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A DESCRIPTION OF SPLENOMEGLAY IN A HOSPITAL HAEMATOLOGY SETTING

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A research report submitted to the Faculty of Health Sciences,

University of the Witwatersrand, Johannesburg,

in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Internal Medicine

Johannesburg, 2017

DECLARATION

I, Michelle Venter declare that this research report is my own, unaided work.

It is being submitted for the Degree of Master of Medicine in Internal Medicine at the University of the Witwatersrand, Johannesburg.

It has not been submitted before for any degree or examination at this or any other University.

_____

21st day of August 2017 in Johannesburg

DEDICATION

To my grandparents, Maud and Gerald- for fostering an enquiring mind,

and to Amelia, for her unending support.

ETHICS COMMITTEE APPROVAL

Consent for this study was obtained from the Committee for Research on Human Subjects, University of the Witwatersrand.

Ethics clearance certificate protocol number: M150339

Reference number: R14/49 Dr. Michelle Venter

ABSTRACT

Background

This study entails a retrospective review and description of splenomegaly in a Hospital Haematology setting. Underlying diagnoses and radiological classification, as well as laboratory parameters were used to further describe the splenomegaly encountered in the Clinical Haematology Unit, Department of Medicine, at Chris Hani Baragwanath Academic Hospital over a 10-year period.

There is a paucity of data with regards to the occurrence of splenomegaly associated specifically with haematological disorders in the South African context. This study aims to better define the clinical, radiological, and laboratory parameters associated with splenomegaly in the setting of haematological disorders encountered in a hospital setting.

Patients and Methods

This study is a retrospective review of adult patients seen at the Clinical Haematology Unit, Department of Medicine at Chris Hani Baragwanath Academic Hospital during a 10-year period (01/01/2004 to 31/12/2013). The aim of the study was to determine the profile of patients who presented with splenomegaly, in particular to assess the demographics, clinical presentation, radiological and laboratory findings in association with splenomegaly.

A total of 1976 files were reviewed. Splenomegaly was evident in 367 patients (15,6%), who were included in the study. There were 194 males (52,8%) and 173 females (47,2%), with a male to female ratio of 1,38:1.

Results and Discussion

In keeping with other studies on the subject of splenomegaly within a haematological setting, the vast majority of patients included in this study had neoplasms of the myeloid (43,3%) and lymphoid (16,6%) lineage, which together accounted for 89% of all patients.

Myeloid neoplasms that were complicated by splenomegaly include CML (89,4%), PMF (100%), PRV (61,5%), ET (44,4%), while lymphoid neoplasms that manifested with splenomegaly include NHL (14,9%), HL (21,1%), CLL (45,9%) and ALL (17%). Interestingly, the traditional haematological aetiologies of splenomegaly such as sickle cell anaemia and thalassaemia did not contribute to the numbers of patients included in the study. Within the lymphoid neoplasm group in particular, the association with HIV seropositivity remained strong. This was not the case for neoplasms of the myeloid lineage.

Conclusion

There is currently no South African data available regarding the detection and quantification of splenomegaly specifically with regard to underlying haematological disorders. Traditional haematological causes of splenomegaly may not be entirely applicable to the African population, as the added impact of (HIV) on the profile of local hematological disorders within the African continent may not be considered. With this paucity of information, there is currently no knowledge on the reproducibility of studies relating to the relative frequencies of haematological aetiologies leading to splenomegaly.

However, the results from this study clearly demonstrate the overlap in the South African setting between predominantly neoplastic and infectious (including HIV-associated malignancies) aetiologies. These results may be extrapolated to better define the haematological settings in which splenomegaly is encountered in the South African context.

Finally, as the study was conducted in a haematology setting, other causes of splenomegaly that may generally not be encountered in haematology patients such as TB, schistosomiasis, portal hypertension, infiltrative disorders and storage diseases do not feature in this review.

ACKNOWLEDGEMENTS

To my supervisor, Professor M. Patel, head of the Clinical Haematology Unit, Department of Medicine, Chris Hani Baragwanath Academic Hospital, University of the Witwatersrand, I thank him for his invaluable input and encouragement.

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ABBREVIATIONS

AFI	Acquired factor inhibitors
AH	Acquired haemophilia
AIDS	Acquired human immunodeficiency syndrome
AIHA	Autoimmune haemolytic anaemia
AML	Acute myeloid leukaemia
ART	Antiretroviral therapy
AT	Arterial thrombosis
AUL	Acute undifferentiated leukaemia
CA	Carcinoma
CD_4	Cluster of differentiation 4
CD	Castleman's disease
CHBAH	Chris Hani Baragwanath Academic Hospital
CLL	Chronic lymphocytic leukaemia
CML	Chronic myeloid leukaemia
CMML	Chronic myelomonocytic leukaemia
CT	Computed Tomography
DLBCL	Diffuse large B cell lymphoma
EOS	Eosinophilia
EMHP	Extramedullary haematopoesis
ES	Evans syndrome
ET	Essential thrombocytosis / thrombocythaemia
G6PD	Glucose-6-phosphate dehydrogenase deficiency
GD	Gaucher's disease
HbF	Foetal haemoglobin
HbS	Sickle cell haemoglobin
HC	Haemochromatosis
HCL	Hairy cell leukaemia
HE	Hereditary elliptocytosis
HIV	Human immunodeficiency virus
HL	Hodgkin lymphoma
HP	Haemophilia
HPFH	Hereditary persistence of foetal hemoglobin
HPSM	Hypersplenism

HREC	Human Research Ethics Committee
HS	Hereditary spherocytosis
IQR	Interquartile range
ITP	Immune thrombocytopaenia
MCL	Mid-clavicular line
MDS	Myelodysplastic syndrome
MGUS	Monoclonal gammopathy of undetermined significance
MM	Multiple myeloma
MPN	Myeloproliferative neoplasm
MRI	Magnetic resonance imaging
NHL	Non-Hodgkin's lymphoma
NHLS	National Health Laboratory Service
PMF	Primary myelofibrosis
PNH	Paroxysmal nocturnal haemoglobinuria
Pre-B ALL	Precursor B acute lymphoblastic leukaemia/ lymphoma
PC/ PS	Protein C or Protein S deficiency
PRV	Polycythaemia rubra vera
RIF	Right iliac fossa
RVD	Retroviral disease
SARC	Sarcoma
SCC	Spinal cord compression
SH	Sinus histiocytosis
SLE	Systemic lupus erythematosus
SW	Superwarfarin
TB	Tuberculosis
TCL	T cell lymphoma
THAL	Thalassaemia
TTP	Thrombotic thrombocytopaenic purpura
VTED	Venous thromboembolic disease
vWD	von Willebrand's disease
WHO	World Health Organisation
WM	Waldenstrom's macroglobulinaemia

CHAPTER 1: LITERATURE REVIEW

1.1 Introduction

The involvement of the spleen within the haematopoeitic system was first conceived by van Leeuwenhoek (c. 1632-1723) who proposed that the spleen played a role as a filter for the blood (Bowdler 2001). In the 1780's, Hewson proposed an additional function of the spleen which involved the maturation and regulation of cell populations (with specific emphasis on lymphocyte maturation) (Doyle 2006). It was initially postulated in Hewson's theory that the spleen was responsible for the transformation of white to red blood corpuscles. The clinical association between splenomegaly and leucocytosis was subsequently demonstrated (this association was presumably encountered in the setting of leukaemias). Osler proposed in 1904 that the role of the spleen extended to functions beyond those of the haematological system alone and into the realms of both metabolic functions and infectious disorders (Osler 1904). It also became widely accepted that the spleen was involved in both the production and regulation of white blood cells. The advent of surgical techniques in which the spleen could be successfully removed strengthened the argument that the spleen played a vital role in the immunological system. This link became more apparent as splenectomised individuals were found to have higher mortality rated postoperatively due to overwhelming sepsis. The first account of the association between splenectomised individuals and sepsis was published by King and Schumaker in 1952 (King and Shumacker 1952).

The current understanding is that the spleen is involved in multiple roles such as supporting the erythroid and lymphoid cell lines, as well as forming a constituent of the reticuloendothelial system (where it functions in the removal of senescent red blood cells, as well as in the removal of circulating bacteria).

1.2 Aetiology of Splenomegaly

1.2.1 Classification of the pathophysiological mechanisms of splenomegaly

There are many disease processes which result in splenomegaly. Splenomegaly is therefore most often associated with disease in a secondary nature. It is less common to develop splenomegaly in the setting of a primary pathology of the spleen.

Although the disorders leading to splenomegaly are protean, the common pathophysiological mechanisms for splenic enlargement include the following (Kasper, Braunwald et al. 2005):

1) Splenic hyperplasia
   a) Intrahepatic (e.g. haemochromatosis)
   b) Extrahepatic (e.g. massively enlarged intra-abdominal lymph nodes secondary to underlying haematological processes)

2) Splenic work hypertrophy
   Hyperplasia that occurs in response to stimuli, which results in both increased vascularity and cellularity of the spleen. The increased workload may be as a result of either an immunological or a haemolytic process.
   a) Immunological hyperplasia may result from either a response to infection (e.g. HIV/ AIDS, malaria) or from an immune dysregulation disorder (e.g. immune thrombocytopaenia)
   b) Haemolytic processes cause activation and hyperplasia of the reticuloendothelial system as the defective erythrocytes are removed from the circulation. The major haematological settings in which this is encountered are in membranopathies (e.g. spherocytosis), haemoglobinopathies (e.g. thalassemia major) and in other haemolytic anaemias.

3) Deposition of products of metabolism result in splenomegaly in diseases such as Gaucher's disease and in amyloidosis.

4) Infiltration of the spleen, either by malignant or non-malignant processes, resulting in splenomegaly.
    a) Haematological causes of infiltration of the spleen include the leukaemias, the lymphomas (Hodgkin Lymphoma and non-Hodgkin's Lymphoma) and the myeloproliferative syndromes.
    b) Non-haematological diseases with cellular proliferation associated with splenomegaly include splenic hamartomas and secondary metastatic spread to the spleen via contiguous, haematological or lymphatic channels.

Massive splenomegaly is defined as a spleen extending well into the left lower quadrant of the abdomen (or into the pelvis), or a spleen which may be palpated crossing the midline of the abdomen. Massive spleens weigh at least 500g (and may weigh as much as 1000g).

Haematological conditions that commonly result in massive splenomegaly may be either myeloproliferative or lymphoproliferative in nature:

a) Myeloproliferative neoplasms commonly implicated in massive splenomegaly include chronic myeloid leukaemia, primary myelofibrosis and polycythaemia vera.
b) Lymphoproliferative disorders include mantle cell lymphoma, hairy cell leukaemia, extranodal marginal zone lymphoma, T-cell lymphoma and the prolymphocytic leukaemias.

Non-haematological conditions that result in massive splenomegaly may be of either an infectious or miscellaneous cause:

a) Infections resulting in massive splenomegaly include schistosomiasis, hyper-reactive malarial splenomegaly syndrome and leishmaniasis.
b) Portal hypertension should also be considered in the differential as a cause of massive splenomegaly.

1.2.2 Classification of the aetiological mechanisms of splenomegaly

Splenomegaly rarely presents as a manifestation of a primary disorder within the spleen. It is most often encountered as a manifestation of an underlying disorder. The primary disease states that result in splenomegaly may be broadly classified as being of either an infectious, haematological, malignant and non-malignant aetiology (Pozo, Godfrey et al. 2009).

Table 1: The aetiology of splenomegaly

Aetiology	**Subgroup**	**Examples**
Infections	Acute	Viral hepatitis Cytomegalovirus infection Splenic abscess Toxoplasmosis
	Subacute and chronic	Tuberculosis Infective endocarditis Brucellosis
	Tropical/ parasitic	Malaria Leishmaniasis Schistosomiasis
Haematological disorders	Myeloproliferative disorders	Myelofibrosis Chronic myeloid leukaemia Polycythaemia vera Essential thrombocytosis
	Miscellaneous	Megaloblastic anaemia Iron deficiency anaemia
Neoplasms	Haemato-lymphoid	Acute leukaemia Chronic leukaemia Prolymphocytic leukaemia Hairy cell leukaemia Lymphoma Plasma cell dyscrasias
	Metastatic	Carcinoma (lung and breast) Melanoma
	Benign	Hamartoma Haemangioma
Non-malignant processes	Immune proliferations and non-infectious granulomatous disorders	Systemic lupus erythematosus Rheumatoid arthritis Rheumatic fever Sarcoidosis

	Congestive splenomegaly	Portal cirrhosis Wilson's disease Haemochromatosis Portal vein thrombosis Budd-Chiari syndrome Congestive cardiac failure Constrictive pericarditis
	Storage diseases	Gaucher's disease Amyloidosis

1.2.3 Haematological pathophysiological mechanisms of splenomegaly

The haematological system comprises both the blood and the organs related to the homeostasis of the formation and destruction of blood within the human body. These organs comprise what is known as the reticuloendothelial system. Components of this system include the lymphatics, the liver, the spleen and the bone marrow.

The incidence of splenomegaly and disorders of the haematological system have long been associated. This association between the various disorders of the haematological system (and the spleen particularly) are due to the intricate role that the spleen plays in the regulation of, and the response to, changes within the haematological system. Splenomegaly occurs in the setting of haematological disease due to several mechanisms. The different pathophysiological mechanisms that lead to splenomegaly may be broadly classified as follows (Kasper, Braunwald et al. 2005):

Table 2: The haematological physiological causes of splenomegaly

Aetiology	**Subgroup**	**Examples**
Enlargement due to increased demand for splenic function	Reticuloendothelial system hyperplasia	Spherocytosis, ovalocytosis, sickle cell anaemia, thalassaemia, haemoglobinopathies, paroxysmal nocturnal haemoglobinuria, nutritional anaemias
	Immune hyperplasia	Infectious mononucleosis, AIDS, viral hepatitis, cytomegalovirus, infective endocarditis, tuberculosis, histoplasmosis, malaria Rheumatoid arthritis, systemic lupus erythematosus, immune haemolytic anaemia, immune thrombocytopaenia

Extramedullary haematopoesis		Myelofibrosis, marrow infiltration (tumours, leukaemias, Gaucher's disease)
Enlargement due to abnormal splenic or portal blood flow		Cirrhosis, hepatic vein obstruction, splenic vein obstruction, portal hypertension
Infiltration of the spleen		Gaucher's disease, amyloidosis Leukaemia, lymphoma, myeloproliferative disorders
Unknown aetiology		Idiopathic splenomegaly, iron deficiency anaemia

1.3 Signs and Symptoms of Splenomegaly

The signs and symptoms of splenomegaly depend on the size of the spleen, as well as the aetiology of the underlying disorder (acute vs chronic). An acute aetiology may result in tenderness on palpation of the left upper quadrant, due to the rapid splenic enlargement and subsequent stretching of the capsule of the spleen. If the aetiology of the splenomegaly is more chronic in nature, symptoms may be more subtle and include early satiety, weight loss, referred pain to the left shoulder, and pain while lying on the side.

A study by Gielchinsky et al. attempted to correlate spleen size and symptoms of an enlarged spleen (i.e. abdominal pain, abdominal discomfort, early satiety, pain on lying on the side and colicky pain). In this study, there was no statistically significant correlation between the size of the spleen and any one of the five symptoms studied (Gielchinsky, Elstein et al. 1999).

It is therefore reasonable to surmise that the clinical features associated with an enlarged spleen may not always be present and may not correlate with the degree of splenic enlargement.

1.4 Clinical Assessment of Splenomegaly

The clinical assessment of splenomegaly relies on both palpation and percussion techniques. Studies have concluded that a clinically palpable spleen is present in the setting of a significant splenomegaly (Schloesser 1963).

As a rule, a spleen has increased in size by at least 40% before it becomes clinically palpable (Blackburn 1953). This is because the spleen enlarges initially in a posterior-superior direction before enlarging antero-inferiorly.

Palpation of the spleen may be performed using various techniques ranging from bimanual palpation, ballottement of the spleen and palpation of the spleen while the examiner stands at the side of the patient. It has been shown that a combination of manoeuvers yields the highest sensitivity and specificity for the detection of splenomegaly (Yang, Rickman et al. 1991). A combination of palpation of the spleen standing at the side of the patient and Castell's method of percussing the spleen (the examiner percusses at the intersection of the left anterior axillary line and 9th intercostal space) was shown to have the highest likelihood ratios (Tamayo, Rickman et al. 1993).

False positive and false negative findings in the palpation of an enlarged spleen are possible. The accuracy with which an enlarged spleen may be palpated relies on the experience of the examining clinician, the body habitus of the patient, the size of the spleen and the presence of ascites (Barkun, Camus et al. 1989).

There are numerous clinical grading systems of splenomegaly. These systems rely on measurement of the spleen by either clinical or radiological methods, or by specimen weight and size (as determined at the time of splenectomy).

Clinical methods of grading splenomegaly rely on the palpation of the spleen below the border of the left costal margin, as the spleen enlarges in a downward and contralateral direction. Hackett's grading system for splenomegaly is based solely on the clinical examination (Hackett 1945). Massive splenomegaly is defined according to Hackett's grading system as ≥ 3.

