidence of these hematological causes of splenomegaly is swamped by the great preponderance of splenic enlargement caused by the parasitic tropical infections, malaria, leishmaniasis and schistosomiasis. The "Tropical Splenomegaly syndrome" is seen in large numbers in patients in New Guinea and Central Africa. Splenomegaly is also associated with thalassemia, which have a wide distribution throughout tropics. Because of the multiple factors responsible for Splenomegaly in tropical regions, more than one pathology contributes to splenomegaly in a particular patient [54]. A study on splenomegaly in infants and children in 1973, found congestive disorders as the most common cause of splenomegaly followed by hematologic [55]. which differs from observations in the present study. In the United States, infection was the most common cause of splenomegaly in children in 1979 [56]. A study from Brazil in 1998 concluded infections as the most common cause of splenomegaly [51].

Among 38% of hematological disorders in this study, 27% caused by hemolytic anemias, 9% caused by lymphomas, and 2% caused by leukemias. These observations are somewhat consistent with observations by Champatiray & colleagues who found that hemolytic anemia represented 27.9%, and malignancy represented 8.1% [42].

In current study, malaria was reported in 19% of cases. This rate is lower than 29.3% malaria cases reported by Somaiah et al [42], and also lower than 25.2% observed by Champatiray & colleagues [43].

Enteric fever accounted for 5% in this study which is lower than 13.3% observed by Somaiah et al [45]. Septicemia accounted for 4% in this study which is higher than 2.7% observed by Somaiah et al [45].

As regard for visceral leishmania in this study, it represented 6% of cases. This rate of leishmania is near to 4.5% reported by Bricks et al from Brazil [51]. Leishmaniasis is a public health problem in Yemen, where it has a nationwide distribution [56]. It is endemic in Yemen. There is no solid data on the incidence of leishmania infections in Yemen, but the disease is certainly underreported, especially in women and children. Visceral leishmaniasis (VL) or kala-azar is a major health problem in Yemen and affects predominantly infants and young children [57]. It is primarily widespread in arid and semi-arid areas [58]. This diagnosis is generally missed or delayed for months or years, and some patients are treated blindly [57,59]. According to the WHO, leishmaniasis affects around two million people annually, 500000 cases of which are of the visceral form. It is estimated that 350 million people are exposed to the risk of infection, with a global prevalence of 12 million infected individuals [57].

Among 6% of storage disease, glycogen storage disease represented 3.5%, and mucopolysaccharidosis represented 2.5%. These rates are slightly higher than rates by Champatiray & colleagues where glycogen storage disease and mucopolysaccharidosis represented 0.6% each [42].

In current study, cases of congestive blood flow represented 4% which is close to 5% reported by Champatiray & colleagues [42].

In current study, connective tissue disease represented 3.5% which is close to 4% reported by Champatiray & colleagues [42].

Chapter 5: Conclusion & Recommendations

Splenomegaly is an important sign in pediatrics. In most cases it is the result of a systemic disease. The underlying etiologies observed in this study were hematologic (38%), infectious (34%), infiltrative, storage disease (6%), congestive (4%), connective tissue disease (3.5%), miscellaneous (4.5%), and unknown etiology (10%). Most cases seen in the age group under 10 years, and most of cases presented with moderate degree of splenomegaly.

Proper investigation workup is mandatory for identifying causes of splenomegaly and management. Since, the clinical outcome of patients who presented lately is much poorer than those presented earlier, the greater degree of suspicion and quick referral can improve the outcome significantly. For conditions like storage disorders, connective tissue diseases and leukemias, a greater degree of suspicion regarding these conditions and proper workup and early referral to respective specialized centers is mandatory.

Acknowledgement

I would like to express great thanks to the all lecturers and academic staff, and all members of Scientific Council of Pediatrics.

My thanks and gratitude to my family for their unfailing support and continuous encouragement throughout my years of study and through the process of researching and writing this thesis. This accomplishment would not have been possible without them. Thank you.

