THE MAGNITUDE OF HYPER-REACTIVE MALARIA SPLENOMEGALY AMONG PATIENTS WITH MASSIVE SPLENOMEGALY AT MUHIMBILI NATIONAL HOSPITAL, TANZANIA

Flora N. Ndobho, MD

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By

Flora N. Ndobho

A Dissertation Submitted in (partial) Fulfillment of the Requirement for the Degree of Master of Medicine (Haematology and Blood Transfusion) of

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CERTIFICATION

The undersigned certify that she has read and hereby recommend for acceptance by Muhimbili University of Health and Allied Sciences a dissertation titled; **‘‘ The magnitude of hyper-reactive malaria splenomegaly among patients with massive splenomegaly at Muhimbili National Hospital, Tanzania’’,** in (partial**)** fulfilment for the degree of Master of Medicine (Haematology and Blood Transfusion) of the Muhimbili University of Health and Allied Sciences.

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Prof. Lucio Luzzatto

(Supervisor)

_____

Date

_____

Prof. Julie Makani

(Co-supervisor)

_____

Date

DECLARATION AND COPYRIGHT

I, **Dr Flora N. Ndobho**, declare that this **dissertation** is my own original work and that it has not been presented and will not be presented to any other university for a similar or any other degree award.

Signature..... **Date**.....

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DEDICATION

To my beloved husband Bavoo Junus and our sons Bavon Jeremy Junus and Timothy René Junus

ABSTRACT

Background: Hyper-reactive malarial splenomegaly (HMS) is a syndrome of massive splenomegaly occurring in a malarious region. There is limited information about the prevalence in Tanzania overall and how these patients present clinically.

Aim: To assess the magnitude of HMS among patients with massive splenomegaly at Muhimbili National hospital, Tanzania

Participants: All patients with massive splenomegaly aged 15 years and above who were seen at MNH for 3 months period, from January-March 2017

Study design: Descriptive cross sectional study

Methods: Consenting participants were recruited from the EMD, cold OPD and outpatient clinics of MNH, A structured questionnaire was used to obtain social demographic particulars; the same also recorded symptoms associated with massive splenomegaly, history of recurrent malaria, history of hepatitis, alcohol abuse, exposure to schistosomiasis, family history of hemoglobinopathies, signs and symptoms of portal hypertension. On physical examination pallor, jaundice, lymphadenopathy, spleen and liver sizes were recorded.

After exclusion of all other causes of massive splenomegaly, i.e. ≥ 10cm below left coastal margin, a diagnosis of HMS was made based on a patient coming from a malaria endemic country, and having a, raised serum IgM.

Results: in a total of 99 study participants, 5 were found to have HMS: 3 of these were females. The median age of HMS patients was 35 years. With respect to common complaints on presentation, all 5 patients had abdominal distension, all 5 had abdominal pain, and 4 had symptoms of anaemia. Upon physical examination, all patients had pallor, splenomegaly and hepatomegaly. All HMS patients had severe anaemia with a median (IQR) haemoglobin concentration of 6.4g/dl (5.0-7.5) and significantly raised serum IgM, which were well above 2SD above the local mean. Other causes of massive splenomegaly were also determined; 37

had chronic myeloid leukemia, 16 had lymphoma, 13 had chronic lymphocytic leukemia and 8 had acute leukemia. In 6 patients a clear diagnosis was not made and SCD in 4 patients.

Conclusion: These data confirm that, like in other malaria endemic countries, HMS exists in Tanzania. The fact that HMS only accounts for 5% of cases underscores the importance of a systematic approach to the differential diagnosis of massive spenomegaly. This work supports the notion that a very high (non-monoclonal) serum IgM level is the key to diagnosis.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

BMA	-	Bone marrow aspiration
CBC	-	Complete blood count
CLL	-	Chronic lymphoid leukemia
CML	-	Chronic myeloid leukemia
EMD	-	Emergency Medical Department
HMS	-	Hyperreactive malaria splenomegaly
HPLC	-	High performance liquid chromatography
IgM	-	Immuneglobulin M
MCV	-	Mean cell volume
MNH	-	Muhimbili National Hospital
MUHAS	-	Muhimbili University of health and allied sciences
OPD	-	Out-patient department
WHO	-	World Health Organization

DEFINITION OF KEY TERMS

Massive splenomegaly is enlargement of the spleen more than 1000g. Poulin et al defined it as a spleen greater than 20 cm or 10 cm below the left coastal margin.

Immunoglobulin M or IgM is a basic antibody that is produced by B cells. It is by far the physically largest antibody in the human circulatory system. It is the first antibody to appear in initial exposure to an antigen

CHAPTER ONE

1.0 INTRODUCTION

Hyper-reactive malarial splenomegaly (HMS) is the term used to indicate a syndrome of massive splenomegaly occurring in a malarious region, accompanied by lassitude, weight loss and a raised serum IgM. A clinical response to prolonged antimalarial prophylaxis is diagnostic (1).

Studies on the pathogenesis of HMS suggest a critical role of aberrant immunologic response to malaria antigens after repeated infection, resulting in splenic hypertrophy, sometimes associated with secondary hypersplenism (2). The interaction between repeated malarial infection and genetic factors class II HLA DR2, IGHG3G (Igg-3 chain C region) and enviromental factors lead to the production of cytotoxic IgM antisuppressor lymphocyte (CD8+) antibodies. This results in inhibition of suppressor Tcells which are the regulator IgM production. This ends up with uninhibited B-cell formation of IgM and cryoglobulins (IgM aggregates and immune complexes). The need to clear these macromolecular aggregates stimulates the reliculoendothelial system; leading to hyperplasia.

This causes the progressive and massive enlargement of the spleen and liver. The spleen is greatly enlarged and shows dilated sinusoids lined with reticulum cells with marked erythrophagocytosis and lymphocytic infiltration of the pulp. The liver shows sinusoidal dilatation, infiltration with lymphocytes, and hyperplasia of the Kupffer's cells with phagocytosis of cellular debris and red cells (3).
For diagnosing HMS, other causes of massive splenomegaly need to be excluded, such as (kal-azar), schistosomiasis (portal hypertension), myelofibrosis, chronic myeloid leukemia (CML) and lymphoproliferative disorders(4).

Antimalarial are the cornerstones of treatment of HMS. The selection of drug is based on the pattern and prevalence of drug resistance in the patient's geographic area. In malaria endemic areas, treatment should be prolonged (months to years) and continued regularly. However, the exact duration of treatment has not been ensured. Response may be seen within months after

commencing treatment, and relapses may occur when therapy is discontinued (5). Presumably, antimalarial clear the antigenic stimulus caused by repeated malarial infections and helps the immune system to return to normal.

The selection of antimalarial depends upon the local sensitivity pattern. Chloroquine weekly or Proguanil daily have been found to be effective. Pyrimethamine may be an alternative to the above medications (6). Data regarding the usefulness of other antimalarial drugs in HMS is limited. The response to therapy is guided by reduction in splenic size, a decrease in serum IgM levels, correction of anemia and lymphocytosis, and general improvement in the patient's well-being. Severe anaemia may require blood transfusion (7). Despite the burden of HMS in Africa; no studies have been published concerning this problem in Tanzania so far.

1.1 Literature Review

1.1.1 Background

Hyper-reactive Malarial Splenomegaly (HMS) is characterized by massive enlargement of the spleen in the tropics. The condition is prevalent in certain malarious regions of the Old World, mainly in Africa (8).

In a study which was done in Uganda showed that the syndrome is characterized by macroglobulinemia with overproduction of immunoglobulins especially the IgM class, which aggregate with high molecular immune complexes and cause persistent splenomegaly because of prolonged clearance from the reticuloendothelial tissue(9).