Table 3: Clinical grading of splenomegaly according to Hackett's grading system

Grade	Clinical finding
0	Normal, impalpable spleen
1	Spleen palpable only on deep inspiration
2	Spleen palpable on the mid-clavicular line halfway between the umbilicus and the costal margin
3	Spleen expands towards the umbilicus
4	Spleen extends past the umbilicus
5	Spleen extends towards the symphysis pubis

There are many techniques to determine enlargement of the spleen by percussion. The best known is by percussion of Traube's semilunar space, as described by Ludwig Traube in 1868 (Talbott 1970). The borders of this space are the left sixth rib superiorly, the mid-axillary line laterally and the left costal margin inferiorly. This area is usually resonant, even during full inspiration. If the spleen is enlarged, the note which is usually resonant (owing to the underlying gastric bubble), becomes dull or is noted to be dull during full inspiration.

False positive notes using percussion of Traube's semilunar space are possible if the patient has a pleural effusion on the left, or if the patient is examined shortly after eating (Barkun, Camus et al. 1989). This method has a reported sensitivity of 62% and a specificity of 72% when compared to the gold standard of ultrasonography to determine the presence of splenomegaly (Chongtham, Singh et al. 1997).

The sensitivity and specificity of ultrasound in detecting an enlarged spleen is 95% and >90%, respectively (Petzoldt, Lutz et al. 1976).

1.5 Radiological Assessment of Splenomegaly

Radiological assessment of an enlarged spleen may make use of plain radiographs, ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI).

a) Plain radiographs: the spleen is normal in size if it is not seen in the abdominal plain film, if it is ≤ 5 cm in width, or if it is < 85% of the size of the normal kidney (Thipphavong, Duigenan et al. 2014). It is considered enlarged if it is ≥ 6cm wide or 13,0 cm long, or if its surface area (length x width) is > 75 cm^2.

b) Ultrasound: the length of the spleen is measured as a cranio-caudal length when using ultrasound. In healthy individuals, mean spleen length by ultrasound is 10,8 cm. A normal spleen is defined as ≤ 13 cm in length. The normal cranio-caudal length on an ultrasound measurement ranges from 11 cm to 13 cm (Bezerra, D'Ippolito et al. 2005). The cranio-caudal length by ultrasound has been shown to correlate well with splenic volume (length x width x depth) by CT scan when the length is measured with the patient in the right lateral decubitus position (Lamb, Lund et al. 2002). A combination of clinical examination and point-of care ultrasound has been shown to increase sensitivity from 40% to 100% when compared to clinical examination alone (Olson, Trappey et al. 2015).

c) CT scan: CT scans allow for a more accurate measurement as both splenic length and splenic index (length x depth x width) can be calculated (Robertson, Leander et al. 2001). Splenomegaly is defined on CT scan as a spleen length of greater than 10 cm (Bezerra, D'Ippolito et al. 2005).

The “gold standard” of splenomegaly measurement remains the weight of the spleen. On average, the weight of the normal spleen is between 100 g to 250 g. Spleen weight varies, depending on the age, gender and body habitus of the patient. The median splenic weight in adult patients is 150 g (Picardi, Martinelli et al. 2002).

1.6 Laboratory Disorders Associated with Splenomegaly

The major laboratory abnormalities associated with splenomegaly are determined by the underlying aetiology of the splenomegaly.

As an organ in which lymphopoeisis occurs, the spleen contains approximately 25% of the pool of circulating lymphocytes. Increased destruction or sequestration of leukocytes causes the leuocopenia that may be observed in splenomegaly. Leuocopenia is closely related to the degree of neutropenia, for similar reasons as stated above.

Neutropenia, which is defined as an absolute neutrophil count of $< 2 \times 10^9$/l, is the result of an increase in the marginated granulocyte pool, a proportion of which are in the spleen. Sequestration may also play a role in the genesis of neutropenia.

The anaemia observed in splenomegaly results from the sequestration of red blood cells from the circulating blood volume and haemodilution.

Approximately 30% of the total platelet mass exists as an interchangeable pool in the spleen. Increased splenic platelet pooling is the primary cause of the thrombocytopenia observed in the setting of hypersplenism, in patients with hypersplenism, as much as 90% of the total platelet mass may be sequestrated in the spleen. The platelet count in the setting of hypersplenism is usually between 50-150 x 10^9/l (Bashour, Teran et al. 2000).

Some studies have demonstrated that there is no predictable relationship between the degree of splenomegaly and the presence or degree of these cytopenias. However, this data is extrapolated from patients with massive splenomegaly due to Gaucher's disease, and may not necessarily be applicable to other disease states (Gielchinsky, Elstein et al. 1999).

1.7 Current Understanding of Splenomegaly in Haematological Disorders

Large retrospective studies on the causes of splenomegaly in patients in the United States have been carried out to better understand the underlying disorders resulting in splenomegaly (O'Reilly 1998, Swaroop and O'Reilly 1999). The most common disorders in these studies that were associated with splenomegaly were (in decreasing order of occurrence): haematological, hepatic, infectious, congestive or inflammatory and primary splenic disease.

Among the haematological disorders associated with splenomegaly in these studies, the most prevalent were: lymphoma (16-44%), chronic myeloid leukaemia (8-29%), haemoglobinopathies (7-25%), chronic lymphocytic leukaemia (0-20%) and myelofibrosis (9-16%).

These large retrospective studies demonstrated that there were no significant differences in the causes of splenomegaly between rural and urban settings in the United States. Massive splenomegaly was associated with haematological abnormalities in 33% of the cases (the remaining 66% were accounted for by hepatic, infectious and "other" aetiologies) (Swaroop and O'Reilly 1999).

Marked differences are noted in the causes of splenomegaly between the developed and the developing world. In Africa, the most common causes of splenomegaly remain of an infectious aetiology. The two predominant aetiologies of massive splenomegaly in Africa are the tropical splenomegaly syndrome due to malarial infection, and schistosomiasis infection (Lowenthal, Hutt et al. 1980, Bedu-Addo and Bates 2002). In the Asian subcontinent, a similar picture is seen, with predominantly infective causes causing splenomegaly (Gazin 2004). This is in stark contrast to the developed world, where the cause of massive splenomegaly is usually of haematological (31%), hepatic (17%) and infectious causes (8%) (O'Reilly 1998).

The current knowledge base in the local setting on splenomegaly within the adult haematological setting is lacking. No studies have been done to define and describe the splenomegaly encountered specifically in association with haematological disorders in South Africa.

The proportion of South Africans infected with human immunodeficiency virus (HIV) has increased from 10,6% in 2008 to 12,2% in 2012, according to the Human Science Research Council's National HIV Prevalence, Incidence and Behaviour Survey (Shisana, Rehle et al. 2014). The total number of infected South Africans is estimated at 6,4 million people. This is 1,2 million more people than in 2008.

This increased prevalence is thought to be in part due to the increased uptake of antiretroviral therapy (ART) by the population, with resultant increased longevity of the population.

Women aged between 30-34 years and men aged between 35-39 years had the highest rates of infection: 36% of females and 28,8% of males in urban settings in these respective age groups were HIV positive. Black Africans had the highest HIV infection rate compared to all other ethnic groups (15%), followed by coloured people (3,1%), Indians or Asians (0,8%) and whites (0,3%).

The association between HIV and haematological disorders is well documented (Patel, Philip et al. 2011, Patel, Philip et al. 2015). It is suggested that the underlying haematological aetiologies associated with HIV are those that are the high-grade, more aggressive subtypes of lymphoma (Ziegler, Bragg et al. 1984). The association between HIV and an incidental finding of splenomegaly has been studied in a Swiss cohort study. In this prospective cohort of 70 patients, splenomegaly was present by physical examination in 23% of patients and by radiological methods (ultrasonography) in 66%. During a 1-year follow up, splenomegaly at enrolment was not predictive of any clinical event, and splenomegaly was not associated with a higher risk of developing Acquired Immunodeficiency Syndrome (AIDS) during a median follow up of 6,1 years (Furrer 2000).

The period of this study is relevant, as it encompasses the transition in South Africa from a pre-ART to a post-ART era. Non-Hodgkin's lymphoma is the most prevalent form of haematological malignancy in adult patients in South Africa. Hodgkin lymphoma is becoming increasingly prevalent in South Africa owing to its association with HIV/AIDS (Patel, Philip et al. 2011).

As well as the HIV-related haematological disorders, a large proportion of patients seen in the outpatient department of the Clinical Haematology Unit, have non-HIV related haematological

problems. This study aims to evaluate these patients, to gain a better understanding of the landscape of splenomegaly.

CHAPTER 2: PATIENTS AND METHODS

2.1 Rationale for the Study

Given the paucity of data surrounding the understanding of splenomegaly in South Africa, this study aims to shed some light on splenomegaly in haematological conditions in both HIV seropositive and HIV seronegative individuals. The added burden of HIV in our setting and the associated haematological conditions encountered provide an interesting opportunity to better define the clinical scenarios in which splenomegaly is encountered in a local setting.

2.2 Aim of the Study

The aim of this study is to describe the aetiologies and integrate the clinical, radiological and laboratory associations in which splenomegaly is encountered within a tertiary adult hospital haematological setting.

2.3 Objectives of the Study

- To determine the prevalence of splenomegaly in adult haematological disorders, in a tertiary referral hospital setting.
- To correlate the degree of splenomegaly with other clinical parameters such as hepatomegaly, cytopenias, as well as the underlying diagnosis.
- To determine the clinical accuracy of the measurement of spleen size, in relation to radiological assessments.

2.4 Study Design

A single centre retrospective, observational study conducted on all patients who attended the adult Clinical Haematology Unit in the Department of Medicine at Chris Hani Baragwanath Academic Hospital (CHBAH) between 01/01/2004 to 31/12/2013. This study contains both descriptive and comparative elements.

2.5 Sample Population

The records of all adult patients attending the outpatient Haematology clinic at CHBAH over a 10-year period between 01/01/2004 and 31/12/2013 were reviewed.

CHBAH is a tertiary level academic hospital situated in Soweto, Johannesburg, which has a predominantly black African demographic.

CHBAH serves a population of approximately 1,3 million people, as estimated in the census of 2011 (2012). This accounts for approximately one third of the total population of Johannesburg.

A total number of 2 343 patients were seen at the Clinical Haematology Unit in the 10-year period of the study. In total, 1 976 files were available for review from this period, as 367 files were unable to be located for assessment. From the 1 976 files that were reviewed, a total of 367 patients were eligible for inclusion in this study, based on a finding of splenomegaly.

2.5.1 Inclusion criteria

- All newly diagnosed adult patients presenting to the Clinical Haematology Unit in the Department of Medicine at Chris Hani Baragwanath Academic Hospital between 01/01/2004 and 31/12/2013.
- Documented splenomegaly on presentation, either by clinical clerking notes, or by initial radiological investigations.

2.5.2 Exclusion criteria

- Patients whose files could not be located in the clinic.
- Patients in whom no splenomegaly is noted, or in those in which the measurement of the splenomegaly is omitted in the file.
- Patients in whom treatment was started before the measurement of splenomegaly was carried out.

2.6 Data Extraction

All patient records at the Clinical Haematology Unit, Department of Medicine at Chris Hani Baragwanath Academic Hospital were evaluated for the presence of splenomegaly during the period 01/01/2004 to 31/12/2013. Clerking notes and radiological reports were used to identify patients with splenomegaly.

Once patients with documented splenomegaly were identified, the necessary data was extracted from the file and laboratory parameters were extracted from the National Health Laboratory Service (NHLS) database.

The following parameters were evaluated:

- Demographics: age, gender, ethnic group
- Retroviral disease status, cluster of differentiation 4 (CD_4) count, antiretroviral (ART) use, stratification of ART use per CD_4 subgroup and duration of ART use.
- Clinical parameters: pallor, jaundice, lymphadenopathy (extent, size), hepatomegaly (size, radiographic modality used to detect hepatomegaly) and splenomegaly (with relevant dates and radiographic modality used to detect splenomegaly).
- Laboratory parameters: haemoglobin, red cell count, white cell count, platelet count, differential count (neutrophils, basophils, eosinophils, monocytes and lymphocytes).
- Histological parameters: bone marrow aspirate and trephine biopsy, as well as any other histological specimens (e.g. lymph node biopsy)

2.7 Definitions

2.7.1 Definitions of clinical parameters

Splenomegaly: a palpable spleen on examination, or a cranio-caudal length of larger than 12 cm on ultrasonography or on computerised tomography.

Massive splenomegaly:

- A spleen that measures > 12 cm below the midpoint of its enlargement at the costal margin.
- A spleen that is palpated at or beyond the umbilicus, from a line drawn parallel to the costal margin.
- A spleen that is more than two thirds the distance from the costal margin to the umbilicus.
- A spleen that extends up to or beyond the umbilicus.
- A spleen that is palpable in one or both lower quadrants of the abdomen.
- A spleen that measures > 20 cm in cephalo-caudal length when measured radiologically.
- A spleen that weighs > 1 000 g at splenectomy.

Hepatomegaly:

- A liver that is palpable below the costal margin in the midclavicular line (MCL), provided that the upper border of the liver is in the normal anatomical site at between the 5^{th} and 6^{th} intercostal space.
- A liver span in the MCL that is > 13 cm.

Significant lymphadenopathy:

- A lymph node that is larger than 1 x 1 cm in diameter

To maintain uniformity and standardization across all measurements of splenomegaly, a standardized grading system were used across all conditions. The clinical grading of both splenomegaly and hepatomegaly were graded using the following parameters:

Table 4**:** Grading of organomegaly

Parameter	**Mild**	**Moderate**	**Moderate to massive**	**Massive**
Splenomegaly (cm below CM)	≤ 4,0 cm	4,1-8,0 cm	8,1-12,0 cm	> 12 cm
Hepatomegaly (cm below CM)	≤ 4,0 cm	4,1-8,0 cm	8,1-12,0 cm	> 12 cm or liver in the RIF and not pushed down

cm= centimeters; CM= Costal Margin; RIF= Right Iliac Fossa

2.7.2 Definition and grading of haematological parameters

The haematological parameters assessed in this study were graded as per WHO definitions:

Table 5: Grading of haematological parameters

Parameter	**Global Reference Range**	**Borderline / Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Haemoglobin (g/dl)	M 14-18 F 12-16	M ≥ 11, <14 F ≥ 11, <12	9,5-10,9	8,0-9,4	6,5-7,9	< 6,5
White cell count ($x10^9$/l)	4-11		3,0-3,9	2,0-2,9	1,0-1,9	< 1,0
Platelet count ($x10^9$/l)	150-400	≥ 100	75-99	50-74	25-49	< 25

g/dl= grams per deciliter; M= male; F=female

2.8 Data Analysis

All data was collected on Microsoft Excel® 2013. Data analysis was then performed using GraphPad Instat™ Version 7. Descriptive statistical analysis (mean, median) were used for demographic statistics and the degree of variation of continuous variables were assessed using standard deviations. The Shapiro Wilk W test was used to test for normality of distribution. Because most variables were not normally distributed, medians and interquartile ranges (IQRs) were used to represent the central tendency and measure of statistical dispersion, respectively. Statistical significance was represented by a p-value of $< 0,05$.

A statistician was consulted to verify the statistical methods and results obtained.

2.9 Ethics

Ethics approval was granted unconditionally by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand (clearance certificate number: M 150339). No informed consent was required from patients due to the retrospective nature of the analysis.

CHAPTER 3: RESULTS

A total number of 2 343 patients were seen at the adult Clinical Haematology Unit in the Department of Medicine at Chris Hani Baragwanath Academic Hospital (CHBAH) in the 10 years of the study from 01/01/2004 to 31/12/2013. In total, 1 976 files were available for review from this period. A total of 367 files were ineligible for assessment. From the 2 467 files that were reviewed, a total of 367 patients (15,6 %) were eligible for inclusion in the study.

3.1 Demographic Results

3.1.1 Demographics: gender, age, ethnic group

Of the 367 patients included in the study, 194 (52,8%) were male, and 173 (47,2%) were female. The male to female ratio was 1,38:1.

Ethnic demographics were as follows: 331 (90,2%) of the patients who were included in this study were black Africans, 25 (6,8%) of White and Coloured (mixed race) ethnicity, and 11 (3,0%) of Indian descent.