The researcher

References

1. Paterson A, Frush DP, Donnelly LF, Foss JN, O'Hara SM. A pattern-oriented approach to splenic imaging in infants and children. Radiographics. 1999. 19: 1465-1485.
2. Pozo AL, Godfrey EM, Bowles KM. Splenomegaly: investigation, diagnosis and management. Blood reviews. 2009. 23: 105-111.
3. Lakshmanaswamy A. Disorders of Gastrointestinal System. 3 ed: Wolters Kluwer Health/Lippincott Williams and Wilkins. 2013.
4. Hilmes MA, Strouse PJ. The pediatric spleen. Seminars in Ultrasound, CT and MRI, Elsevier. 2007.
5. O'Reilly RA. Splenomegaly in 2,505 patients at a large university medical center from 1913 to 1995. 1963 to 1995: 449 patients. Western journal of medicine. 1998. 169: 88.
6. Odom LF, Tubergen DG. Splenomegaly in children: Identifying the cause. Postgraduate Medicine. 1979. 65: 191-200.
7. Stacey S, William F. Morphogenesis of the Liver and Biliary System. In: R. Kliegman, B. Stanton, J. St. Geme, N. Schor, editors. Nelson's textbook of pediatrics. 2017. 1918-1919.
8. Malarkey DE, Johnson K, Ryan L, Boorman G, Maronpot RR. New insights into functional aspects of liver morphology. Toxicologic pathology. 2005. 33: 27-34.
9. Benz E. Clinical manifestations and diagnosis of the thalassemias. Up To Date. 2013.
10. Hosea S, Brown E, Burch C, Berg R, Frank M. Impaired immune response of splenectomised patients to polyvalent pneumococcal vaccine. The Lancet. 1981. 317: 804-807.
11. Giebink GS, Le CT, Schiffman G. Decline of serum antibody in splenectomized children after vaccination with pneumococcal capsular polysaccharides. The Journal of pediatrics. 1984. 105: 576-582.
12. Vichinsky EP. Overview of the clinical manifestations of sickle cell disease. In: UpToDate; Jennifer S Tirnauer, editor. UpToDate, Waltham. 2022.
13. Pizzi M, Fuligni F, Santoro L, Sabattini E, Ichino M, et al. Spleen histology in children with sickle cell disease and hereditary spherocytosis: hints on the disease pathophysiology. Human pathology. 2017. 60: 95-103.
14. Gehrs BC, Friedberg RC. Autoimmune hemolytic anemia. American journal of hematology. 2002 69: 258-271.
15. Barkun AN, Camus M, Green L, Meagher T, Coupal L, et al. The bedside assessment of splenic enlargement. The American journal of medicine. 1991. 91: 512-518.
16. Megremis SD, Vlachonikolis IG, Tsilimigaki AM. Spleen length in childhood with US: normal values based on age, sex, and somatometric parameters. Radiology. 2004. 231: 129-134.
17. McClain K, Mahoney D, Armsby C. Approach to the child with an enlarged spleen. In: UpToDate; William C Mentzer, editor. UpToDate: Waltham, MA. 2022.
18. Suttorp M, Classen CF. Splenomegaly in children and adolescents. Frontiers in Pediatrics. 2021. 9.
19. Tamayo SG, Rickman LS, Mathews WC, Fullerton SC, Bartok AE, et al. Examiner dependence on physical diagnostic tests for the detection of splenomegaly. Journal of general internal medicine. 1993. 8: 69-75.
20. Sneller MC, Wang J, Dale JK, Strober W, Middelton LA, et al. Clinical, immunologic, and genetic features of an autoimmune lymphoproliferative syndrome associated with abnormal lymphocyte apoptosis. Blood, The Journal of the American Society of Hematology. 1997. 89: 1341-1348.
21. Arico M, Janka G, Fischer A, Henter J, Blanche S, et al. Hemophagocytic lymphohistiocytosis. Report of 122 children from the International Registry. FHL Study Group of the Histiocyte Society. Leukemia. 1996. 10: 197-203.
22. Hughes D, Sidransky E. Gaucher disease: Pathogenesis, clinical manifestations, and diagnosis. In: UpToDate; Sihoun Hahn, editor. UpToDate: Waltham, MA. 2022.
23. Swaroop J, O'Reilly RA. Splenomegaly at a university hospital compared to a nearby county hospital in 317 patients. Acta haematologica. 1999. 102: 83-88.
24. Bern C. Clinical manifestations and diagnosis of visceral leishmaniasis. In: date Ut, editor.: Waltham, MA. 2016.
25. Leoni S, Buonfrate D, Angheben A, Gobbi F, Bisoffi Z. The hyper-reactive malarial splenomegaly: a systematic review of the literature. Malaria journal. 2015. 14: 1-11.
26. Al-Samkari H, Berliner N. Hemophagocytic lymphohistiocytosis. Annual review of pathology: mechanisms of disease. 2018. 13: 27-49.
27. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. Blood, The Journal of the American Society of Hematology. 2011.118: 4041-4052.
28. Haidar NA, Diab A, El-Sheik A. Visceral Leishmaniasis in children in the Yemen. Saudi medical journal. 2001. 22: 516-519.
29. Wilson ME, Jeronimo SM, Pearson RD. Immunopathogenesis of infection with the visceralizing Leishmania species. Microbial pathogenesis. 2005. 38: 147-160.
30. Ready PD. Epidemiology of visceral leishmaniasis. Clinical epidemiology. 2014. 6: 147.
31. Kumar R, Nylén S. Immunobiology of visceral leishmaniasis. Frontiers in immunology. 2012. 3: 251.
32. Sundar S, Rai M. Laboratory diagnosis of visceral leishmaniasis. Clinical and vaccine immunology. 2002. 9: 951-958.