1.1.2 Epidemiology

Different studies have shown that HMS is restricted to native residents and visitors of the malaria belt, which roughly encompasses equatorial regions of South America, Africa, the Middle East, South Asia, and Southeast Asia.

HMS has been reported in Algiers, Congo, Madagascar, Ivory Coast, Sudan, New Guinea, Nigeria, India, Philippines, Brazil, China, Uganda, Yemen, Bangladesh, Ethiopia, Hong Kong, Ghana, Somalia, Zambia, and Chile. The incidence of HMS is highest among the people of the Upper Watut Valley in Papua New Guinea, where the rate is estimated to be 80%(10). Accurate assessment of the incidence of HMS is difficult because many conditions that cause splenomegaly are prevalent in areas where malaria is endemic. These conditions include hemoglobinopathies, lymphoreticulardisorders, schistosomiasis, hepatic cirrhosis, leishmaniasis, typhoid, and tuberculosis.

The incidence of massive splenomegaly is estimated to be 1-2% in rural Nigeria, (11) and HMS accounts for 11-45% of massive splenomegaly cases in Africa (12).

Studies conducted in The Gambia reported prevalence: 1.6 per 1,000 subjects aged ten years or older (7, 2). Other authors studied the proportion of splenomegaly caused by HMS. In northern Nigeria, 30 splenomegalic patients out of 75 (40%) were classified as having HMS,

and so were 137 out of 334 subjects in northern Zambia (again, 40%), 38 patients out of 131 (31%) in Kenya, 91/221 (41%) in Ghana and 87/114 (76%) in eastern Sudan (1, 11, 12-14).

In Papua New Guinea, the overall mortality rate in a series of 75 untreated patients during a 72-month period was 36%, reaching 57% in patients with grade V splenomegaly (15, 16). In another study, the reported mortality rate in adults was 26% at ten years follow-up, but it fell to 13% in subjects under chloroquine prophylaxis (16). The main causes of death were infectious diseases, acute haemolysis and multi-organ failure (MOF) (17, 18, 19).

HMS is associated with high mortality rate in individuals; overwhelming infections are the leading cause of death. A 5-year mortality rate of 50% was reported in Uganda and New Guinea, (15) with a mortality of 85% in hospitalized patients (7). However, other series found a much lower mortality rate (19). HMS is most common in young and middle-aged adults, although the process probably commences during childhood. HMS is rare in children younger than 8 years but was reported in a 3-year-old patient (20).

1.1.3 Clinical presentations

The most common presenting symptoms of HMS are chronic abdominal swelling (64%) and ragging abdominal pain (52%), mainly during adult life (3). Almost all patients (97%) have weight loss. Bleeding complications, such as epistaxis, is uncommon because thrombocytopenia secondary to hypersplenism is usually mild (16). Some patients may experience recurrent sharp pains in the upper abdomen, possibly due to perisplenitis or splenic infarcts. Other patients may have weight loss and cachexia. On examination, there is massive splenomegaly and hepatomegaly. The patients typically lack malarial parasitaemia and fever on presentation (4).

In non-endemic areas, the diagnosis of hyper reactive malarial syndrome (HMS) can be a challenge. Extensive testing may be needed to exclude conditions that cause massive splenomegaly and are more prevalent. However, the mere exclusion of other disease processes causing splenomegaly is insufficient to establish a diagnosis of HMS. Fakunle was the first to establish diagnostic criteria for the definitive diagnosis of HMS(3). Bates and Bedu-Addo

refined these major criteria in 1997 to the current accepted list. When these stricter criteria are applied, as many as one half of patients with splenomegaly may not have HMS (21).

Major criteria include the following; Gross splenomegaly 10 cm or more below the costal margin in adults for which no other cause can be found, elevated serum IgM level 2 standard deviations or more above the local mean, clinical and immunologic responses to antimalarial therapy, regression of splenomegaly by 40% by 6 months after start of therapy and high antibody levels of *Plasmodium* species (≥1:800) (22).

Minor criteria include the following; Hepatic sinusoidal lymphocytosis, normal cellular and humoral responses to antigenic challenge, including a normal phytohemagglutination response, hypersplenism, lymphocytic proliferation and familial occurrence

1.1.4 Haematologic manifestations

Normocytic normochromic anemia is almost always present and is related to the degree of splenomegaly. Several factors contribute to its etiology, including pooling of RBCs in the spleen, hypersplenism, and increased RBC destruction and turnover; however, the major factor is increased plasma volume. The reticulocyte count is increased and reflects erythroid hyperplasia. Acute episodes of haemolysis can also occur and seem to be associated with an autoimmune, cold-agglutinin-mediated response triggered by non-patent parasitaemia (23). Deficiency of vitamin B-12, folic acid, or glucose-6-phosphate dehydrogenase has not been demonstrated.

Leukopenia is common and is sometimes associated with lymphocytosis. Thrombocytopenia is generally mild. Both neutropenia and thrombocytopenia are due to splenic trapping. Peripheral smears usually do not reveal the malaria parasite (24).

1.1.5 Other findings

Patients with HMS have high titers of malarial antibodies. Titers of cold agglutinins, rheumatoid factor, antinuclear factor, cryoproteins, and thyroglobulins may be high (24,25,26) and Imaging tests are of limited value. Ultrasonography of the abdomen may help to document and monitor hepatosplenomegaly (27).