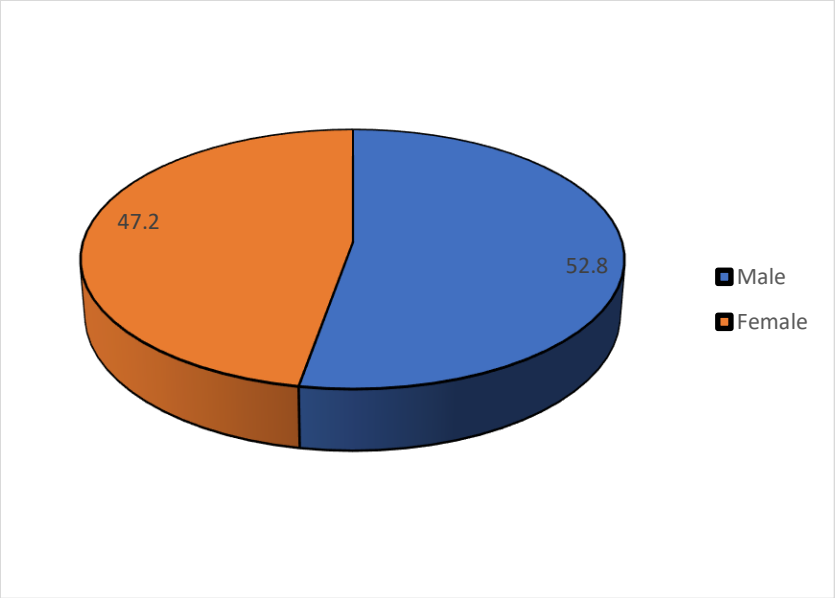


Figure 1: Gender Breakdown of Included Patients by percentage

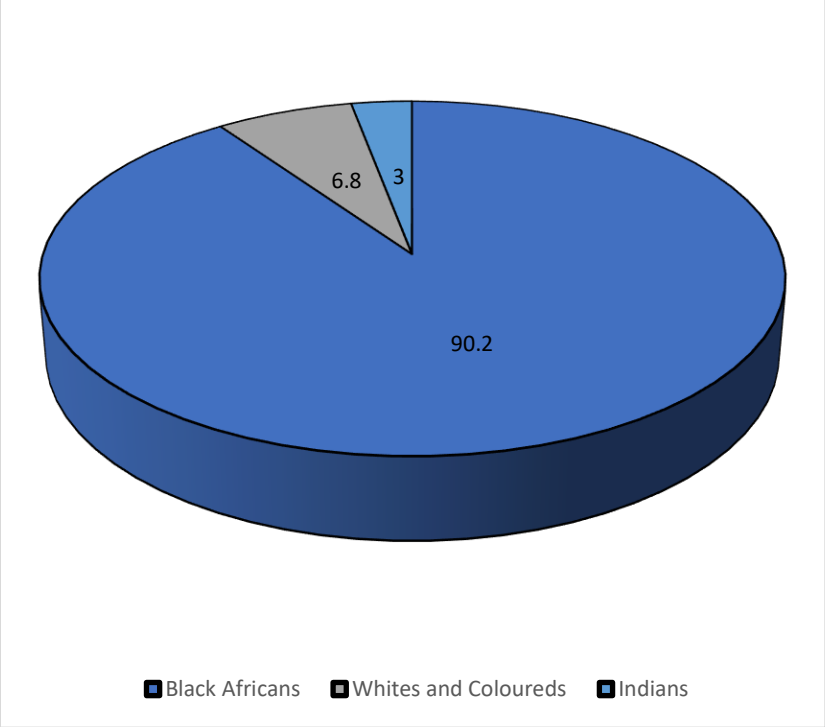


Figure 2: Ethnic Group Breakdown of Included Patients by percentage

The relative ages at initial presentation were divided across all aetiologies as follows: 14-20 years (22 patients- 6,0%), 21-30 years (49 patients- 13,3%), 31-40 years (90 patients- 24,6%), 41-50 years (63 patients- 17,1%), 51-60 years (65 patients- 17,7%), 61-70 years (45 patients- 12,5%), 71-80 years (26 patients- 7,1%), > 80 years (7 patients- 1,9%).

The youngest age at presentation was 14 years and the oldest age at presentation was 91 years (median age 44 years; IQR 34-58 years).

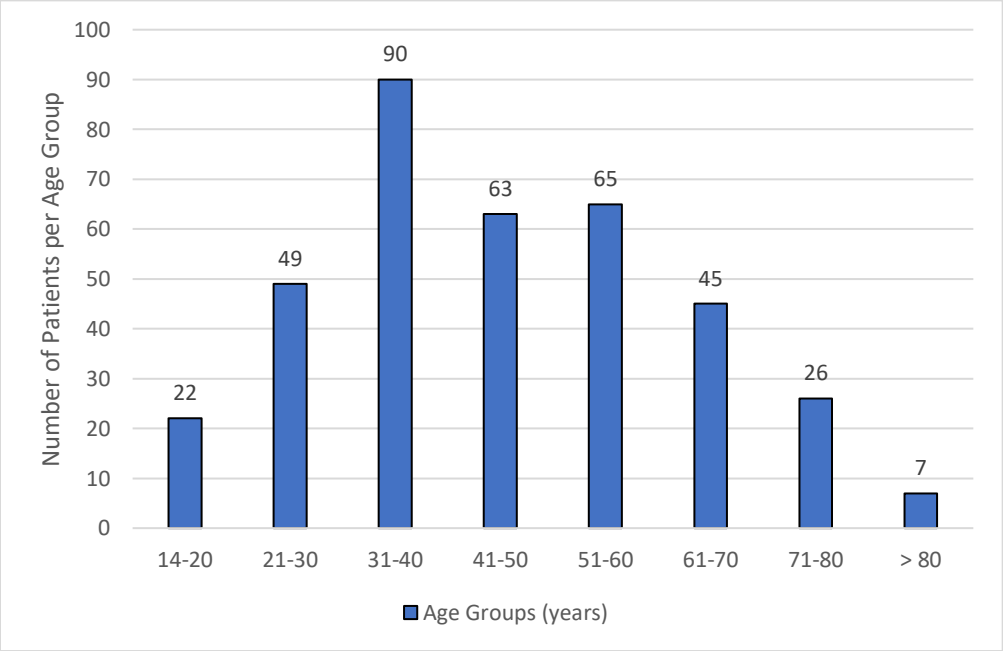


Figure 3: Age variables by numbers of patients included

3.1.2 Demographics: Human Immunodeficiency Virus (HIV) disease status, CD4 on presentation, antiretroviral (ARV) use and duration of antiretroviral use

One hundred and thirty-one (35,7%) of the patients enrolled in the study were HIV seropositive on enrolment. There were 239 patients (64,3%) who were HIV seronegative. None of the patients enrolled into the study had an unknown HIV serostatus.

Of the patients who were HIV seropositive, 38 (29,0%) had a CD_4 count of ≤ 100 cells/ µL, 42 (32,0%) had a CD_4 count between 101-200 cells/ µL, 19 (14,5%) had a CD_4 count between 201-350 cells/ µL, and 9 (6,9%) had a CD_4 count that was between 351-500 cells/ µL. A total number of 23 patients (17,6%) had a CD_4 count that was ≥ 501 cells/ µL.

Of those patients demonstrated to be HIV seropositive, 41 (31,3%) were noted to be taking ART at the time of the diagnosis of their haematological disorder. The remaining 90 (68,7%) were ART naïve at the time of the diagnosis of their haematological disorder.

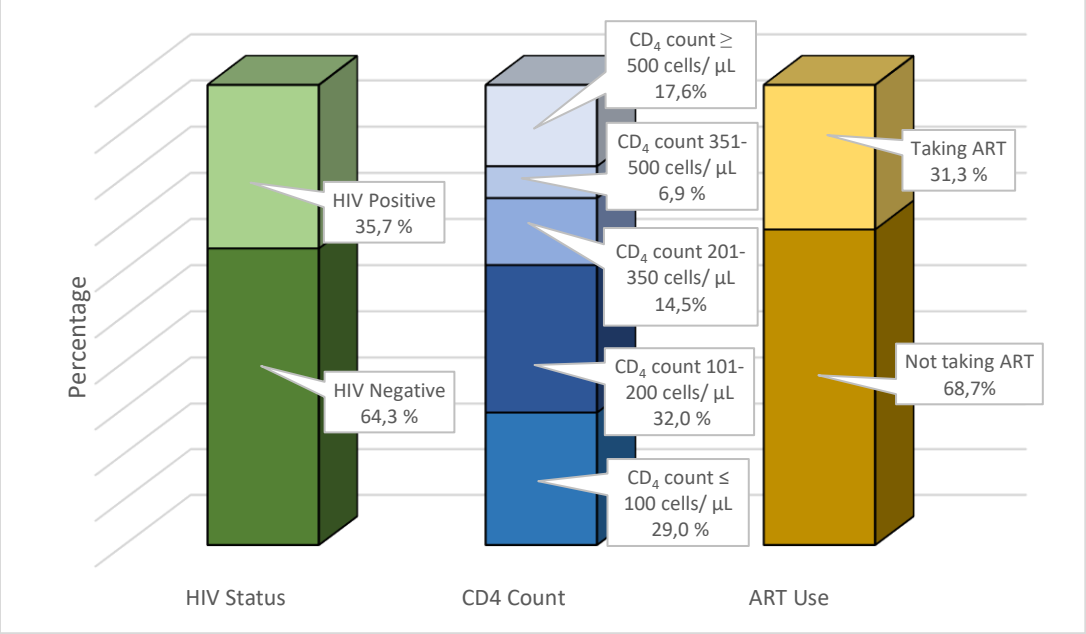


Figure 4: HIV disease demographic variables by percentage

3.2 Results of Specific Haematological Conditions Included

Over the 10 years of the study, 367 patients met the criteria as defined (previously) were included in the study. In order to assess splenomegaly across a broad range of haematological disorders, the underlying disorders were grouped as follows: (see table 6).

Table 6: Classification of haematological conditions

Haematological condition	**Subgroups**	**Disorders**	
Neoplasms of the Myeloid lineage	Acute Myeloid Leukaemia		
	Myeloproliferative Neoplasms	Chronic Myeloid Leukaemia Primary myelofibrosis Polycythaemia Rubra Vera Essential thrombocythaemia	
	Myelodysplastic Syndrome/ Myeloproliferative Neoplasm Variant	Chronic myelomonocytic leukaemia	
	Other conditions	Acute undifferentiated leukaemia	
Neoplasms of the Lymphoid lineage	B cell Lymphomas	Precursor lymphomas	Precursor B acute lymphoblastic leukaemia/ lymphoma Acute lymphoblastic leukaemia
		Peripheral/ mature lymphomas	Chronic Lymphocytic Leukaemia Waldenstrom's macroglobulinaemia Hairy Cell Leukaemia
	T cell/ Natural Killer Cell Lymphomas		
	Hodgkin Lymphoma		
	Plasma cell dyscrasias	Multiple myeloma Monoclonal gammopathy of undetermined significance Plasmacytoma Amyloidosis	
Bone marrow failure syndromes	Inherited	Fanconi's anaemia	
	Acquired	Hypoplastic anaemia Aplastic anaemia	
Nutritional anaemias	Iron deficiency anaemia Megaloblastic anaemia		

Haemolytic anaemias	Inherited	Membranopathies	Hereditary spherocytosis Hereditary elliptocytosis
		Metabolic derangements	Glucose-6-phosphate dehydrogenase deficiency
		Haemoglobinopathies	Sickle cell disease (trait and homozygous) Hereditary persistence of foetal hemoglobin
	Acquired	Immune	Autoimmune haemolytic anaemia Evans syndrome
		Non-immune	Paroxysmal nocturnal haemoglobinuria
Haemostatic abnormalities	Platelet disorders	Qualitative	
		Quantitative	Consumptive- Thrombotic Thrombocytopaenic Purpura Immune- Immune Thrombocytopaenic
	Coagulation abnormalities	Inherited	Haemophilia von Willebrand's disease
		Acquired	Protein C or Protein S deficiency Acquired factor inhibitors Superwarfarin
	Thrombosis	Venous thromboembolic disease Arterial thromboembolic disease Mixed venous and arterial thromboembolic disease	
Miscellaneous conditions	Carcinoma, Castleman's disease, Eosinophilia, Gaucher's disease, Haemochromatosis, Hypersplenism, Rheumatoid arthritis, Sarcoma, Sinus histiocytosis, Spinal cord compression, Systemic lupus erythematosus, Tuberculosis		

Using the classification system above, the 1 976 files that were initially assessed for inclusion were grouped as follows:

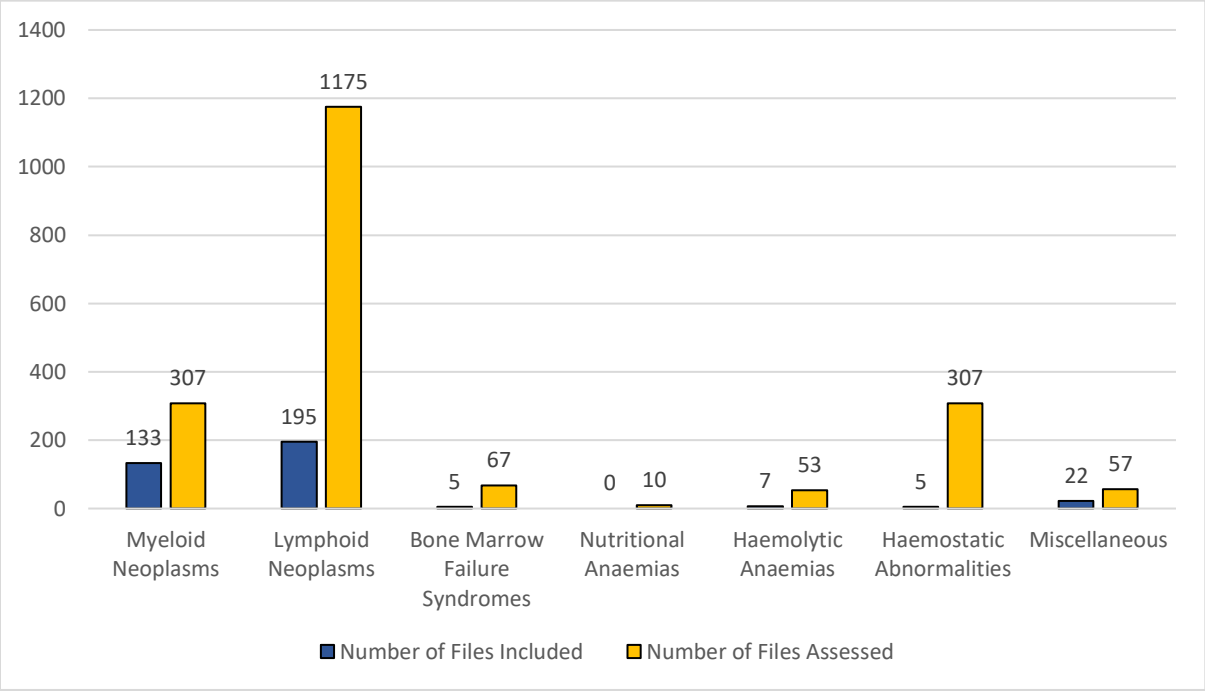


Figure 5**:** Number of files assessed and included per underlying Haematological condition over a 10 year period

This data may also be interpreted in terms of the overall makeup of the 367 patients who were included, as relative proportions of the total.

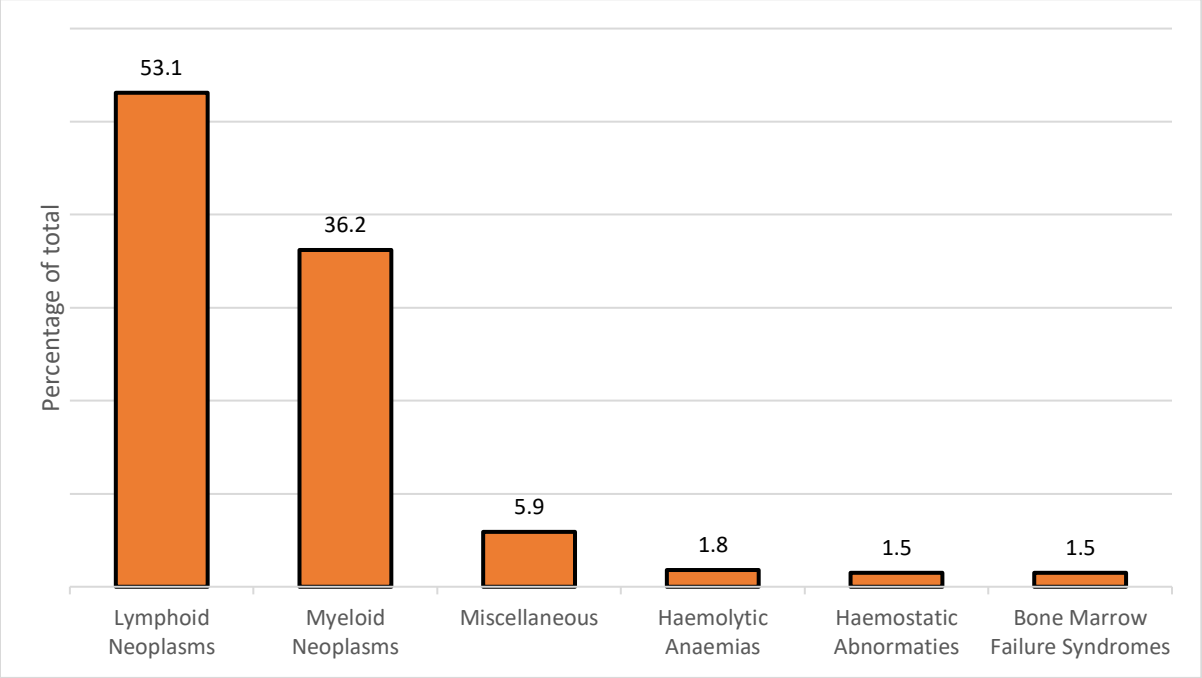


Figure 6: Diagnoses by percentage included in the study

3.2.1 Neoplasms of the myeloid lineage

A total of 307 files of patients with neoplasms of the myeloid lineage were assessed for inclusion over the 10 years of the study. In total, 133 patients (43,3%) with myeloid neoplasms were included in the study. The underlying haematological disorders encountered are described below (figure 7):