33. Palumbo E. Visceral leishmaniasis in children: a review. Minerva pediatrica. 2010. 62: 389-395.
34. World Health Organization. World malaria report 2020: World Health Organization; 2021.
35. Laub Z, Robinson K. Yemen in crisis. Council on Foreign Relations. 2016. 19: 1-7.
36. Burki T. Yemen health situation "moving from a crisis to a disaster". The Lancet. 2015. 385: 1609.
37. El Bcheraoui C, Jumaan AO, Collison ML, Daoud F, Mokdad AH. Health in Yemen: losing ground in war time. Globalization and health. 2018.14: 1-12.
38. Qirbi N, Ismail SA. Health system functionality in a low-income country in the midst of conflict: the case of Yemen. Health policy and planning. 2017. 32: 911-922.
39. Sullivan JL. Clinical manifestations and treatment of Epstein-Barr virus infection. In: UpToDate; Martin S Hirsch SLK, editor. UpToDate: Waltham, MA. 2022.
40. Demmler-Harrison G. Cytomegalovirus infection and disease in newborns, infants, children and adolescents. In: UpToDate; Morven S Edwards LEW, editor. UpToDate: Waltham, MA. 2022.
41. Rosenthal DS, Schrier S, Timauer J. Evaluation of the peripheral blood smear. In: UpToDate; Robert A Brodsky, editor. UpToDate: Waltham, MA. 2022.
42. Champatiray J, Panigrahi D, Mondal D, Satpathy SK. Study of aetiological profile, clinical presentation and outcome of hepatosplenomegaly in children between 1 month and 14 years of age. International Journal of Contemporary Pediatrics. 2017. 4: 927-932.
43. Ali N, Anwar M, Ayyub M, Nadeem M, Ejaz A, et al. Hematological evaluation of splenomegaly. JOURNAL-COLLEGE OF PHYSICIANS AND SURGEONS OF PAKISTAN. 2004. 14: 404-406.
44. Rajender PR, Patruni M. Assessment of etiological factors and clinical outcome of splenomegaly among the children admitted under paediatric department, Siddipet district, Telangana state. International Journal of Paediatrics and Geriatrics. 2020. 3: 25-27.
45. Somaiah G, Anusha G, Siddique AM, Srikanth B, Babu MS, Et Al. Study of etiological and clinical profile of hepatosplenomegaly in children between 1 month and 15 years of age. Scholars Journal of Applied Medical Sciences. 2014. 2: 554-557.
46. Al-Mekhlafi A, Al-Mekhlafi H, Mahdy M, Azazy A, Fong M. Human malaria in the highlands of Yemen. Annals of Tropical Medicine & Parasitology. 2011. 105: 187-195.
47. Alshebami A. Exploring the Potential of Microinsurance for challenging the Vulnerabilities in Poverty Sector of Yemen. International Journal for Modern Trends in Science and Technology. 2020. 6: 13-220.
48. Elayah M, Schulpen L, Abu-Osba B, Al-Zandani B. Yemen: A forgotten war and an unforgettable country. 2017.
49. Gallardo AR, Burkle FM, Ragazzoni L, Della Corte F. Yemen's unprecedented humanitarian crisis: implications for international humanitarian law, the Geneva convention, and the future of global health security. Disaster medicine and public health preparedness. 2016. 10: 701-703.
50. Bakather AM, Binsaeedu AS, Abbad AAB, Bajaber AO, Bawazir AA, et al. Healthcare of yemen: advancements and challenges. Current Politics and Economics of the Middle East. 2019. 10: 27-80.
51. Bricks LF, Cocozza AM, Resegue R, Sucupira ACS, Rodrigues D, et al. Experience in the evaluation of children with hepatosplenomegaly at a teaching ambulatory, Sao Paulo, Brazil. Revista do Instituto de Medicina Tropical de São Paulo. 1998. 40: 269-275.
52. Curovic Rotbain E, Lund Hansen D, Schaffalitzky de Muckadell O, Wibrand F, Meldgaard Lund A, et al. Splenomegaly–Diagnostic validity, work-up, and underlying causes. PLoS One. 2017. 12: e0186674.
53. Fawaz R, Baumann U, Ekong U, Fischler B, Hadzic N, et al. Guideline for the evaluation of cholestatic jaundice in infants: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. Journal of pediatric gastroenterology and nutrition. 2017. 64: 154-168.
54. Mitchell S Lewis. The spleen. In: A Victor Hoffbr, Daniel Catovsky, Edward GD, Tuddenham, editors. Postgraduate haematology. 5 ed. New York: Blackwell Publishing; 2005. p. 358-369.
55. Reddi YR, Jayalakshmi, SudhakarV. Splenomegaly in infants and children. (A study of 100 consecutive cases). Indian Pediatrics. 1973. 10: 177-180.
56. Hotez PJ, Fenwick A, Savioli L, Molyneux DH. Rescuing the bottom billion through control of neglected tropical diseases. The Lancet. 2009. 373: 1570-1575.
57. Hamid GA, Gobah GA. Clinical and hematological manifestations of visceral leishmaniasis in Yemeni children. Turkish Journal of Hematology. 2009. 26.
58. Ali A. Development of affordable molecular techniques for the diagnosis of leishmaniasis in Yemen: Gießen, Justus-Liebig-Universität, Diss., 2011. 2011.
59. Pearson RD, de Queiroz Sousa A. Clinical spectrum of leishmaniasis. Clinical infectious diseases. 1996. 1-11.