1.2 Conceptual Framework

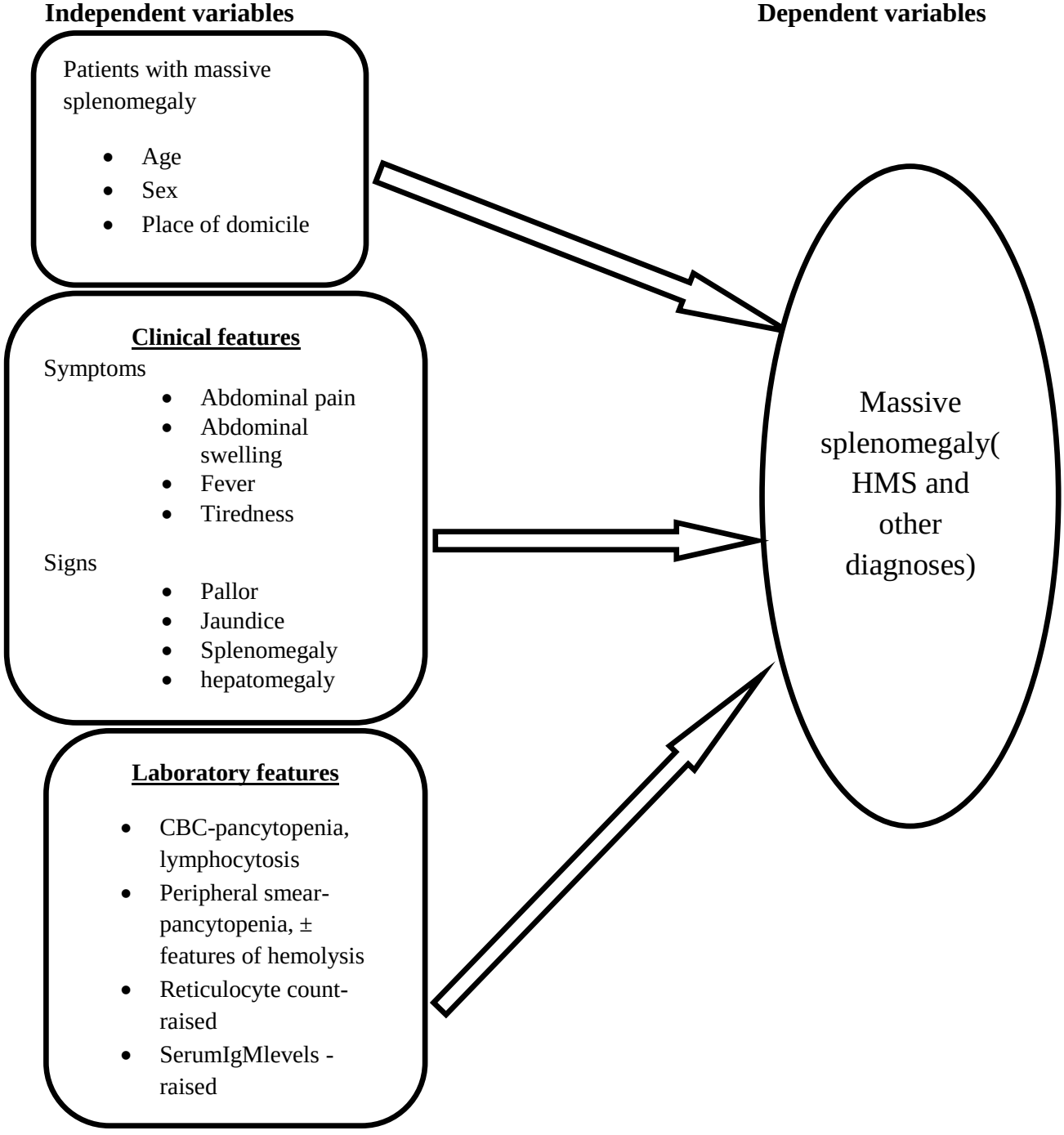


Figure 1: Conceptual Framework

1.3 Problem Statement

There have been a high number of patients with massive splenomegaly in MNH both in the wards and in the outpatient clinics. Most patients if a clear diagnosis is not made splenectomy is sometimes carried out.

There are many studies in Africa. Although in Tanzania malaria is common no study has been published so far about HMS. The diagnosis of HMS is important because “treatment with antimalarias is available”. If instead the diagnosis is not made the patient may suffer unnecessarily.

1.4 Rationale

Tanzania being a malaria endemic country, finding out the magnitude of this problem can raise awareness and serve as an eye opener to include it as a differential diagnosis, hence work up of the patients in reaching the final diagnosis and appropriate management. Without treatment the disease is eventually fatal.

Splenectomy does not stop the disease process and it is not free of risks.

1.5 Research Questions

This study aims to answer the following question in the set up of MNH

1. What is the prevalence of hyper-reactive Malaria splenomegaly?
2. What are the clinical characteristics of patients with hyper-reactive malaria splenomegaly?
3. What are the laboratory characteristics of patients with hyper-reactive malaria splenomegaly?

1.6 Objectives

1.6.1 Broad Objective

To determine the magnitude of Hyper-reactive Malaria Splenomegaly among patients with massive splenomegaly at Muhimbili National hospital, Tanzania.

1.6.2 Specific Objectives

1. To determine the prevalence of Hyper-reactive Malaria splenomegaly among patients with massive splenomegaly at MNH during the study period.
2. To describe the clinical characteristics of patients with Hyper-reactive Malaria splenomegaly.
3. To describe the laboratory features of patients with Hyper-reactive Malaria splenomegaly

CHAPTER TWO

2.0 MATERIALS AND METHODOLOGY

2.1 Study design

This was a hospital based descriptive cross sectional study.

2.2 Study area and Study Populations

The study was conducted at Muhimbili National Hospital in Dar es Salaam Tanzania. MNH is the largest referral hospital in the country, catering for a population in Dar es Salaam and surrounding regions.

2.3 Study Time

The study was conducted for a period of three months, January - March, 2017

2.4 Inclusion criteria

Patients aged 15 years and above (20) who attended MNH with spleen size measuring at least 10 cm from the left lower costal margin were eligible to participate in the study.

2.5 Exclusion criteria

1. Exclusion from the study was to those patients who were below 15 years of age.
2. Patients who refused to provide consent.

2.6 Sample size calculation

Convenient sampling technique was used since HMS is a diagnosis of exclusion hence all patients with massive splenomegaly aged 15 years and above were included so as to obtain these patients.

2.7 Recruitment of study subjects

These patients were obtained once registered for admission at the EMD, cold OPD and speciality clinics through the help of different focal persons, who were giving notifications once these patients arrived. All Patients aged 15 years and above with massive splenomegaly i.e.(spleen size ≥ 10cm) that were seen and recruited into the study when they fulfilled the inclusion criteria.

2.8 Procedure and Data Collection

Data collection was in the form of a questionnaire. This included the name initials, sex, age, occupation, level of education and address. History of Abdominal swelling, abdominal pain, loss of weight, fever, tiredness, history of recurrent malaria, history of hepatitis, alcohol abuse, exposure to schistosomiasis, family history of hemoglobinopathies and history of portal hypertension. Subjects also participated in physical examination. Signs of Pallor, jaundice and lymph nodes enlargement were assessed. Abdominal examination was done manually to elicit splenomegaly and hepatomegaly. Spleen size was assessed by abdominal examination using a tape measure from the left coastal margin.

HMS is a diagnosis of exclusion hence the diagnosis was made when the patient had the following; living in a malaria endemic area, Spleen size of 10cm and above below left coastal margin and raised serum IgM levels. However the following were excluded first as causes of massive splenomegaly;

Chronic Myeloid Leukemia, this diagnosis was base on BMA cytology. 0.5-1mls of bone marrow was aspirated from the posterior iliac bone; the aspirate was stained with Leishman and read by the principle investigator. This was later be confirmed by a haematologist. A diagnosis of CML was made by persistent polymorph leukocytosis with basophilia. PCR analysis of peripheral blood was done at the Lancets Laboratories to confirm the presence of BCR/ABL1 translocation.

Myelofibrosis, this diagnosis was made based on trephine biopsy. 1-1.5cm of bone tissue sample was taken from the posterior iliac bone then fixed in alcohol. Processing was done in the histopathology department then stained by using H an E stain (hematoxylin and eosin)-pearl's Prusian-blue (iron stain). A diagnosis of myelofibrosis was made by replacement of bone marrow by fibrous tissue.

Lymphoproliferative disorders, for lymphoma a diagnosis was base on excisional lymph node biopsy which was done by a surgeon then processed in the histopathology department then stained by using H and E stain This was read by one pathologist to remove observer bias. Chronic lymphocytic leukaemia was diagnosed by complete blood count and peripheral blood smear by the presence of increased mature lymphocytes. The blood collection and procedure for CBC and peripheral blood film was done as explained below.

Acute leukemias both myeloid and lymphoid types were diagnosed based on BMA cytology. 0.5-1mls of bone marrow was aspirated from the posterior iliac bone; the aspirate was stained with Leishman and read by the principle investigator. This was later confirmed by a haematologist. A diagnosis of acute myeloid or lymphoid leukemia was made by the presence of blast cells (myeloid/lymphoid) of more than 20% of the differential counter.

Sickle cell disease, this diagnosis was based on haemoglobin electrophoresis and HPLC results.

Portal hypertension was ruled out by performing an abdominal ultrasound as described below.

For each of the study participant, 10 mls of venous blood was drawn for laboratory tests (haematological, biochemical studies). The blood was collected into sterile vacutainers for haematological tests (EDTA anticoagulants) and biochemical tests (heparin anticoagulants). All the tests were run at central pathology laboratory at Muhimbili National Hospital. Haematological tests were run within 24 hours after collection and the samples for biochemical tests were separated within 24 hours and the serum frozen. The tests were done studies by using Architect *plus*ci 4100 automated machine from the chemistry laboratory at MNH.