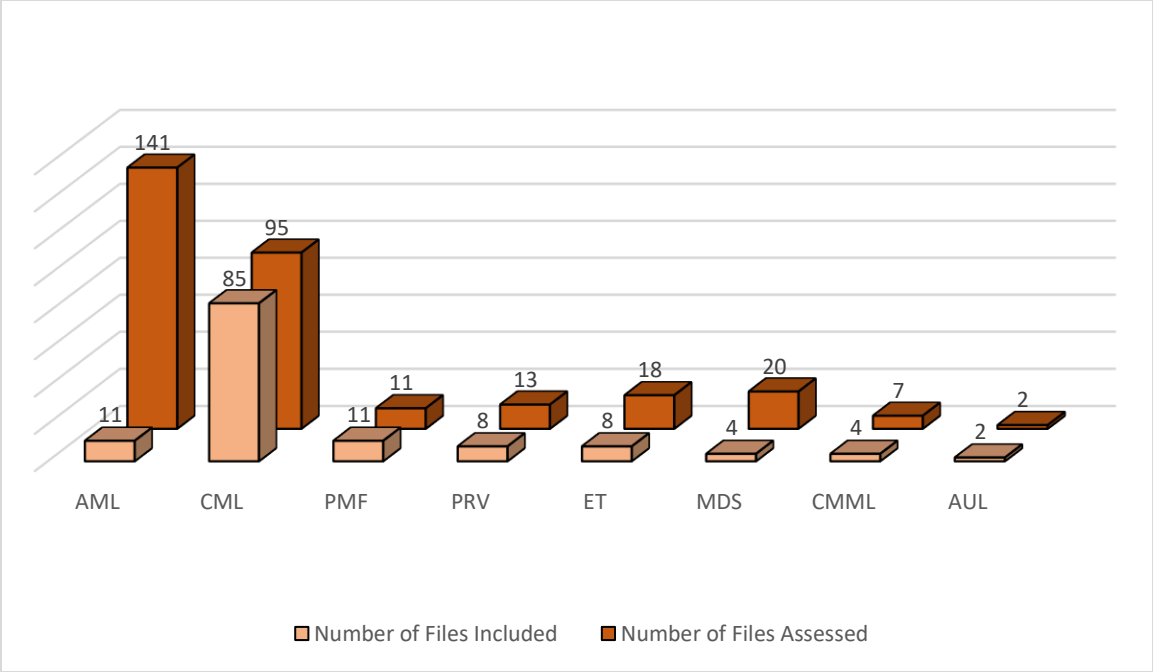


Figure 7**:** Breakdown of the numbers of files seen and included in the Myeloid neoplasm group

On clinical examination, 115 (86,4%) of the patients with myeloid neoplasms had clinical evidence of pallor, with 3 patients (2,3%) having evidence of clinical jaundice.

Of the 133 patients included, 123 were found to have splenomegaly clinically, while in 10 patients there were no clinical notes regarding the finding of splenomegaly.
However, splenomegaly was documented on radiological studies. The median size of the spleen as palpated below the costal margin for the myeloid neoplasms was 14 cm. The smallest measurement was 2cm and the largest measurement was 32 cm (IQR 10 cm-19 cm).

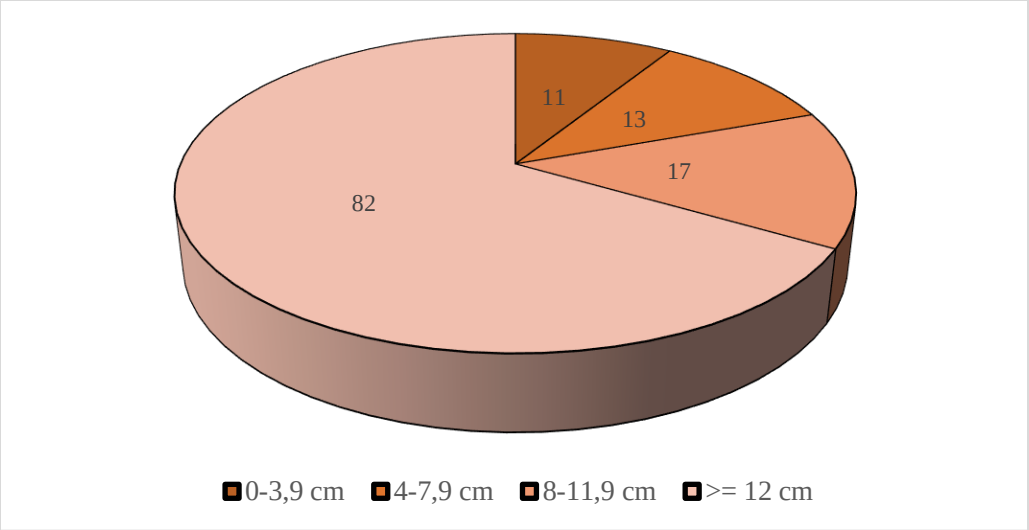


Figure 8**:** Breakdown of clinical splenomegaly within the Myeloid neoplasm group

Eighty-two patients (61,7%) met the criteria for massive splenomegaly, defined as a spleen length of greater than 12 cm measured below the costal margin.

The conditions that were associated with massive splenomegaly were CML (73 / 85 cases; 85,9% had massive splenomegaly) and PMF (9 / 11 cases; 81,8% had massive splenomegaly).

In these two conditions, the grading of splenomegaly was as follows: (table 7)

Table 7: Grading of splenomegaly in CML and PMF

	Mild	**Moderate**	**Moderate to massive**	**Massive**
CML (85 Patients)	0	0	12	73
PMF (11 patients)	0	0	2	9

Ninety-eight patients (73,6%) had clinical evidence of hepatomegaly that was associated with the splenomegaly. Massive hepatomegaly was present in 23 patients (17,3%) within the myeloid neoplasm group.

Massive hepatomegaly was present in CML (17 / 23 cases), AML (2 / 11 cases), PMF (1 / 9 cases), PRV (1 / 8 cases), CMML (1 / 4 cases) and AUL (1 / 2 cases).

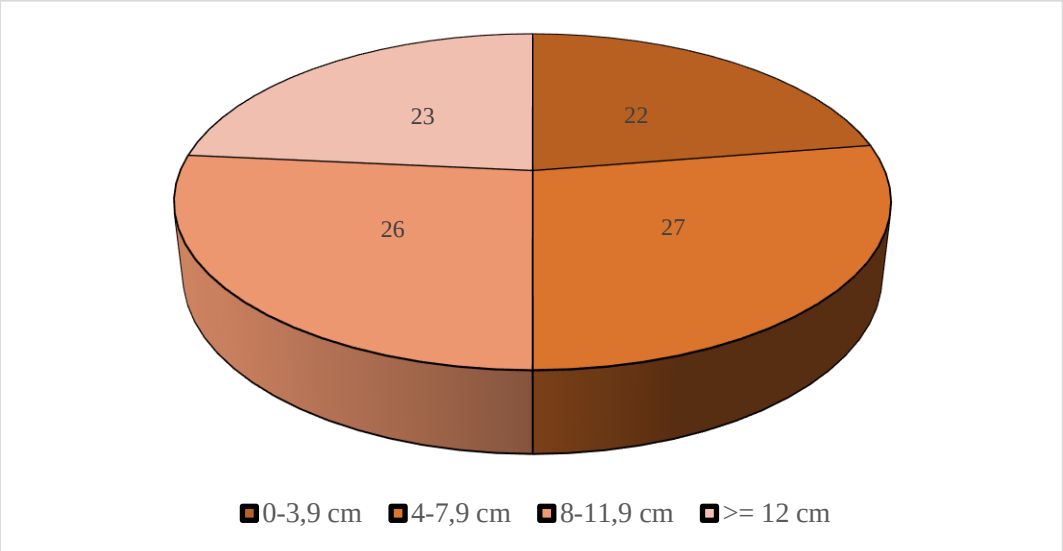


Figure 9: Breakdown of clinical hepatomegaly associated with clinical splenomegaly within the Myeloid neoplasm group

The accuracy with which splenomegaly was measured clinically versus ultrasound was assessed. The clinical measurement of splenomegaly ranged from 2 cm below the costal margin to 27 cm below the costal margin (median = 15 cm; IQR = 12-22 cm). Ultrasound measurements for the same group ranged from 9 cm to 32 cm (median = 17 cm; IQR = 14 cm).

Of the 65 patients that were eligible for the comparison between clinical and ultrasound measurements, 17 (26,2%) reported measurements that were accurate within 20 % of each other. An almost equal amount of 20 patients (30,8%) had measurements that were disparate by over 50%. The figure below (figure 10) maps the levels of concordance of clinical and ultrasound measurements in terms of the percentage difference between the measurements.

A difference of <10% in this instance equated to a difference in measurement of 1 cm and a difference in this instance of >70 % equated to 7 cm.

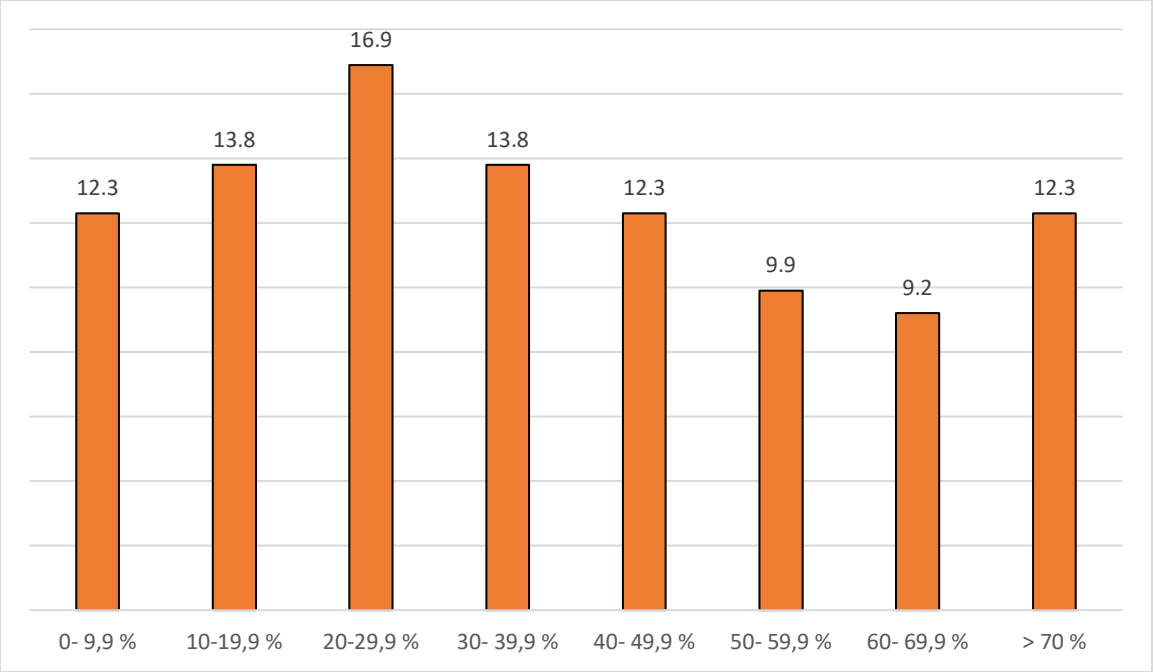


Figure 10: Comparison of the differences between clinical and ultrasound measurements of splenomegaly within the Myeloid neoplasm group

Only 2 patients were eligible for the comparison between the clinical and CT scan measurement of splenomegaly. This lack of data points prohibited the extrapolation of conclusions. Two patients had both ultrasound and CT scan measurements available, and similarly, this small data set precluded accurate analysis.

Haematological records for 2 of the 133 patients were unable to be located, therefore the results below represent the remaining 131 patients. The haematological findings associated with the myeloid neoplasms are depicted and graded in the figure below (figure 11):

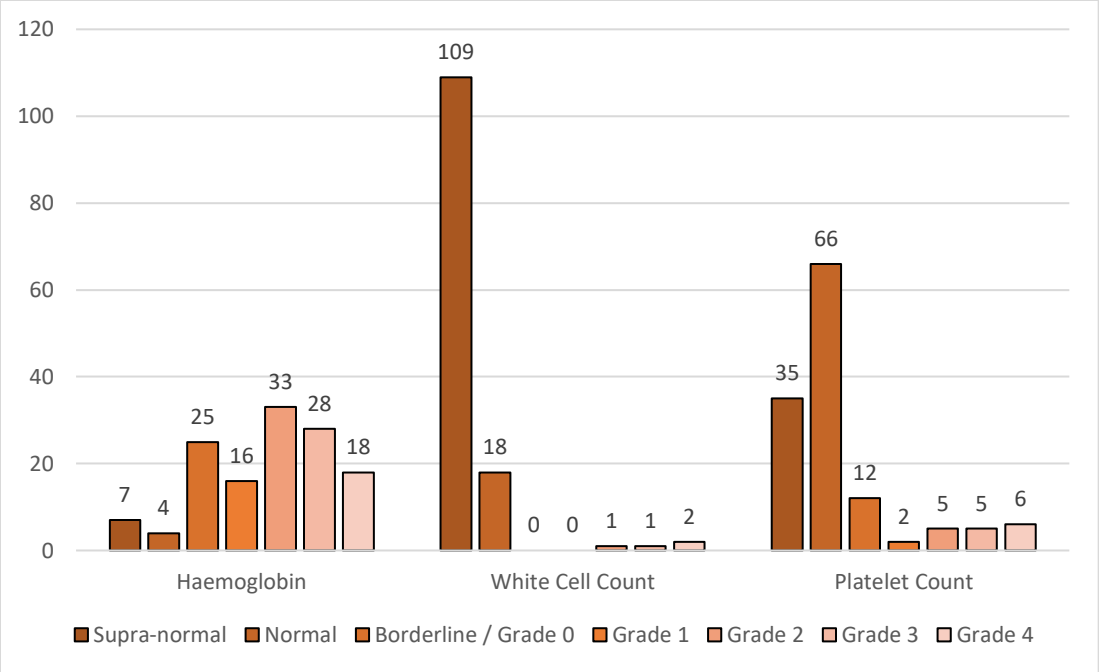


Figure 11: Grading of haematological parameters within the Myeloid neoplasm group

Each haematological disorder within the myeloid neoplasm group was assessed for significant correlation with haematological results obtained. These are expressed as p-values and significant findings are highlighted in bold typeface in the table below (table 8):

Table 8: Significance of the degree of splenomegaly versus laboratory parameters within the Myeloid neoplasm group

	Haemoglobin	Red Cell Count	White Cell Count	Platelets
Myeloid neoplasms (n=140)	0,317	0,305	0,659	0,183
AML (n=11)	0,052	0,556	0,858	0,191
CML (n=85)	0,659	0,995	0,234	0,776
PMF (n=11)	0,980	0,202	0,721	0,640
PRV (n=8)	0,524	0,640	0,052	0,092
ET (n=8)	0,222	0,805	0,051	**0,040**
MDS (n=4)	Too few data	Too few data	Too few data	Too few data
CMML (n=4)	Too few data	Too few data	Too few data	Too few data
AUL (n=2)	Too few data	Too few data	Too few data	Too few data

Increasing spleen size was plotted against laboratory findings and p-values were calculated using regression analysis. Haematological parameters are plotted against increasing spleen sizes:

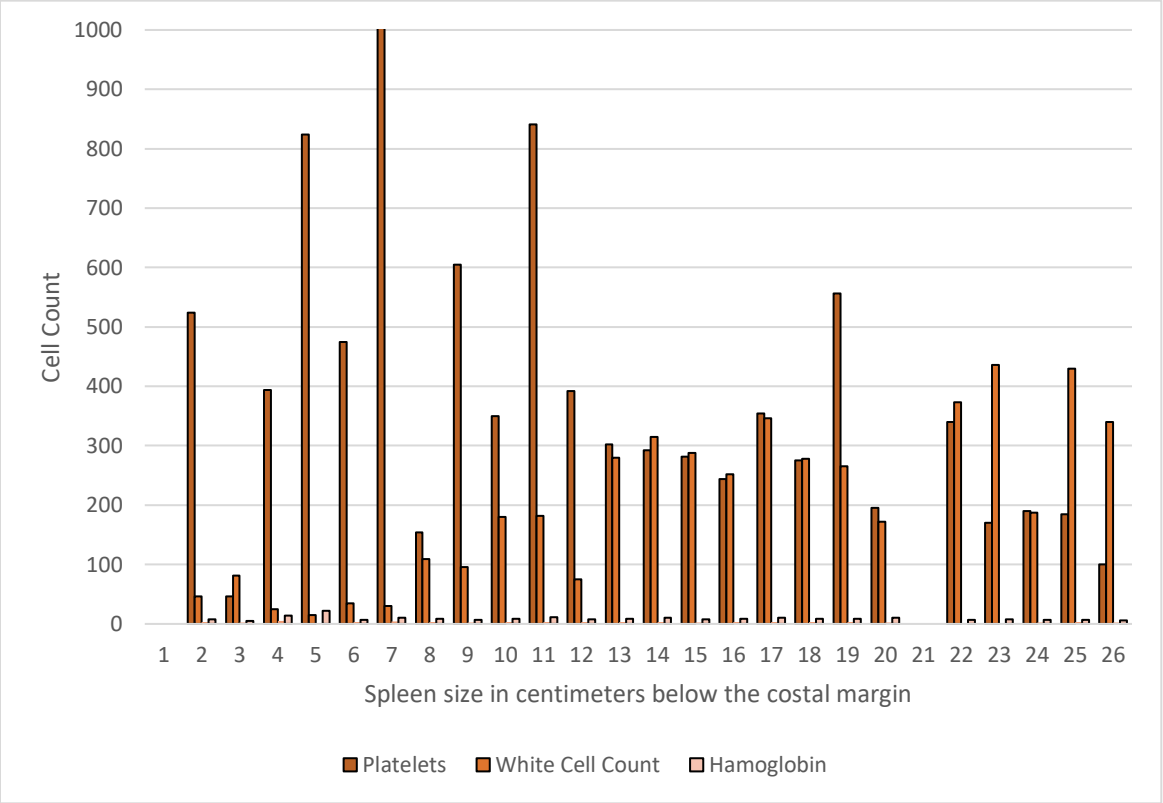


Figure 12: Association between spleen size and haematological values within the Myeloid neoplasm group

3.2.2 Neoplasms of the lymphoid lineage

A total of 1 175 files of patients with neoplasms of lymphoid origin were assessed.