CBC was done using the 3700 Celldyn machine. Peripheral blood films were stained with Leishman stain and i performed reticulocyte counts manually by adding equal amount of blood samples with new methylene blue stain, the mixture was incubated for 20 minutes in water bath at 37 °C, then films were made, and reticulocytes were counted microscopically. These were reported then verified by a consultant Haematologist. Biochemical studies (serum IgM and serum bilirubin levels) were obtained by using Abbott Architect *plus*ci 4100 chemistry and immunoassay analyzer automated machine from the chemistry laboratory at MNH. Bilirubin total and direct was reported from the automated sample, indirect bilirubin was deducted from them.

Serum IgM was done on 25 patients regardless of their age, (8 patients with no diagnosis, 10 patients with CLL who had peripheral lymphocyte count < 10×10^9/L and those who had no lymphadenopathy and 7 patients with portal hypertension, since no further investigation was done to rule out the cause aside from the ultrasound results). Serum IgM was important in the diagnostic process; we first needed to verify that quoted reference values for serum IgM were applicable to our population. To this an addition of 10 normal control samples were taken randomly from healthy individuals and tested.

2.9 Imaging

Abdominal ultrasound was done to document the findings on the spleen and liver as well as the portal vein. Findings of central lymph nodes were noted as well. The procedure was performed by a radiologist.

2.11 Data management and analysis plan

Data was collected using a pre-tested data collection questionnaire. Information from this questionnaire was entered on a Microsoft Excel spread sheet with appropriate skips and checks. The database was then exported into SPSS v.20.0 statistical software for further data cleaning and analysis. Data analysis included calculation of medians and interquatile ranges for numerical data and the clinical presentations of hyper-reactive malaria splenomegaly which are categorical data were summarized by frequencies.

Hypothesis testing was further undertaken to determine the relationship of various clinical presentations and laboratory features for hyper-reactive malaria splenomegaly and other causes of massive splenomegaly. The non parametric tests were used for assessing the statistical significance of laboratory features as numerical variables, and Fisher's exact test for assessing the clinical presentations as categorical variables. A p value < 0.05 was considered statistically significant.

2.11 Ethical consideration

Ethical approval was obtained from the Research and Publications committee of Muhimbili University of Health and Allied Sciences. Permission to conduct the study was obtained from Muhimbili National Hospital. Patients were explained about the study and written informed consent was obtained from all the study participants. Non consenting patients and those not eligible for the study were attended in their respective units and departments. All results were communicated to patients when diagnosis was confirmed and prompt treatment was given accordingly. As the study entails collecting venous blood, aseptic technique was employed to avoid contaminations. Patient's names were not used; information collected on questionnaires was entered into computer using identification numbers to maintain confidentiality.

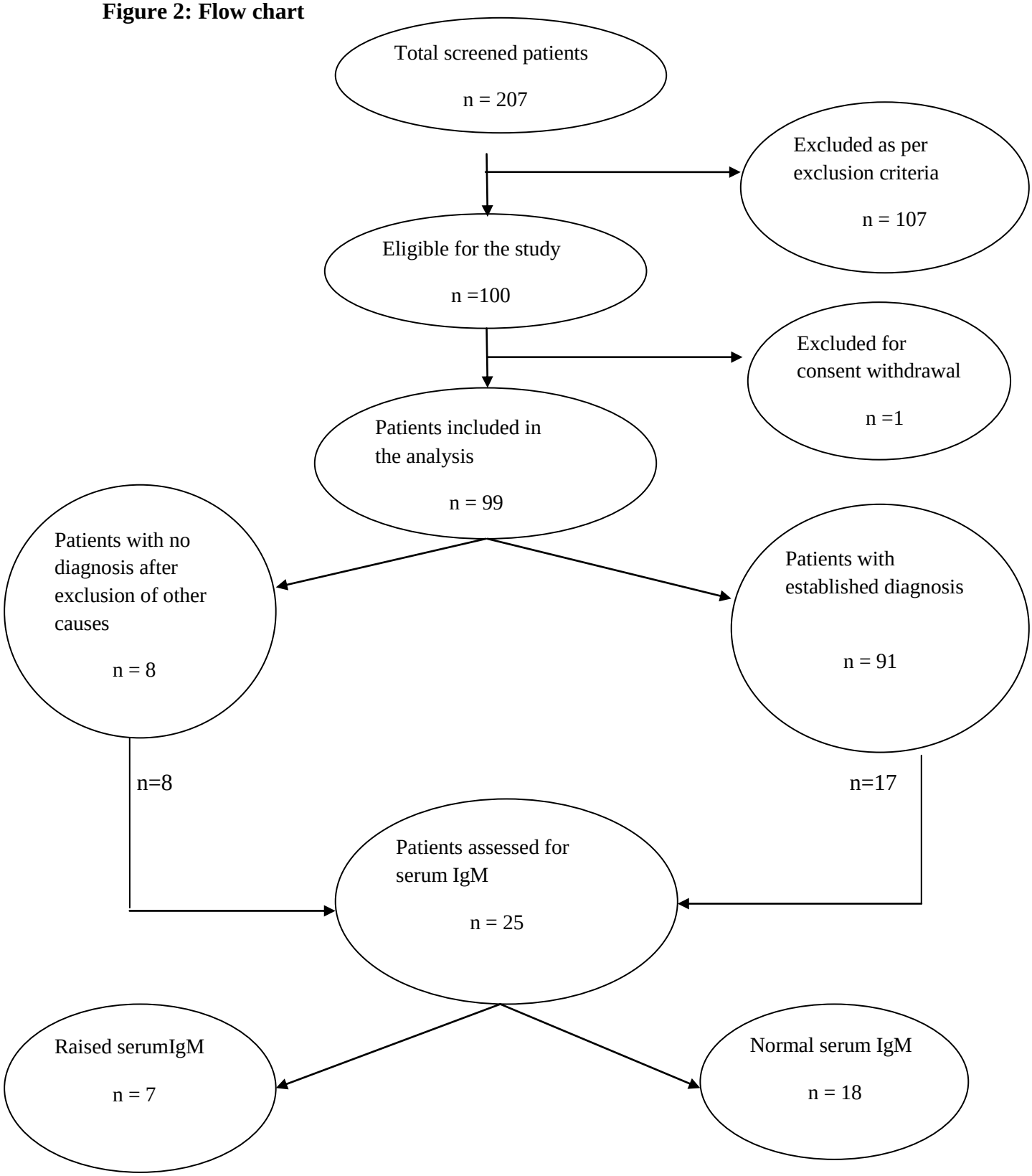
CHAPTER THREE

3.0 RESULTS

3.1 The study population

Figure 2 shows the study flow chart. 207 Patients with splenomegaly were screened between January-March 2017. Of these patients, 107 were excluded as per exclusion criteria. A total of 100 patients were eligible. 1 patient was then removed from the study because of consent withdrawal. The remaining 99 patients were analyzed; a diagnosis was established in 91 patients. 25 patients (10 with CLL, 8 with no diagnosis and 7 with portal hypertension) were assessed for serum IgM and out of those, 18/25(72%) had normal IgM levels and the remaining 7/25(28%) patients had raised serum IgM.

Figure 2: Flow chart



A total of 99 patients 15 years and above with massive splenomegaly attended at MNH in a period of three months and were sequentially recruited and gave their consent to participate in the study.

3.2 Socio-demographic characteristics of the studied population

Of the 99 study participants 44 (44%) were males and 55(56%) were females. Median (IQR) age at interview was 42 (26-58), majority being in the third and firth decade. The youngest patient was 15 years and the oldest was 77 years old. Majority of these patients 45(46%) had primary education, 21(21%) had secondary education and 26(26%) had a higher education. 7 (7%) had no formal education at all and they came from rural areas. A higher proportion of these patients 40(40%) were either self employed or had a job in the government or private sector and 31(31%) were peasants. 47(48%) patients came from Dar es Salaam region, followed by regions in the North Eastern part of Tanzania; Arusha, Moshi and Tanga with 6(6%), 7(7%) and 6(6%) patients respectively. Few patients came from the lake zone with Mara being the leading region with 4(4%) patients.

Table1.Socio-dermographic characteristics of the studied population

Variable	category	n,(%)
Sex	M F	44(44) 55(56)
Age(years) Median (IQR) Minimum maximum	All	 42 (26-58) 15 77
Level of education	No education Primary education Secondary education Higher education	7(7) 45(46) 21(21) 26(26)
Occupation	No employment Employment Students peasants	11(11) 40(40) 17(17) 31(31)

3.3 Prevalence of HMS among patients with massive splenomegaly

Out 0f 99 patients with massive splenomegaly, 5 (5%) had HMS. Of these patients 2(40%) were males and 3(60%) were females. Of the HMS patients 2 came from Dar es Salaam region, 2 came from Mara region and 1 came from Pwani region.

Other causes of massive splenomegaly were also determined in this study: 37 (37%) had Chronic myeloid leukemia, 16(16%) had lymphoma, 13(13%) had chronic lymphocytic leukemia and 8(8%) had acute leukemia. Patients whom a diagnosis was not made and SCD were also found to be common causes of massive splenomegaly at MNH, having 6(6.7%) and 4(4.4%) patients respectively.

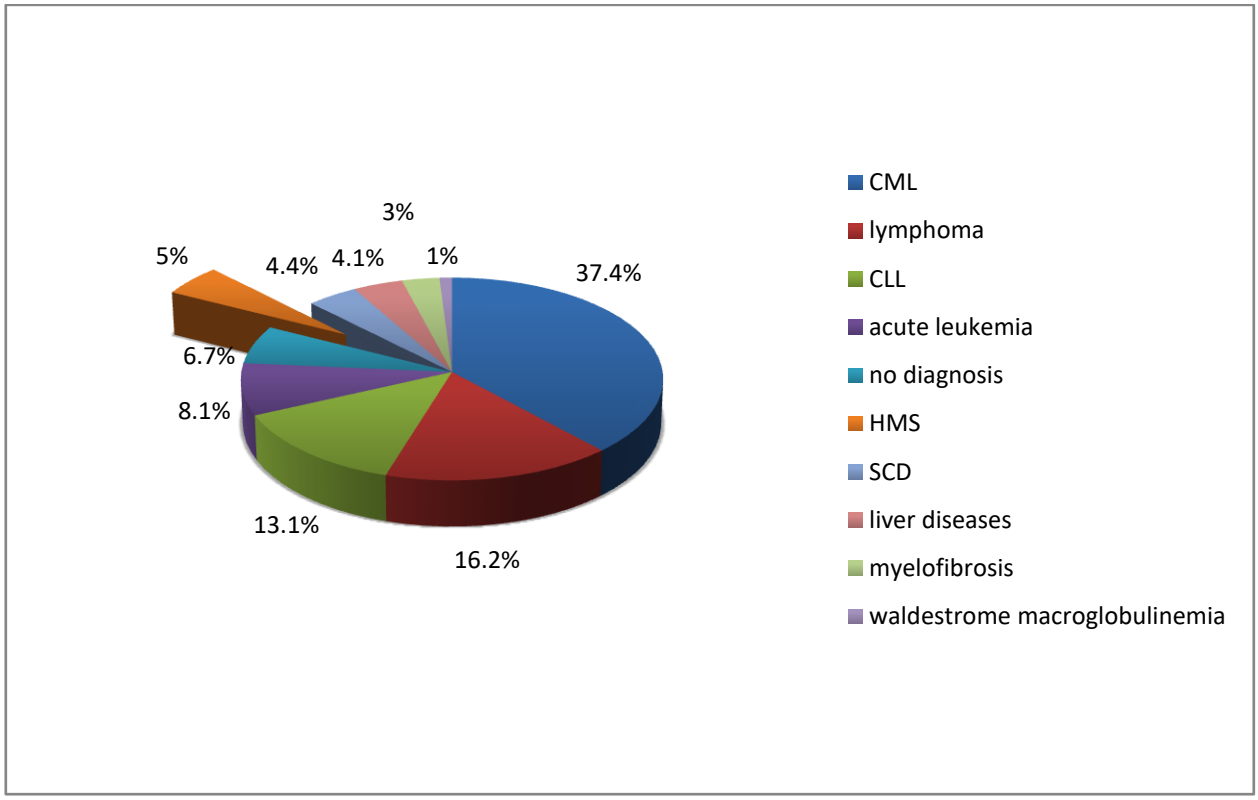


Figure 3: Causes of massive splenomegaly

3.4 Clinical characteristics of patients with HMS.

HMS patients were young adults between the ages of 20-45. Females were 3 and males were 2. Abdominal swelling was the commonest clinical feature among these patients, 3 had abdominal pain as well which was more marked on the left hypochondrium. Tiredness and awareness of heartbeat appeared in 4 patients. Weight loss was seen in 2 patients and fever was the least symptom.

Recurrent Malaria infection was common in 4 patients who reported to have 2- 3 episodes of malaria infections (which were treated successfully) in a year and this was statistically significant with a P-value of <0.001. The median (IQR) duration of symptoms for HMS patients was 24, (10-72) months. Clinically all patients with HMS were pale, 1 was jaundiced, 4 patients had a spleen size of more than 15cm. Hepatomegaly was observed in all patients with HMS and compared to other causes of massive splenomegaly it was statistically significant with a P-value of 0.049.

In comparison with other causes of massive splenomegaly, HMS patients did not present with lymph nodes enlargement and 1 patient presented with bilateral lower limb oedema.

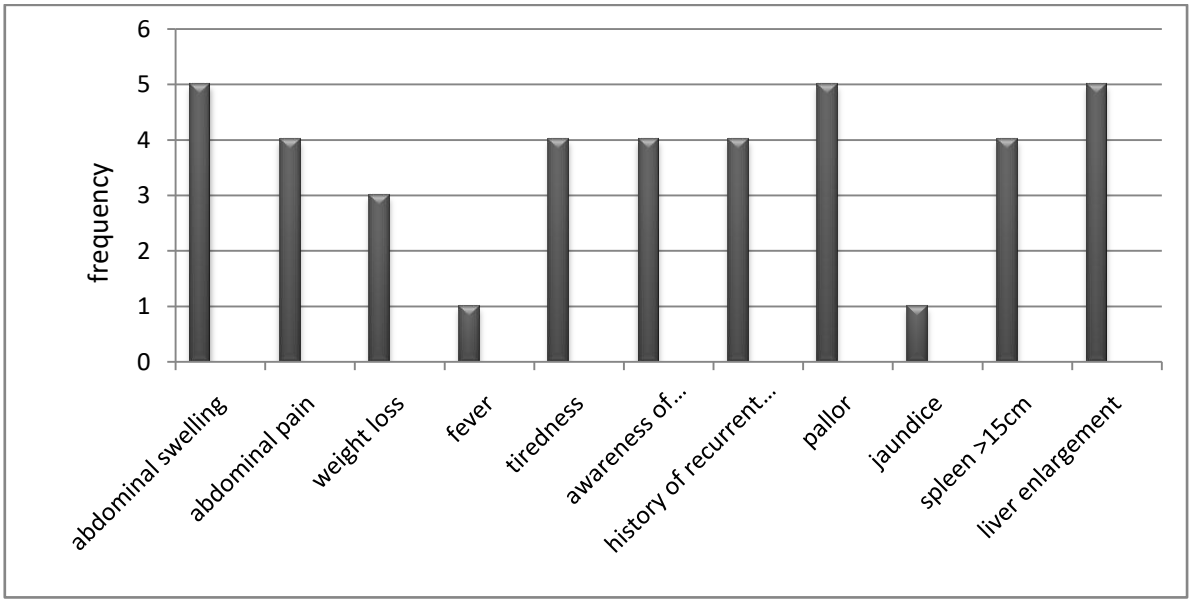


Figure 4: Clinical characteristics of HMS patients

Table2.General distribution of clinical characteristics of HMS patients Vs other causes of massive splenomegaly.