In total, 195 patients (16,6%) were eligible for inclusion in the study.

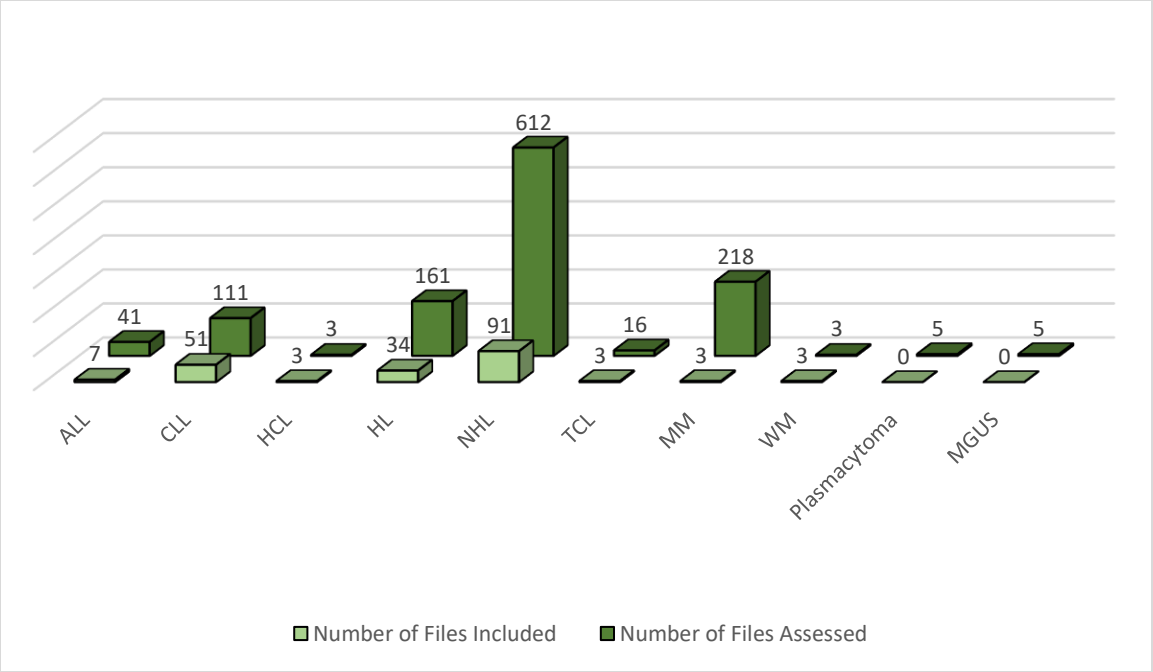


Figure 13: Numbers of files seen and included within the Lymphoid neoplasm group

The patients included in the study with both Hodgkin lymphoma and non-Hodgkin's lymphoma were further classified according to the underlying subtype of disease. Within the Hodgkin lymphoma group, 6 patients' records were labelled as "classical", and no further subtype was provided. In 1 patient record the Hodgkin lymphoma was unclassifiable. These 7 patients have been classified as "unidentifiable" in relation to a specific subtype. Similarly, the subtype of 4 patients included in the non-Hodgkin lymphoma group were unable to be classified histologically and were labelled as unidentifiable.

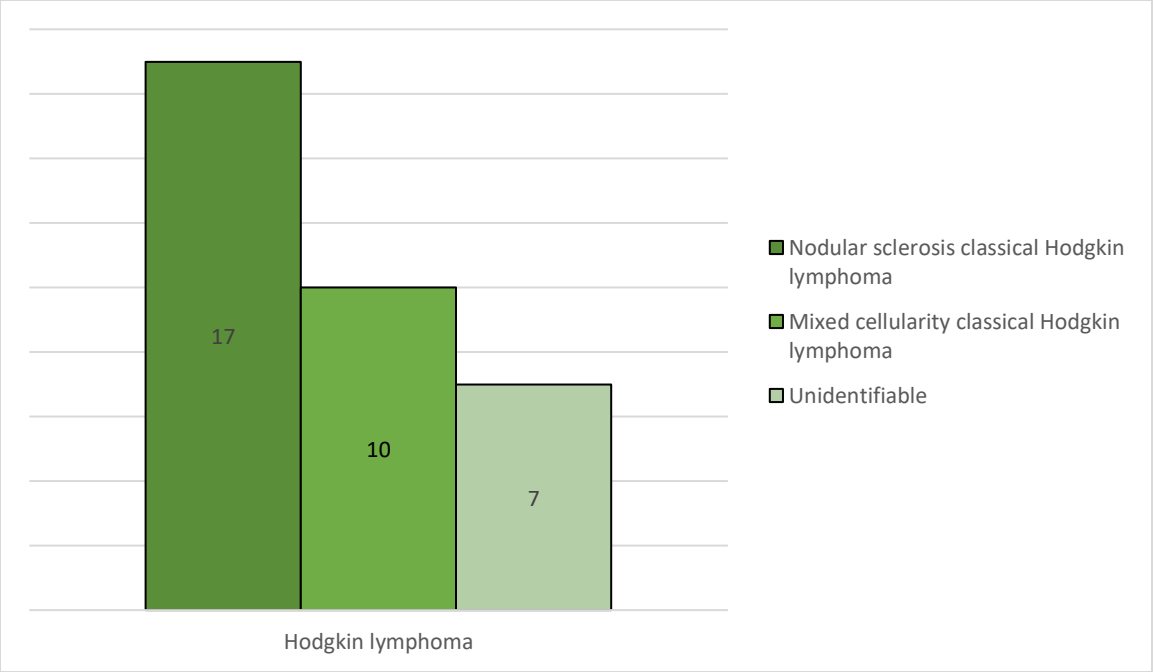


Figure 14: Subsets of Hodgkin Lymphoma included in the study

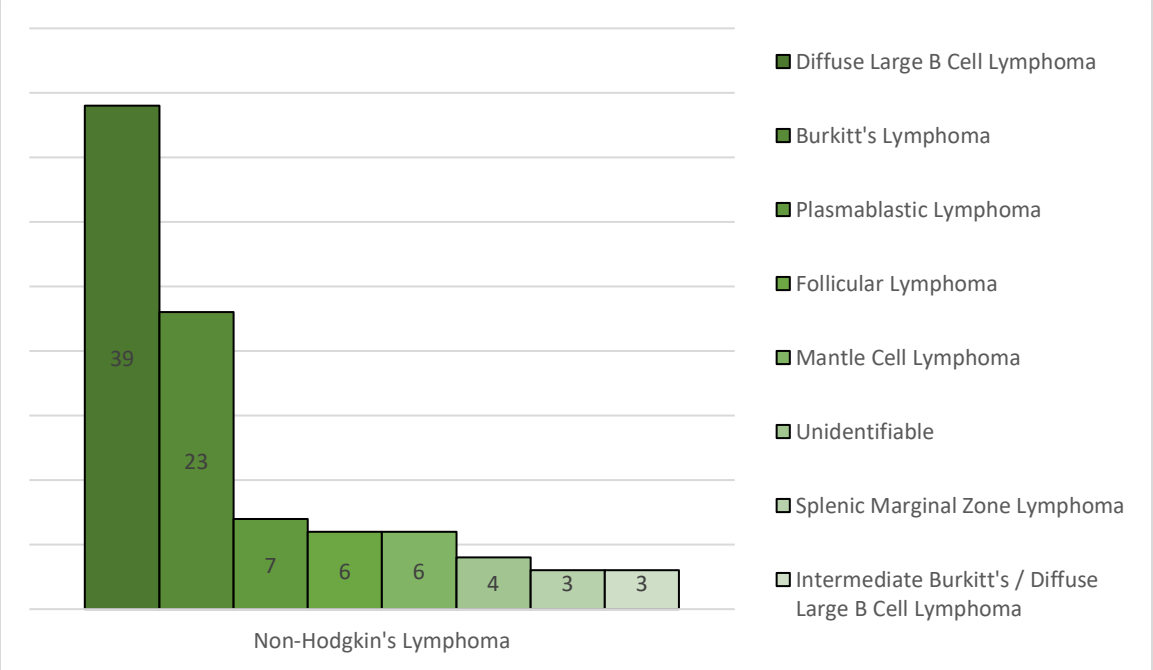


Figure 15: Subsets of Non-Hodgkin Lymphoma included in the study

Almost all the patients with lymphoid neoplasms had clinical evidence of pallor (180 patients; 92,3%), with 21 patients (10,8%) having jaundice detected clinically.
Splenomegaly was detected in 186 patients (95,4%) clinically, and the remaining 9 patients (4,6%) having radiographic evidence of splenomegaly that was not documented clinically. The median size of the spleen overall as palpated below the costal margin for the lymphoid neoplasms was 4 cm. The smallest measurement was 1 cm and the largest measurement was 16 cm (IQR= 3 cm to 7 cm).

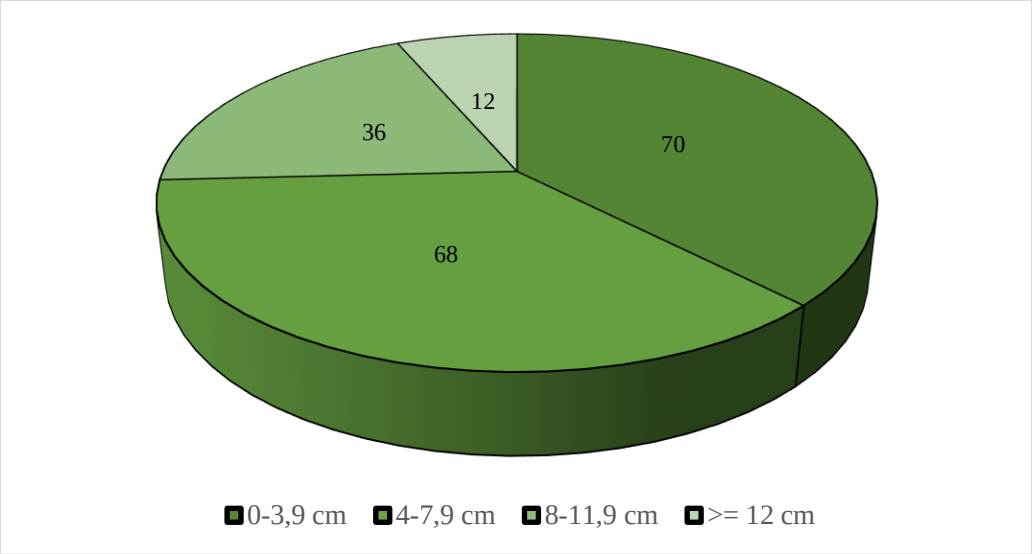


Figure 16**:** Breakdown of clinical splenomegaly within the lymphoid neoplasms

Twelve patients (6,5%) met the criteria for massive splenomegaly. These 12 patients comprised the following: ALL (6 / 7 patients); CLL (2 / 51 patients); NHL (2 / 91 – 1 Mantle cell lymphoma, 1 Diffuse large B cell lymphoma); TCL (2 / 3 patients).

The clinical detection of splenomegaly versus the corresponding measurement by ultrasound were compared. Of the 56 patients who were eligible for this comparison, 30 (53,6%) reported measurements that were accurate to within 20 % (i.e. a discrepancy in measurement of <20 %). This equated to a difference in measurement of within 2 cm.

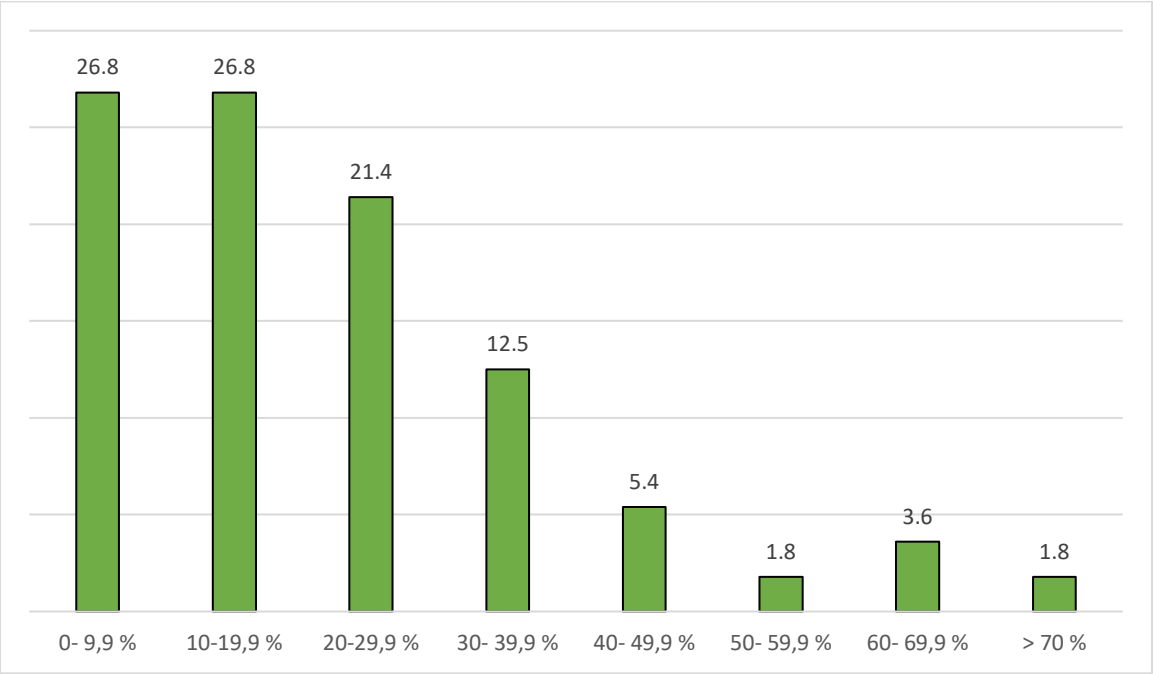


Figure 17: Comparison of the clinical measurement of splenomegaly versus the ultrasound measurement of splenomegaly within the lymphoid neoplasms

The comparison between the clinical measurement of splenomegaly and CT scan measurements were possible in 34 patients. Of these 34 patients, 20 patients (58,8%) reported measurements that were accurate to within 20 %. Ultrasound and CT scan measurements were available in 9 patients. Six (88,9 %) had measurements that were within 20% of each other.