Variable	**Category**	**HMS n (%)**	**Other diagnoses n (%)**	**P-value***
Age(years)	15-19	0(0)	11(12)	
	20-45	5(100)	42(45)	0.077
	>45	0(0)	41(44)	
sex	M	2(40)	42(45)	0.605
	F	3(60)	52(55)	
symptoms	Abdominal swelling	5(100)	94(100)	
	Abdominal pain	3(60)	65(69)	0.501
	Weight loss	2(40)	46(49)	0.259
	Fever	1(20)	36(38)	0.379
	Tiredness	4(80)	87(93)	0.350
	Awareness of heartbeat	4(80)	71(76)	0.649
	History of recurrent malaria	4(80)	6(6)	**<0.001**
Duration of symptoms(months) Median, (IQR)	All	24,(10-72)	10,(6-24)	
Minimum		8	1	0.078
maximum		120	120	
signs	Pallor	5(100)	91(97)	0.855
	Jaundice	1(20)	23(24)	0.649
	Lymph node enlargement	0(0)	26(28)	0.210
	Other signs	1(20)	15(16)	0.432
	Spleen size <15cm	1(20)	23(24)	
	>15cm	4(80)	71(76)	0.649
	Liver enlargement	5(100)	50(53)	**0.049**

Key: p-value = Fisher's exact test

3.5 Laboratory parameters of HMS patients

The median (IQR) haemoglobin concentration in HMS patients was 6.4g/dl (5.0-7.5): There was no much difference compared to the median (IQR) haemoglobin 6.5g/dl (5.2-8.2) in other causes of massive splenomegaly with a P-value of 0.707 which was not statistically significant. The median (IQR) white cell count was 1.7K/ul (1.1-2.2) for HMS patients. All HMS patients had leucopenia. Lymphopenia was also observed in all HMS patients median (IQR) 0.3K/ul (0.2-0.4). This was also statistically significant with a P-value of <0.001. Their bone marrow results had erythroid hyperplasia and they had a raised reticulocyte count of 4.9% (2.0-5.3).

Out of 99 study participants 25 were assessed for serum IgM. Patients with HMS had a serum concentration of IgM median(IQR)51.7g/L (43-56.7) equivalent to a mean of 50g/l ±(7.0) and this was statistically significant with a P- value of 0.001 compared to the serum IgM median of patients with CLL, portal hypertension and those with unknown diagnoses which was 1.4 (1.1-2.7) (see figure 5). The mean value for 10 healthy controls from the study area was 1.7g/L± (0.8); hence the serum IgM in HMS patients was more than 2SD above the local mean.

Table 3: Laboratory parameters of HMS Vs other causes of massive splenomegaly

Variable	**HMS Median(IQR)**	**Other causes of massive splenomegaly Median(IQR)**	**P value***
WBC(K/uL)	1.7 (1.1-2.2)	31(7.5-193)	**0.001**
Absolute neutrophils	1.0 (0.6-1.5)	8.4 (2.1-113)	**0.006**
Absolute lymphocytes	0.3 (0.2-0.4)	6.5 (2.3-12)	**<0.001**
Haemoglobin(g/dl)	6.4 (5.0-7.5)	6.5 (5.2-8.2)	0.707
MCV	78 (67.5-93.5)	84 (76.7-90)	0.414
platelets	51 (36-71)	121 (62-276)	**0.015**
Reticulocyte count (%)	4.9 (2-5.3)	3.9 (2.9-4.5)	0.943
Direct bilirubin	5 (3.4-38.8)	5.5 (3.2-8.4)	0.842
Indirect bilirubin	4.3 (2.1-14)	4.4 (2.8-9.1)	0.860
Serum IgM(g/l)	51.7 (43-56.7)	1.4 (1.1-2.7)	**0.001**

Key: IQR- Intaquatile range, P-value = Mann-Whitney U Test.

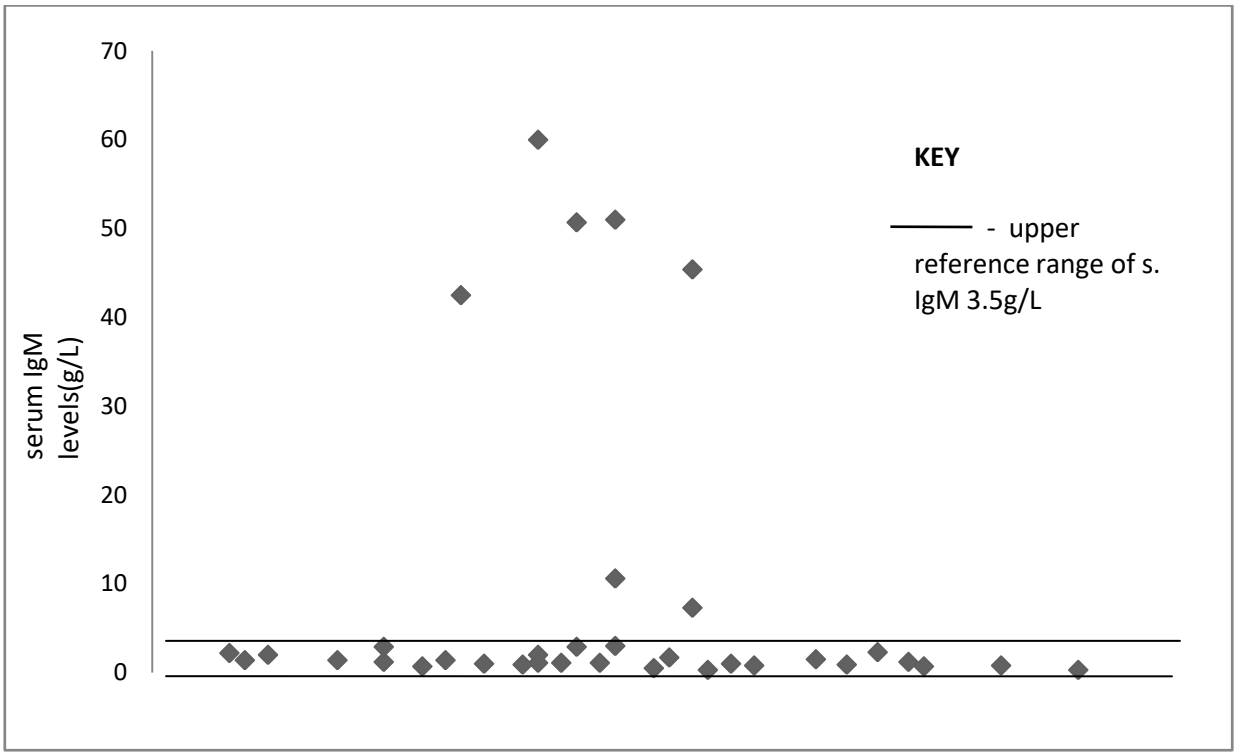


Figure 5: Distribution of serum IgM levels

CHAPTER FOUR

4.0 DISCUSSION

This study has revealed that, just as in other Malaria endemic countries, HMS is also found in Tanzania. According to the 2013 World Malaria Report (28), Tanzania is among six countries with the highest malaria burden in the World Health Organization (WHO) African region. Although malaria is largely under control in Zanzibar, it is still a major public health problem on the mainland (29).

Diagnostic criteria for case definition in this study were; living in a malaria endemic area, Spleen size of 10cm and above below left coastal margin, raised serum IgM levels and exclusion of other causes of massive splenomegaly. All HMS patients fulfilled all the mentioned criteria in the study.

Defining features of HMS include: (1)Residence in high prevalence zone for malaria (2), Chronic splenomegaly, often massive, usually unexplained by other common conditions (3)Serum IgM elevated to more than 2 SD above the local reference mean (4)High malarial antibody titers (5)Hepatic sinusoidal lymphocytosis (6)Clinical and immunological response to long term antimalarial prophylaxis. Most of the previous studies have used combination of 3-4 of the above mentioned criteria for diagnosis of HMS(30, 31).

In two separate studies done by Guptal OP et al and Guptal HL et al, the case definition relied on at least two out of the three Fakunle's major criteria (leaving aside anti-malarial antibody titre that is invariably raised), besides excluding other causes of splenomegaly(32, 33, 34, 35). Mardsen and Crane had suggested the following: persistent splenomegaly, hepatic sinusoidal lymphocytosis, disproportionate elevation of serum IgM levels and high anti-malarial antibody Titre, without considering the response to therapy (36). In other studies, the exclusion of other causes of splenomegaly in an endemic area was enough to consider a patient as affected by HMS (5, 6).

In the presence of very high level of IgM, and in the absence of other causes of splenomegaly, no attempt was made to confirm the diagnosis of HMS with liver biopsy, which is considered a minor criterion and not useful for patient management purposes.

High IgM is a characteristic of the lymphoproliferative disorder known as Waldestrome's macroglobulinemia. In this study, in cases of HMS the alternative diagnosis of Waldestrome's Macroglobulinemia was unlikely because there was no lympho-plasmacytic infiltration in the bone marrow (37). However, a further more definitive criterion is that in Waldestrome's Macroglobulinemia the IgM is, by definition, monoclonal, whereas in HMS it is polyclonal (38): this is being investigated by serum protein electrophoresis.

This study is the first detailed report on the magnitude of HMS in Tanzania. Patients with massive splenomegaly are common at MNH. In a period of 3 months, 99 patients were found to have massive splenomegaly. Five (5%) of these massive splenomegaly were due to HMS. These results indicate that HMS is not among the common causes of massive splenomegaly in Tanzania. This is in agreement with the fact that HMS disorder is most commonly associated with massive splenomegaly worldwide (39, 40).

In Africa HMS is estimated to account for 11-45% of causes of massive splenomegaly in general (12), but prevalence as low as 1-2% has been reported in some parts of Nigeria (11).Studies conducted in The Gambia reported a much lower prevalence: 1.6 per 1,000 in subjects aged ten years or older (41, 42). In Eastern Sudan the prevalence was found to be 9% (14) and very high prevalence of up to 80% has been reported in the Angas of Upper Watut Valley and the related Menya of Tauri Valley in Papua New Guinea (7).

The low prevalence obtained by this study may be due to the fact that majority of patients are not able to attend to MNH due to various reasons, some being financial constraints and distance from their place of residence to the hospital as majority of Tanzanian are peasants. In more malaria endemic areas of Tanzania the prevalence might be higher than 5% which was obtained from this study.

The HMS patients came from three different regions, 2(40%) patients came from Mara, 2(40%) patients came from Dar es Salaam and 1(20%) came from Pwani region. All the three regions are areas of high malaria risk and more than 80% of infections in Tanzania are due to Plasmodium *falciparum* (28,29).

The study recruited patients from 15 years and above and this was in conjunction with the fact that HMS is a disease of young and middle aged adults and rarely reported below 8 years of age.

This study has shown that the disease was more frequently seen in adults median age 35 years (age group 20-45 years) which is in line with all previous studies carried out in malaria endemic countries(3,7). It was also observed that females (60%) were more affected than males and this as well collarets with previous studies.

Schofield reported that the incidence of HMS predominantly affects more women than men (43).

This study demonstrated that abdominal swelling and abdominal pain were the commonest symptom in HMS patients. Patients had massive spenomegaly with hepatomegaly as an accompanied feature. 2 patients had weight loss.

In separate studies done by Fakunle YM and Crane G, demonstrated the same pattern of clinical features only that, the majority of the patients had weight loss (97%) (3,16). No reason could be found to explain the observation that only 2 of my study participants had weight loss.

All patients had severe anaemia of normocytic normochromic type with a median hemoglobin level of 6.4g/dl. Haemoglobin concentrations of less than 7 g/dl are associated with inadequate oxygen delivery to tissues, and consequently with substantial morbidity (44, 45). Anaemia in massive splenomegaly is due to a combination of pooling in the spleen, increased red-cell destruction, and dilution secondary to increased plasma volume (10). Some HMS patients present with general body malaise and fatigue. Some of the patients may develop leg oedema and dyspnoea. According to Paparello and Hoffman, this may be due to anaemia and hypervolaemia(46). In this study fatigue was a presentation in all patients. All the patients with

HMS had peripheral pancytopenia with a bone marrow erythroid hyperplasia and a raised reticulocyte count. This finding is explained by the massive splenomegaly that these patients have. Among the 5 patients with HMS, one of them had portal hypertension and this is considered as a rare complication in HMS. It is due to a considerable increase in liver blood flow which in turn leads to increase intrasplenic pressure and wedged hepatic venous pressures (WHVP). Secondly, there is an increase in presinusoidal resistance in addition to increase hepatic blood flow (47).

Measurement of total IgM is mandatory in the HMS case definition. In all cases, serum IgM concentration was found to be above the threshold of the mean value plus 2 SD for 10 control individuals from the area (1.7g/L). Although this method was successful in distinguishing HMS from other diseases, Bedu- Addo and Bates have shown that IgM concentration is neither specific nor sensitive in distinguishing HMS from B-lymphoproliferative disorders(1). In this study 2 patients with CLL diagnosed by BMA and trephine biopsy had raised serum IgM.

Again, Bedu-Addo and Bates formulated simple diagnostic factors to differentiate between B limphoproliferative disorders and HMS since raised serum IgM alone would not be enough for resource poor countries like Tanzania where many hospitals do not do immunophenotyping studies to differentiate between the two. Those factors were found to be favouring HMS rather than B-limphoproliferative disorders were; 1) age less than 40 years, 2) absolute lymphocyte count of less than 10×10^9/L. In combination, these two discriminators had sensitivity of 79%, specificity of 83%, and positive predictive value of 90% for a diagnosis of HMS rather than B-limphoproliferative disorders (1).

In this study, patients with splenomegaly of unknown cause who had normal serum IgM, lymphocyte clonality was not determined, and this could have led to under diagnosis of lymphoma.

Clinical response to treatment with anti malarial therapy supports the diagnosis of HMS even further and the study participants with HMS were given proguanil tablets 100mg daily. These patients will be followed up at the MNH general haematology clinic.

CHAPTER FIVE

5.0 CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion

These data confirm that, like in other malaria endemic countries, HMS exists in Tanzania. The fact that HMS only accounts for 5% of cases underscores the importance of a systematic approach to the differential diagnosis of massive spenomegaly. This work supports the notion that a very high (non-monoclonal) serum IgM level is the key to diagnosis.

5.2 Recommendations

- This was a hospital based study, therefore the results do not reflect the true community picture especially in those areas with the highest malaria transmission, and it is therefore recommended to do similar studies using a larger sample size at the community level which would ascertain all patients with splenomegaly who have not yet seek medical interventions hence leading to a diagnosis of HMS and finally treatment.
- The need for more advanced diagnostic tools for patients with massive splenomegaly in different parts of Tanzania, as the causes may vary in prevalence and therefore the need for intervention.
- Lifelong treatment with antimalarials for these patients, since Tanzania is a malaria endemic country.