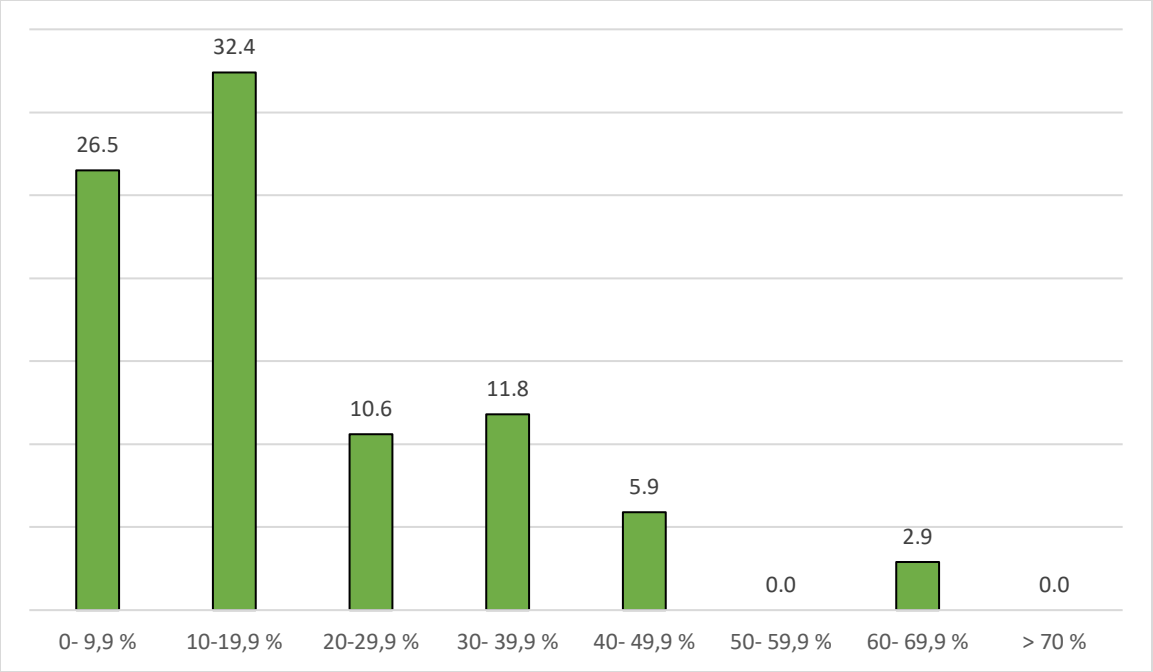


Figure 18: Comparison of the clinical measurement of splenomegaly versus the CT scan measurement of splenomegaly within the lymphoid neoplasms

The clinical finding of hepatomegaly was present in 156 patients (80,0%). The grading of hepatomegaly encountered within the lymphoid group is depicted below:

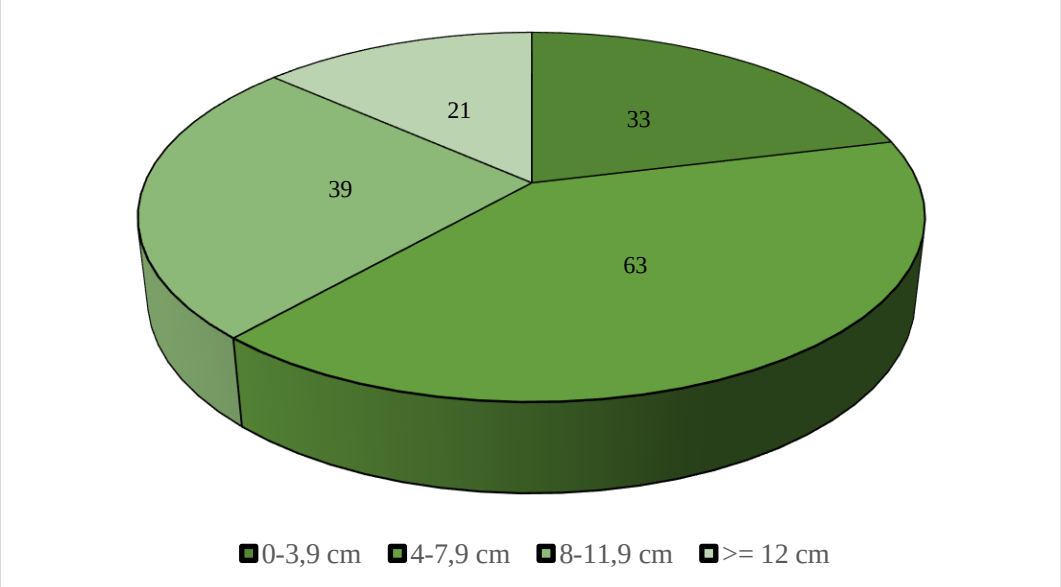


Figure 19: Hepatomegaly associated with clinical splenomegaly within the lymphoid neoplasms

Massive hepatomegaly was detected in 21 patients (10,8%) within the lymphoid neoplasm group. The breakdown of massive hepatomegaly was as follows: ALL (1 / 7 patients); NHL (10 / 91 patients: 7 Diffuse large B cell lymphoma, 1 Follicular lymphoma, 1 Burkitt's lymphoma and 1 undetermined subtype); CLL (5 / 51 patients); HL (3 / 34 patients: 2 Nodular sclerosis and 1 unidentifiable subtype); TCL (1 / 3 patients) and WM (1 / 3 patients).

The haematological records for 6 of the 195 patients were unable to be located, thus the results below are for the remaining 189 patients. The haematological findings associated with the lymphoid neoplasms are depicted in the figure below:

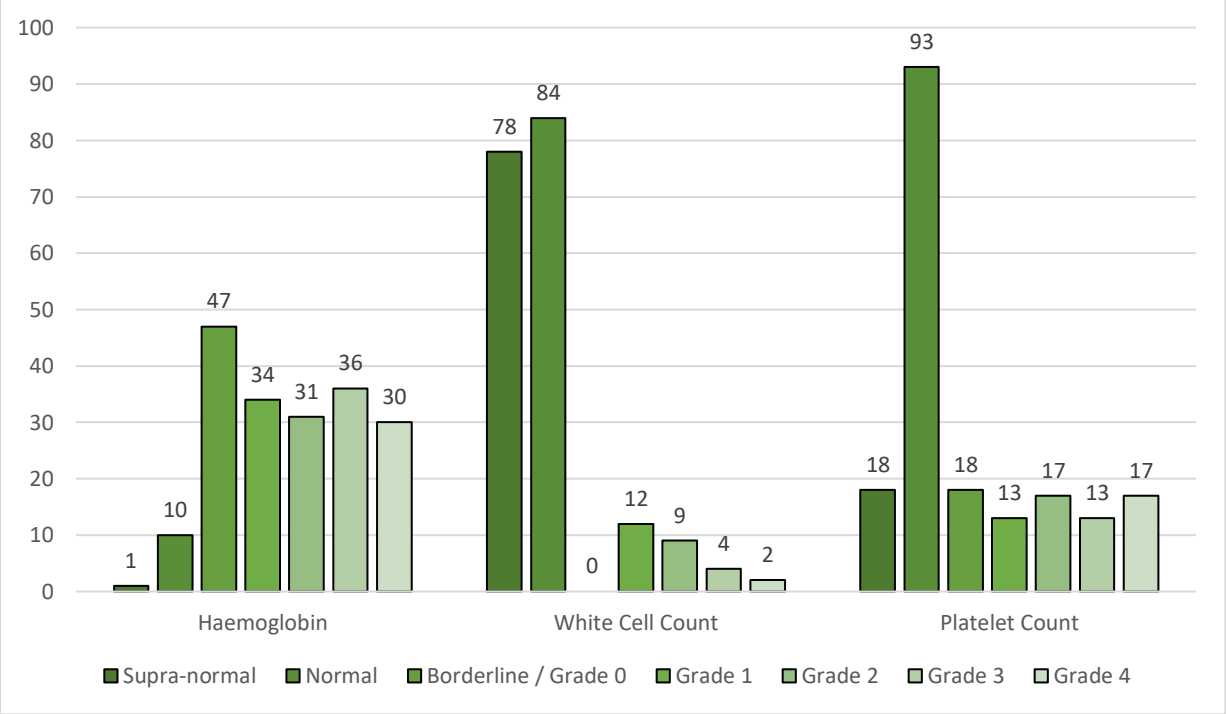


Figure 20**:** Grading of haematological parameters within the lymphoid neoplasms

In attempting to ascertain a correlation between spleen size and possible haematological abnormalities, the results of laboratory findings were plotted against the clinical measurement of splenomegaly. Mean haematological values for platelet count, haemoglobin and white cell count were plotted against corresponding increasing splenic size:

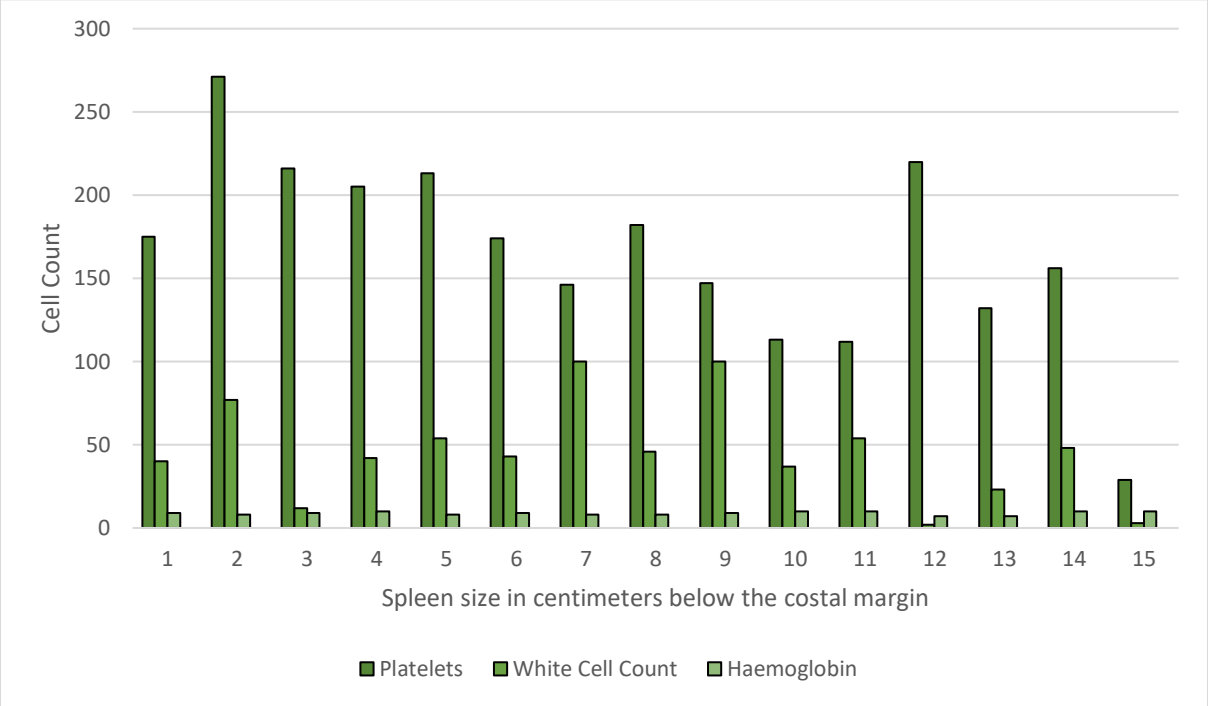


Figure 21: Association between spleen size and haematological values in patients with neoplasms of the lymphoid lineage

Each haematological disorder within the lymphoid neoplasm group was assessed for possible significant correlations with the haematological results. The results are expressed as p-values and significant findings are highlighted in bold typeface in the table below:

Table 9: Significance of the degree of splenomegaly versus laboratory parameters within the Lymphoid neoplasm group

	Haemoglobin	Red Cell Count	White Cell Count	Platelets
Lymphoid neoplasms (n=198)	0,615	**0,040**	**0,024**	**0,002**
NHL (n=91)	0,615	0,950	0,123	0.095
CLL (n=51)	0,087	**0,034**	0,063	0,472
HL (n=34)	0,525	0,830	0,179	0,383
ALL (n=7)	0,064	0,132	0,324	0,980
TCL (n=5)	0,063	**0,011**	0,303	0,968
MM (n=4)	0,054	0,064	0,195	0,355
HCL (n=3)	0,410	0,345	0,761	0,902
WM (n=3)	0,791	0,454	0,895	0,290

The haematological parameters were assessed against the differing subtypes of both Hodgkin lymphoma and non-Hodgkin lymphoma and expressed as p-values in the tables below. Significant findings are highlighted in bold.

Table 10: Significance of the degree of splenomegaly versus laboratory parameters within the Non-Hodgkin Lymphoma group

	Haemoglobin	Red Cell Count	White Cell Count	Platelets
Non-Hodgkin's lymphoma (n=91)	0,615	0,946	0,123	0,096
Diffuse large B cell lymphoma (n=39)	0,432	0,842	0,624	0,754
Burkitt's lymphoma (n=22)	0,146	0,194	0,924	0,310
Plasmablastic lymphoma (n=7)	0,267	0,370	**0,013**	0,595
Follicular lymphoma (n=6)	0,566	0,636	0,167	0,756
Mantle cell lymphoma (n=6)	0,883	**0,040**	0,522	0,076
Undetermined (n=4)	0,490	0,676	0,651	0,882
Splenic marginal zone lymphoma (n=3)	0,932	**0,040**	0,761	0,901
Intermediate Burkitt's / Diffuse large B cell lymphoma (n=3)	0,746	0,541	0,060	0,345
Hodgkin lymphoma (n=34)	0,525	0,829	0,179	0,383
Nodular sclerosis classical Hodgkin lymphoma (n=17)	0,271	0,774	0,472	0,267
Mixed cellularity classical Hodgkin lymphoma (n=10)	0,599	0,612	0,386	0,831
Unidentifiable (n=7)	0,536	0,537	0,298	0,340

3.2.3 Bone marrow failure syndromes

A total of 67 files of patients with bone marrow failure syndromes were assessed. In total, 5 patients (7,5%) were included in the study.

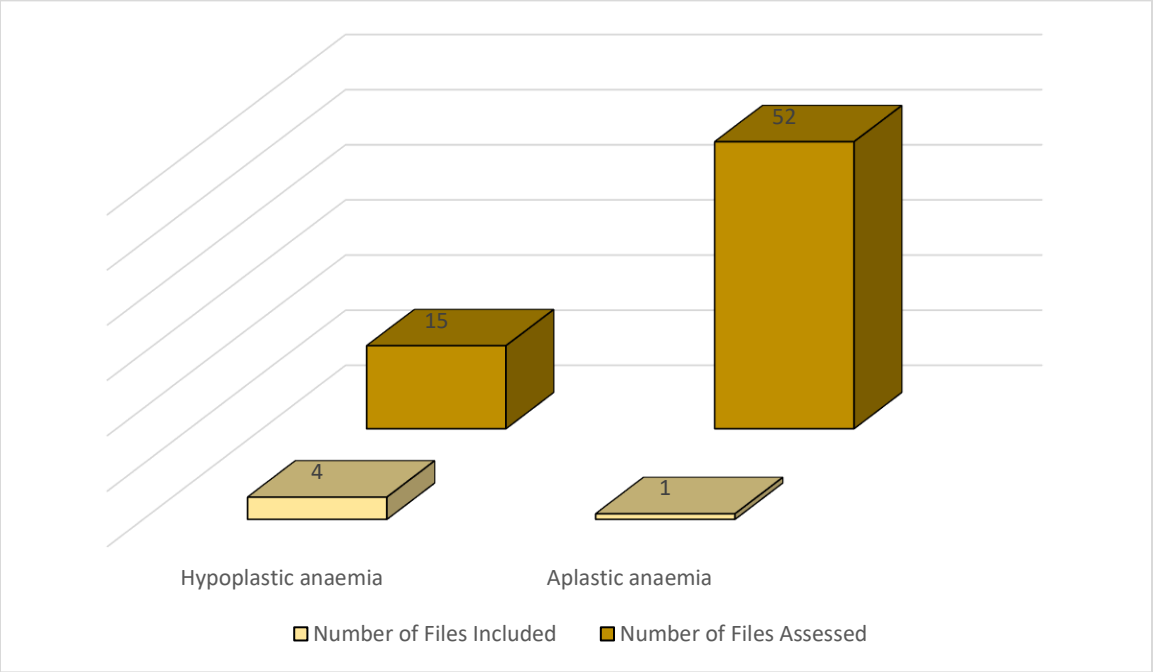


Figure 22: Numbers of files seen and included within the bone marrow failure syndromes

In the 4 patients with hypoplastic anaemia, all 4 had clinical evidence of pallor and all were jaundiced. The patient with aplastic anaemia had pallor and was not jaundiced.

Splenomegaly was detected clinically in all 5 patients. The median size of the spleen as palpated below the costal margin for the bone marrow failure syndromes was 4 cm. The smallest measurement was 4 cm and the largest measurement was 8 cm (IQR= 4 cm-6 cm).

None of the patients in the bone marrow failure group met the criteria for massive splenomegaly. The small numbers in this group preclude the comparison of the different methods to detect splenomegaly.

All the patients with Hypoplastic anaemia had hepatomegaly clinically. None of the patients had measurements fulfilling the criteria for massive hepatomegaly.