5.3 Study limitation

- This study being a hospital based with small study sample size, majority of study population were already in advanced disease which might have overestimated the over role features in HMS patients.
- In this study it was not possible to assess response to anti-malarial therapy in HMS patients due to limited time.

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APPENDICES

Appendix I: Questionnaire (English Version)

Study no.....

DATE (DD-MM-YY)|_|_|-|_|_|-|_|_|

TELEPHONE NUMBER……..

A.DERMOGRAPHIC DETAILS

- Name (initials) .....……..
- Hospital ID……..
- Age……
- Sex……
- Address…….
- Level of education.....
- Occupation.....

B. HISTORY (circle the appropriate)

1. Abdominal swelling……..... NO/YES
2. Abdominal pain……..……. NO/YES
3. Loss of weight……. NO/YES
4. Fever…… NO/YES
5. Tiredness…….....NO/YES
6. Awareness of heartbeat..... NO/YES
7. History of recurrent malaria……..... NO/YES
8. History of hepatitis……..…NO/YES
9. Alcohol abuse……...NO/YES
10. Exposure to schistosomiasis……..... NO/YES
11. Family history of hemoglobinopathies……..... NO/YES
12. History of portal hypertension……..... NO/YES
13. Duration of symptoms…….

C.PHYSICAL EXAMINATION

I. GENERAL EXAMINATION

1. Pallor……NO/YES

2. Jaundice……...NO/YES

3. Lymph node enlargement……NO/YES

4. Others (specify)……..

II. ABDOMINAL EXAMINATION

1. Spleen size 10- 15cm……NO/YES

2. Spleen size >15cm…….NO/YES

3. Liver……..NO/YES

D. **LABORATORY INVESTIGATIONS**

1. CBC; WBC……

Absolute neutrophils…….....

Absolute lymphocytes…….....

Haemoglobin…….....

Mcv…….

Platelets……

2. Peripheral smear…….

3. Reticulocyte count…….....

4. Serum IgM……

5. Serum bilirubin levels

I. Bil. Total…….. ii. Bil. Direct…… iii. Bil. Indirect……

6. Abdominal ultrasound…… 7. Other tests (specify)

i…….. ii…… iii.....

Appendix II: Consent form (English Version)

Consent to participate in the study of hyper-reactive malaria splenomegaly at MNH, Tanzania

Dear Sir/Madam,
Greetings!

My Name is Dr. Flora Ndobho, a resident doctor in the Department of Haematology and Blood Transfusion at MUHAS. I am conducting a study regarding a condition called hyper reactive malaria splenomegaly at MNH. I am requesting for your participation.

Purpose of the study

The aim of this study is to determine the magnitude of hyper-reactive malaria splenomegaly problem in Tanzania.

How to participate

Patients who will be ready to participate will sign a consent form to approve his/her willingness.
Short interview will be done and blood sample for investigation will be taken.

Confidentiality

Information obtained from you will be confidential and will help in improving the care of patients with splenomegaly.

Costs

You will not be required to pay anything for your participation.

Voluntary participation & rights to withdraw

Your participation is voluntary and you have the right to withdraw from participating in our study at any time. Whatever your decision may be, it will not affect in any way your rights to care and treatment.

Risks

Blood sample will be drawn from your arm. We don't expect any complications from drawing blood although you will feel some pain when the needle pierces your skin (on the arm). The skin on your arm will be thoroughly cleaned prior to the procedure so as to prevent infections.

Benefits

Your participation in this study will help you know the cause of your massive splenomegaly. You will as well get the benefit of getting appropriate treatment as per need.

We hope that the information from this research will be useful in contributing to improve the quality of care in patients with massive splenomegaly

Contact persons

If you have any inquiries about this study, please do not hesitate to contact:

Dr. Flora Ndobho

Principal Investigator

Muhimbili University of Health and Allied Sciences (MUHAS)

Department of Haematology and Blood Transfusion

P.O. Box 65001 Dar es Salaam.

Tel. 0714 400 663

OR in case of any information about your rights as a participant in this study please contact:

Professor Said Aboud

The Chairman

Senate Research and Publication Committee Research and Publication Committee

Muhimbili University of Health and Allied Sciences (MUHAS)

P.O. Box 65001 Dar es Salaam

Tel. 2151489

I will be grateful if you willingly agree to participate in this study.

I _____

Have understood the above information and my questions have been answered by the investigator to my satisfaction. I willingly agree to take part in this research.

Name of the participant: _____

Signature of the participant: _____Date _____

Signature of Investigator _____ Date: _____

Appendix III: Consent form (Swahili Version)

Fomu ya makubaliano ya kushiriki katika utafiti

Habari! Mimi ni Dk Flora Ndobho na ni Daktari katika shahada ya Uzamili katika Chuo Kikuu Cha Sayansi Za tiba cha Muhimbili. Nafanya utafiti kuhusu bandama kubwa linalosababishwa na maambukizi ya malaria ya mara kwa mara katika hospitali ya Muhimbili. Ninaomba ushirikiano wako.

Nia ya Utafiti

Dhumuni ni kujua wagonjwa wangapi wenye bandama kubwa ni kutokana na maambukizi ya mara kwa mara ya malaria. Utafiti huu utafanywa miongoni mwa wagonjwa wenye bandama kubwa katika hospitali ya Muhimbili.

Jinsi yaKushiriki

Mgonjwa ambaye yuko tayari kushiriki ataweka sahihi yake, ilikuonyesha utayari. Yatafuata maswali machache ya Utangulizi, kasha vipimo vya damu vitachukuliwa.

Usiri

Taarifa ya magonjwa yako hazitatangazwa kwa yoyote zaidi ya mtafiti. Matokeo ya utafiti kwa ujumla yatasaidia kuboresha huduma ya tiba kwa wagonjwa wenye bandama kubwa.

Gharama

Hutatakiwa kulipa gharama yoyote kwa kushiriki kwako.

Utayari wa kushiriki au kujitoa

Kushiriki kwako ni hiyari na waweza kujitoa. Lakini haitakunyima haki ya kupata tiba zingine.

Athari

Damu kwa ajili ya vipimo itatolewa kwenye mkono. Hatutegemei athari yoyote damu itakapovutwa, isipokuwa waweza kusikia maumivu kidogo. Ili kuepuka kusababisha maambukizi, mara zote ngozi yako itasafishwa vema na dawa kabla ya kuchomwa sindano yoyote.

Faida

Kushiriki kwako katika utafiti huu, kutakusaidia kujua kwanini bandama lako ni kubwa na nini kifanyike baada ya hapo.

Pia utafaidika kupata matibabu halisia kama itakavyokuwa inahitajika. Nitumaini letu kuwa utafiti huu utasidia kuboresha huduma kwa wagonjwa wenye bandama kubwa hapa kwetu na penginepo.

Nitakushukuru kwa kushiriki kwako utafiti huu. Aksante.

Iwapo utakuwa na swali lolote kuhusu utafiti huu wasiliana na Dr. Flora Ndobho, Chuo kikuu Cha Afya Na Sayansi za Tiba Muhimbili; Idara ya Tiba; S.L.P 65001 Dar Es Salaam. Simu 0714 400 663

AU endapo utakuwa na swali lolote kuhusu haki zako kama mshiriki katika utafiti huu wasiliana na:

Prof Said Aboud; Mwenyekiti wa Kamati ya Tafiti na Matoleo Chuoni. Chuo Kikuu Cha Afya na Sayansi **Shirikishi** Muhimbili; S.L.P 65001 Dar Es Salaam. Simu - 2151489.

Mimi……nimeelezwa/ nimesoma yaliyomo katika fomu hii na nimeelewa maana yake. Nakubali kushiriki katika utafiti huu.

Sahihi…….. (Mshiriki) Tarehe……..

Sahihi…….. (Mtafiti) Tarehe……..