The patient with aplastic anaemia did not have hepatomegaly. The relative grading of both splenomegaly and hepatomegaly encountered within the bone marrow failure group is depicted below:

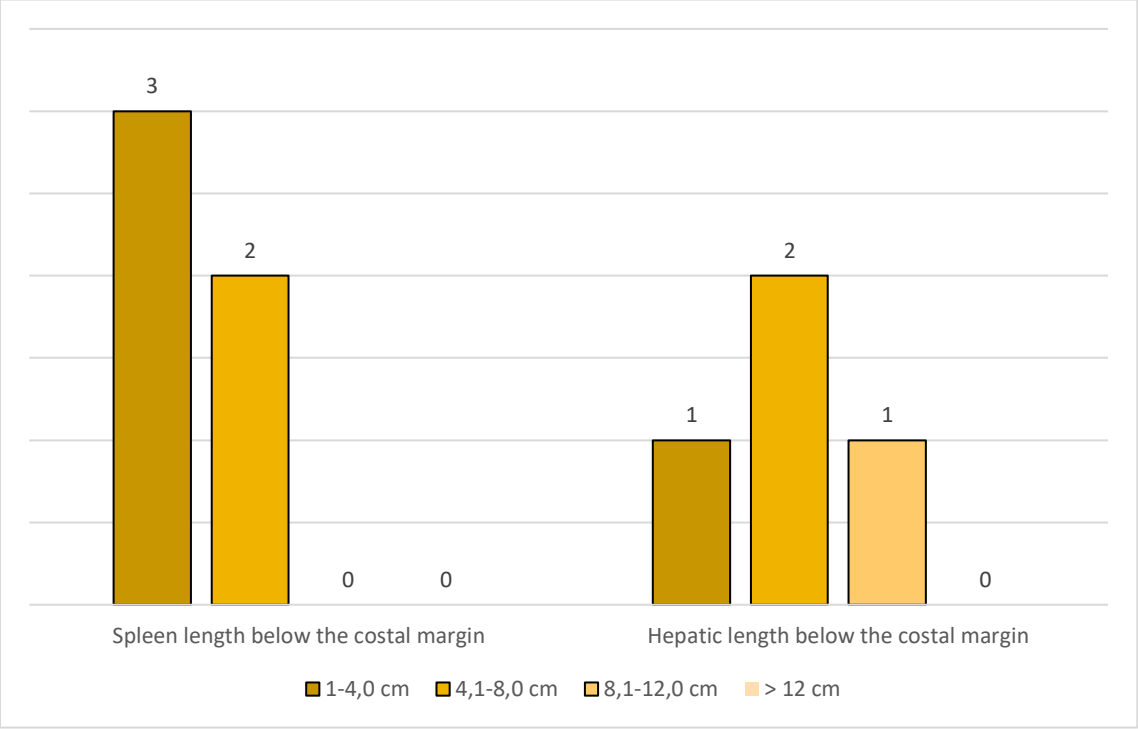


Figure 23: Breakdown of clinical splenomegaly and hepatomegaly within the bone marrow failure syndromes

The small sample size rendered data analysis of splenomegaly and the associated cytopaenias inconclusive. The haematological finding associated with the bone marrow failure syndromes are depicted in the figure below:

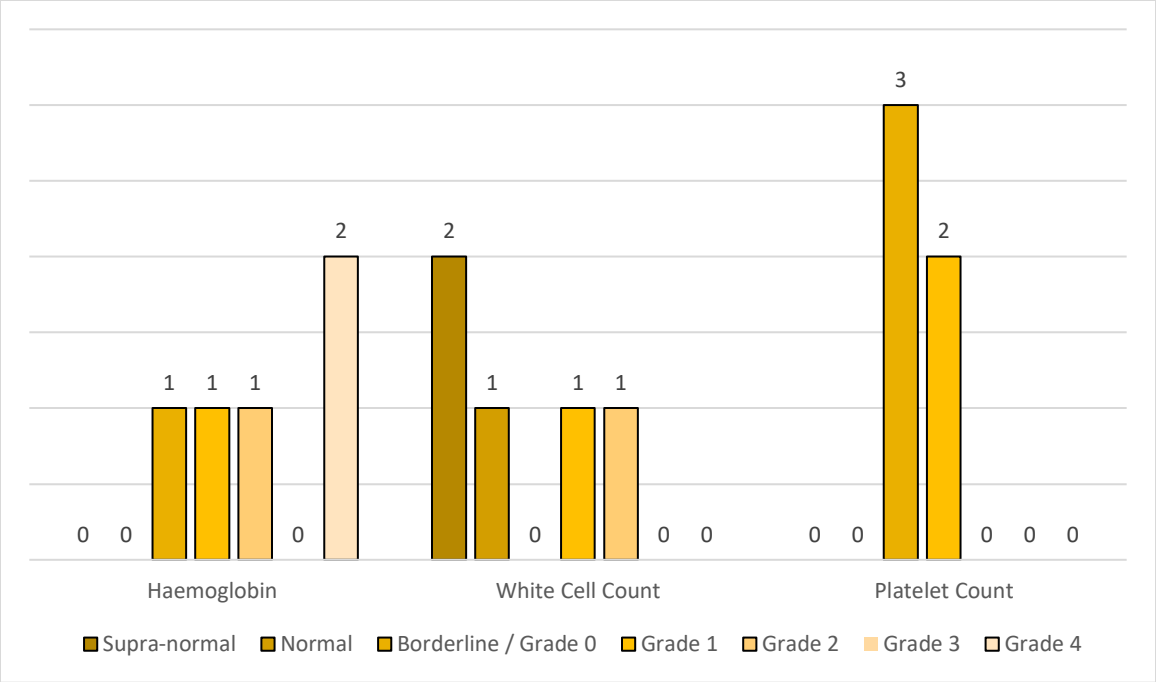


Figure 24: Grading of haematological parameters within the bone marrow failure syndromes

3.2.4 Nutritional anaemias

In total, 10 patients were assessed that had nutritional anaemias. There were 9 patients with iron deficiency anaemia, and 1 patient with megaloblastic anaemia. None of the 10 patients reviewed had either clinical or radiological evidence of splenomegaly.

3.2.5 Haemolytic anaemias

Over the 10 years, 53 files of patients with haemolytic anaemias were assessed. In total, 7 patients (13,2 %) were found to have splenomegaly and were included in the study.

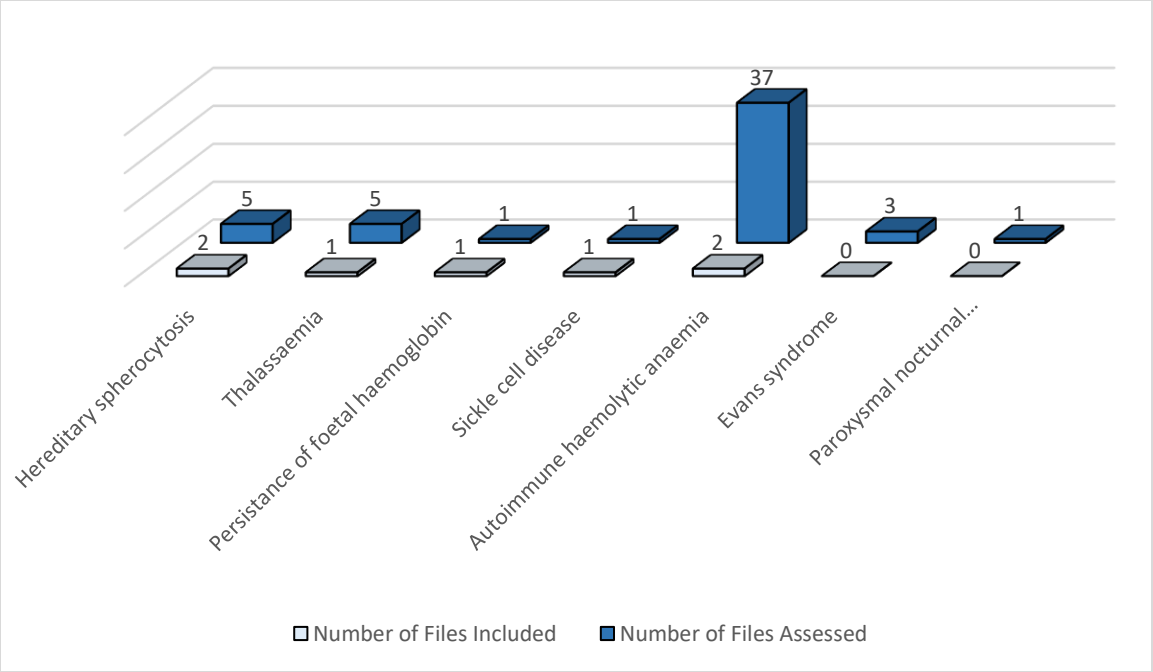


Figure 25: Numbers of files seen and included within the haemolytic anaemia syndromes

In patients with haemolytic anaemia, 6 of the 7 patients had clinical evidence of pallor. Jaundice was detected clinically in 4 of the 7 patients.

Splenomegaly was detected clinically in all 7 patients. The median size of the spleen as palpated below the costal margin was 8 cm. The smallest measurement was 2 cm and the largest measurement was 11 cm (IQR=4 cm- 10 cm).

None of the patients with haemolytic anaemia met the criteria for massive splenomegaly. The low numbers of patients in this group were not statistically significant for analysis.

Five of the 7 patients with haemolytic anaemia had hepatomegaly clinically (none had massive hepatomegaly).

The grading of both splenomegaly and hepatomegaly encountered within the bone marrow failure group is depicted below:

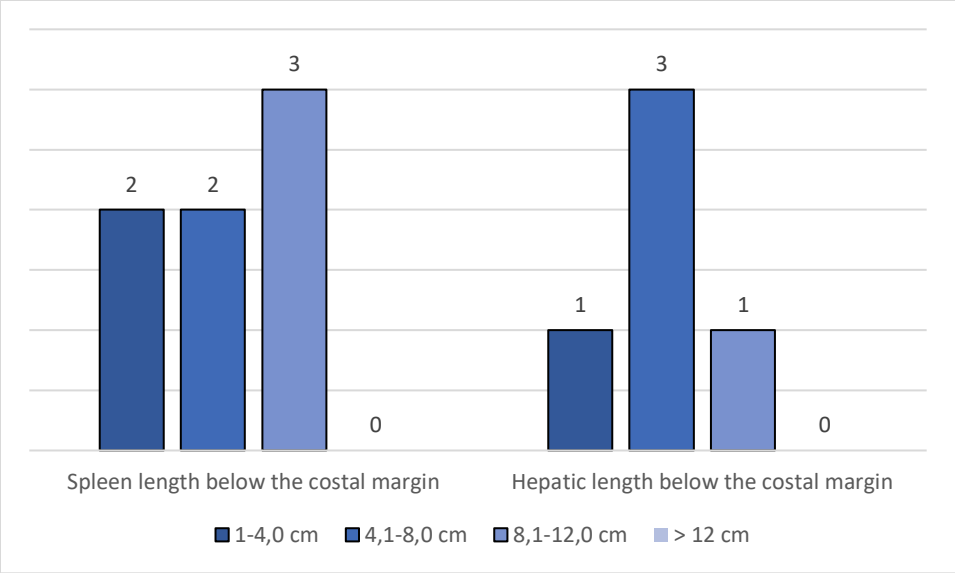


Figure 26: Breakdown of clinical splenomegaly and hepatomegaly within the haemolytic anaemia syndromes

One patient's haematological record could not be found. Thus, the results depicted below are for the 6 remaining patients. The haematological findings associated with the bone marrow failure syndromes are shown below:

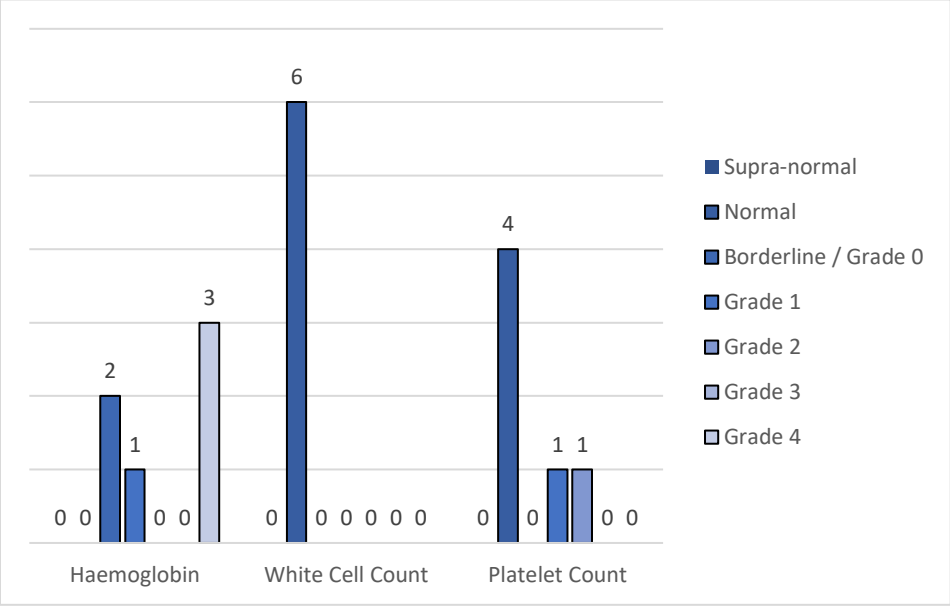


Figure 27: Grading of haematological parameters within the haemolytic anaemia syndromes

3.2.6 Haemostatic abnormalities

A total of 307 files with disorders relating to haemostasis were assessed. In total, 5 patients (1,6%) met the inclusion criteria for the study.

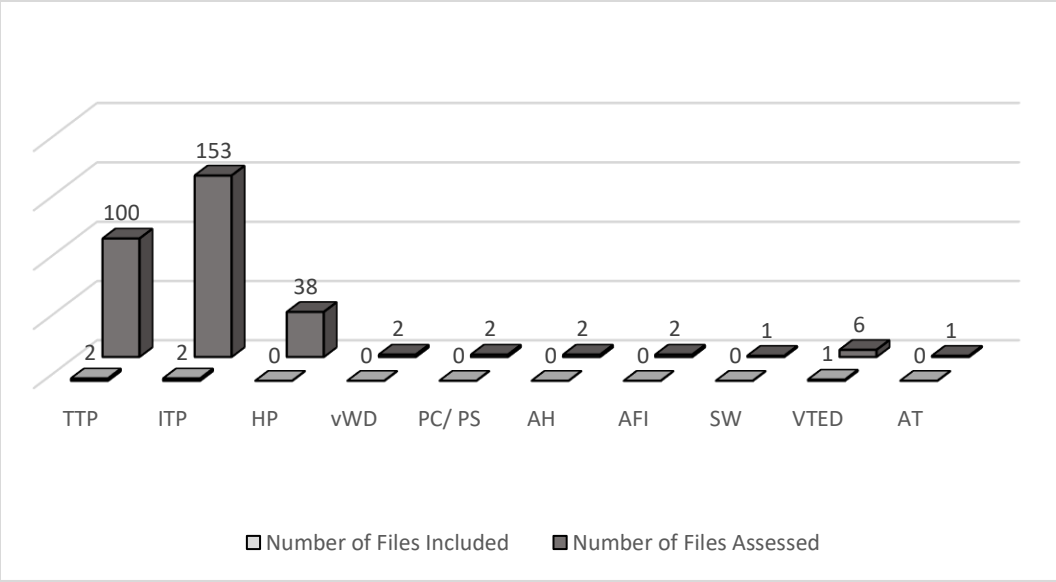


Figure 28: Numbers of files seen and included with disorders of haemostasis group

All 5 patients included had clinical evidence of pallor, with both of the patients with TTP having jaundice clinically.

Splenomegaly was detected clinically in all 5 patients. The median size of the spleen palpated below the costal margin was 9 am. The smallest measurement was 1 cm and the largest measurement was 13 cm (IQR=2 cm to 7 cm). Only the patient with venous thromboembolic disease met the criteria for massive splenomegaly. The cause of the massive splenomegaly on the background of VTED was found to include concomitant portal vein thrombosis, as part of a background pro-thrombotic state.

Four of the 5 patients with haemostatic disorders had hepatomegaly clinically. The patient with VTED did not have hepatomegaly. One of the patients with TTP had massive hepatomegaly. The grading of both splenomegaly and hepatomegaly are shown below:

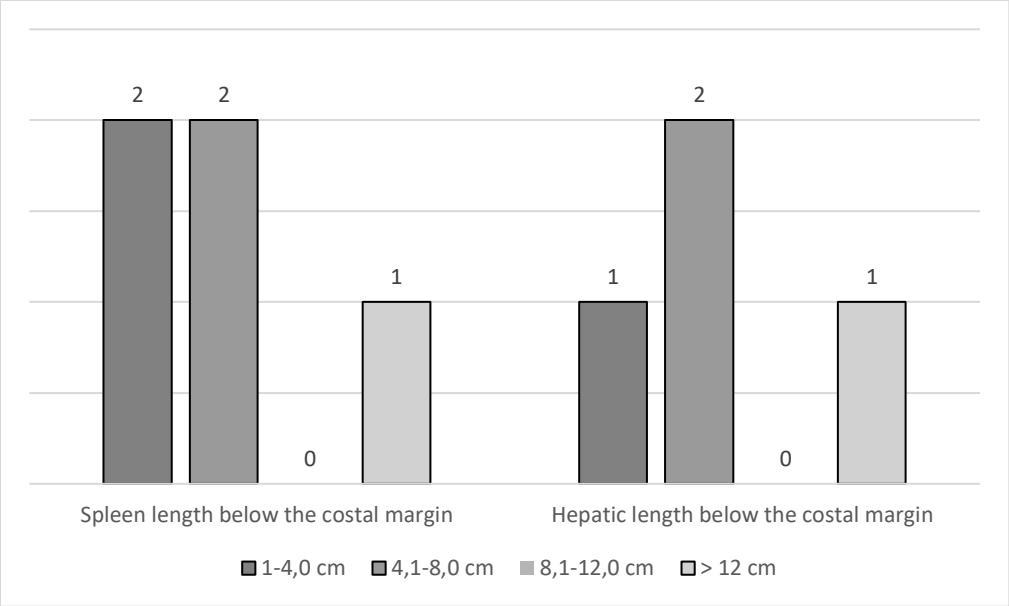


Figure 29: Breakdown of clinical splenomegaly and hepatomegaly within the disorders of haemostasis group

The haematological findings for this group are depicted below:

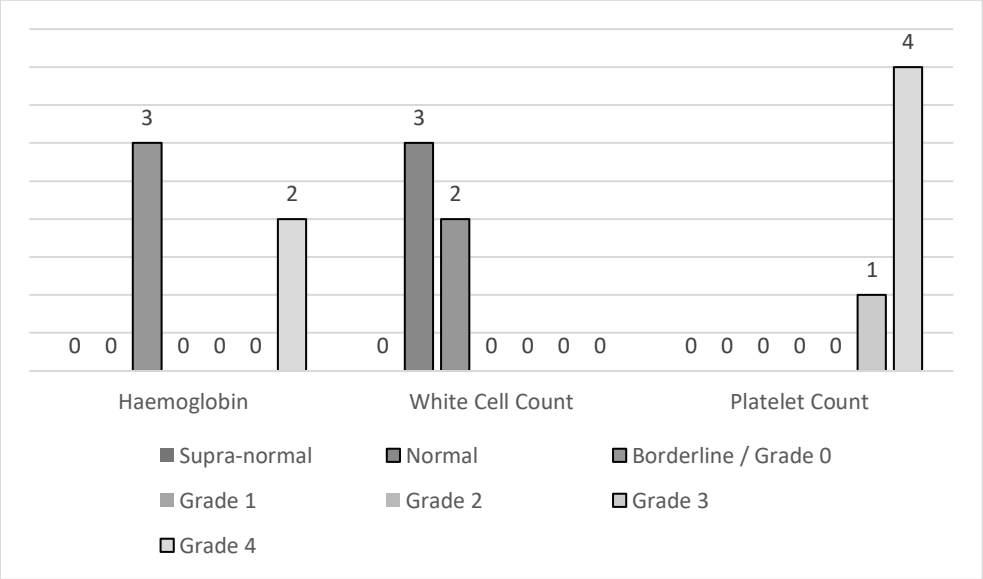


Figure 30: Grading of haematological parameters within the disorders of haemostasis group

3.2.7 Miscellaneous conditions

The miscellaneous conditions comprise the following conditions: carcinoma, Castleman's disease, eosinophilia, Gaucher's disease, haemochromatosis, hypersplenism, retroviral disease, rheumatoid arthritis, sarcoma, sinus histiocytosis, spinal cord compression, systemic lupus erythematosus and tuberculosis.

Fifty-seven files meeting the above diagnoses were assessed, and 22 patients (38,5 %) were eligible for inclusion.

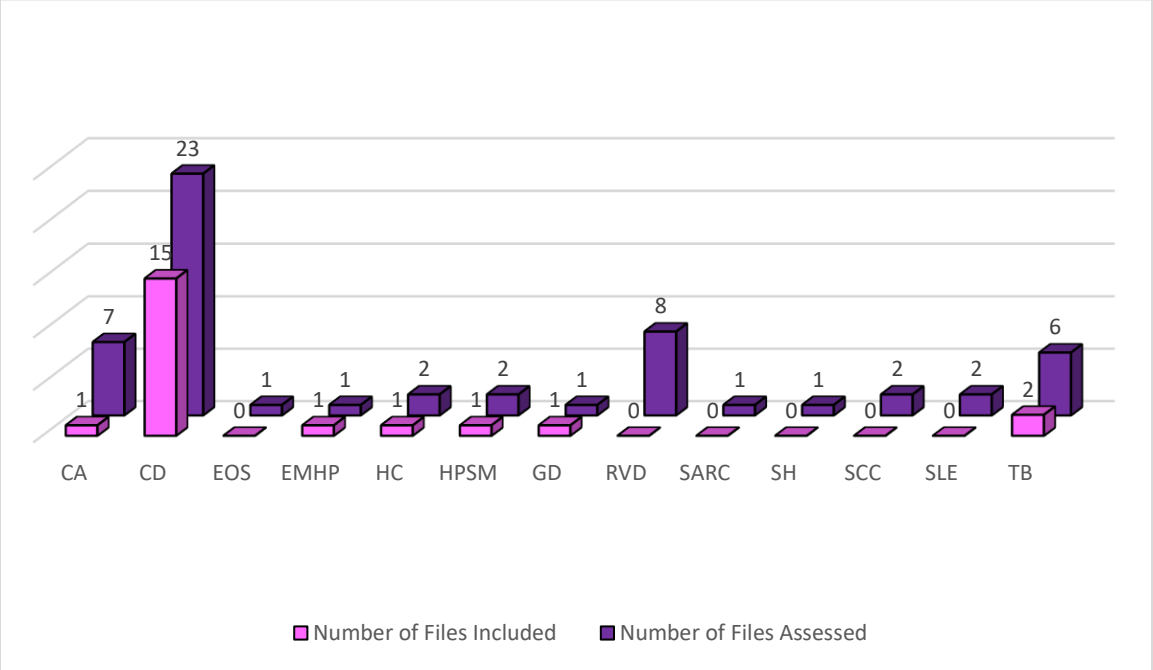


Figure 31: Numbers of files seen and included with miscellaneous haematological conditions

All 22 patients included had clinical evidence of pallor; clinical jaundice was detected in 3 patients (13,6 %).

Splenomegaly was detected clinically in all 22 patients. The median size of the spleen as palpated below the costal margin was 4 cm. The smallest measurement was 1 cm and the largest measurement was 21 cm (IQR= 1 cm to 11,5 cm).

Six of the patients included met the criteria for massive splenomegaly, as previously defined. The underlying conditions in these 6 patients were: CD (3 patients), HPSM (1 patient), EMHP (1 patient) and GD (1 patient). Hepatomegaly was detected in 16 patients, of which none had massive hepatomegaly.

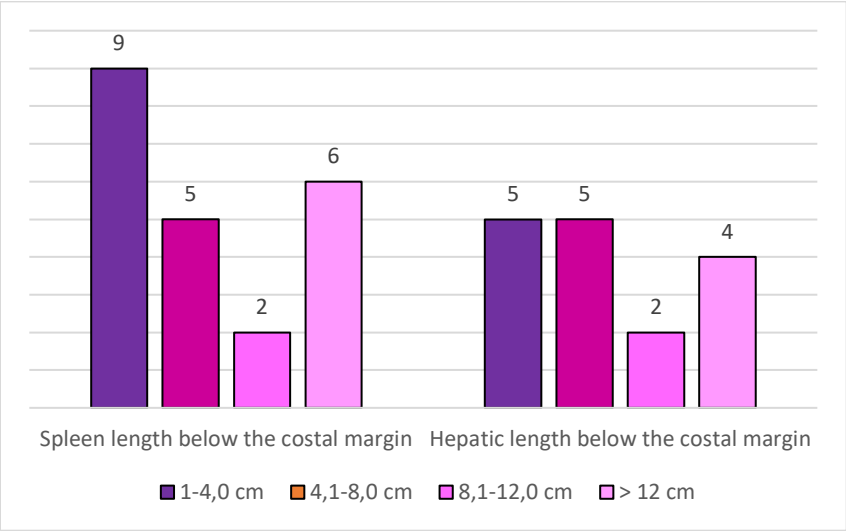


Figure 32: Breakdown of clinical splenomegaly and hepatomegaly within the miscellaneous haematological conditions group

The haematological findings for the miscellaneous conditions are shown below:

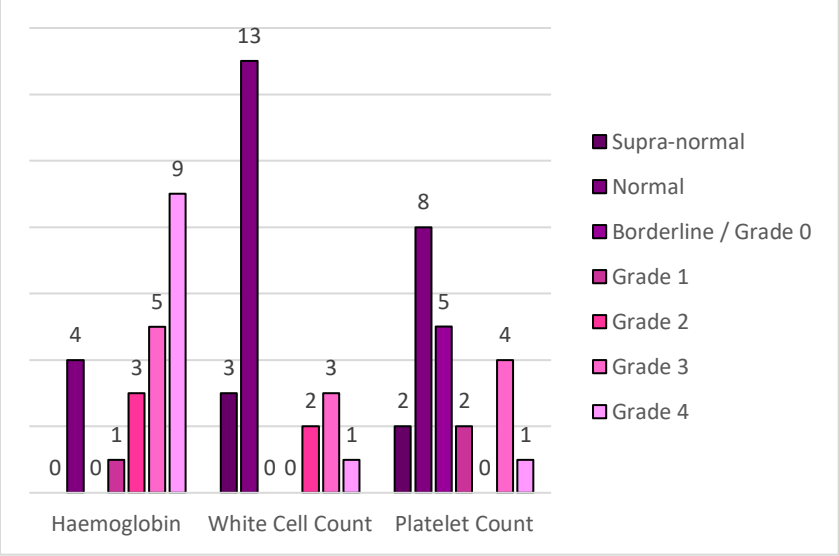


Figure 33: Grading of haematological parameters within the miscellaneous haematological conditions group

3.3 Overall Results of Clinical Parameters

Of the 367 patients included in the study, 10 patients had no laboratory information that could be found. Thus, the data below represents the laboratory findings for the remaining 357 patients.

3.3.1 Presence of haematological abnormalities

The overall number of patients assessed as having pallor was 336 (94,1 %). The laboratory findings of a haemoglobin of < 12 g/dl in females and < 13 g/dl in males were able to corroborate this finding in 305 patients (85,4 %) of cases overall. The data collected is further stratified and represented in the figure below:

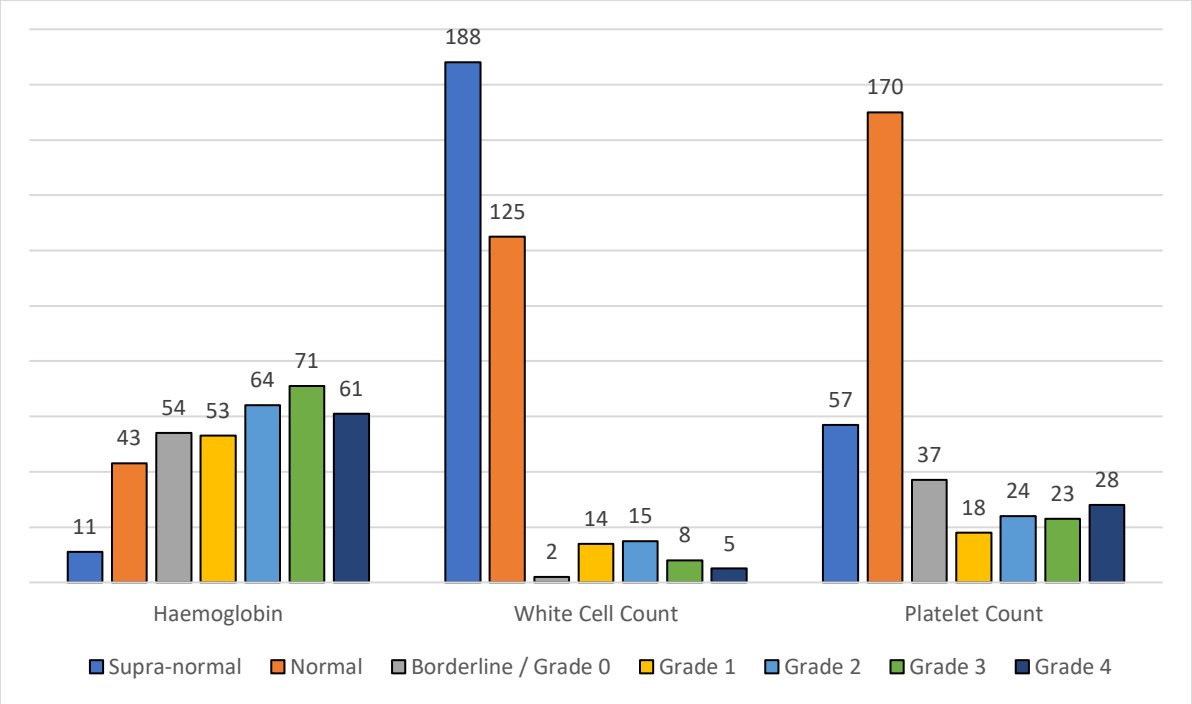


Figure 34: Grading of haematological parameters overall

3.3.2 Presence of clinical jaundice

Clinical jaundice was evident in 36 patients (9,8 %) on presentation. The laboratory correlation in keeping with clinical jaundice was seen in 33 patients (9,0 %).

3.3.3 Presence of lymphadenopathy

The presence of significant lymphadenopathy was present in 166 patients (45,2 %); localised lymphadenopathy was present in 44 patients (26,5 %) and generalized lymphadenopathy was present in 122 patients (73,5 %).

3.3.4 Presence of splenomegaly

Splenomegaly was detected clinically in 345 patients (94,0%) and by radiological methods (ultrasonography and CT scan) in 22 patients (6,0%). In the 22 patients in whom splenomegaly was diagnosed on radiological methods, 5 patients had a normal size spleen according to initial clerking notes, and in 17 patients, no mention of spleen size was made on initial clerking.

The median spleen length below the costal margin was 6 cm for all conditions. The range of splenomegaly in all conditions ranged from 1 cm to 32 cm (IQR= 3 cm to 13 cm).

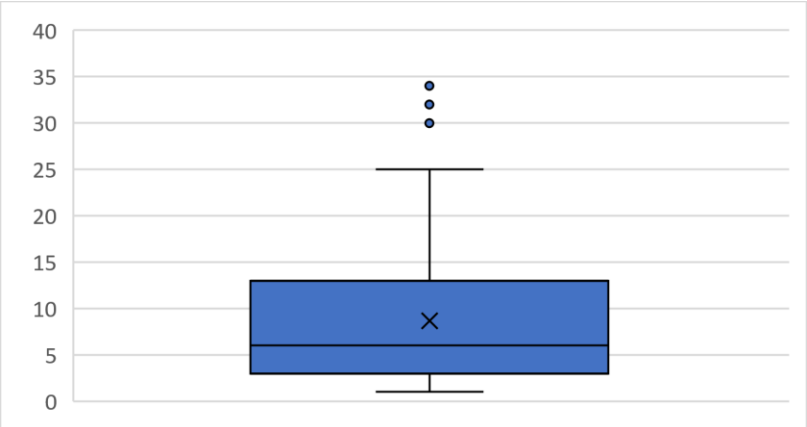


Figure 35: Box and Whisker plot of clinical splenomegaly in all conditions

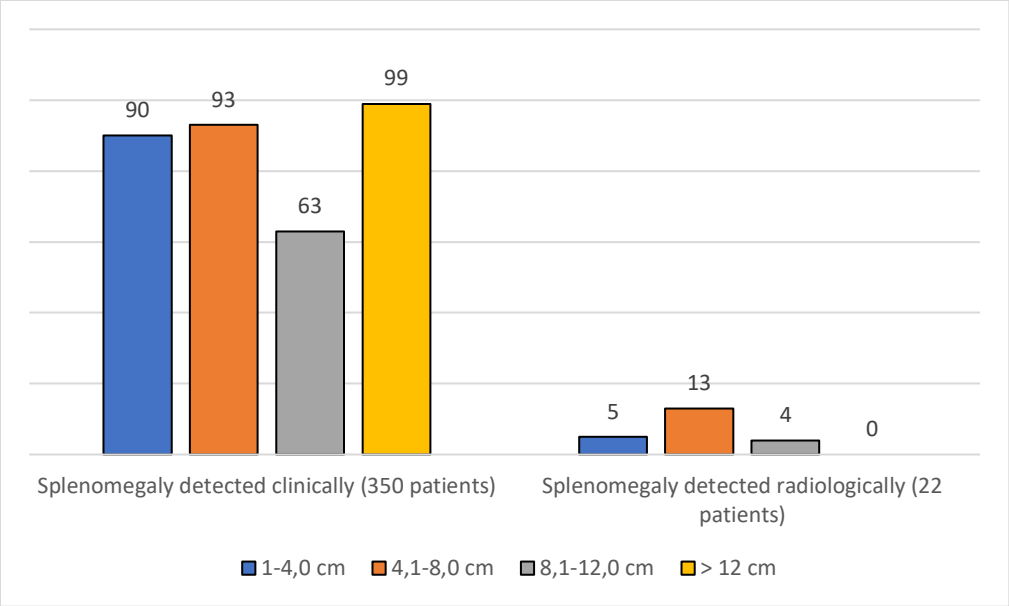


Figure 36: Grading of clinical detection of splenomegaly and radiological detection of splenomegaly in all conditions

3.3.5 Presence of hepatosplenomegaly

A total of 281 patients (76,6%) in the study were found to have hepatomegaly in association with a documented splenomegaly. Hepatomegaly was found clinically in 277 patients (98,6%). In 4 of the patients (1,4 %), the diagnosis of hepatomegaly was made on ultrasound findings alone.

The median hepatic length below the costal margin measured across all conditions was 6 cm (IQR= 4 cm- 10 cm). The range of splenomegaly across all conditions was from 1 cm to 27 cm below the costal margin.

Of the 4 patients in whom hepatomegaly was detected by radiographic methods alone, the ultrasonography measurements (in 3 patients) were from 16 cm to 19 cm, and the single CT scan measurement had a liver span of 19 cm.

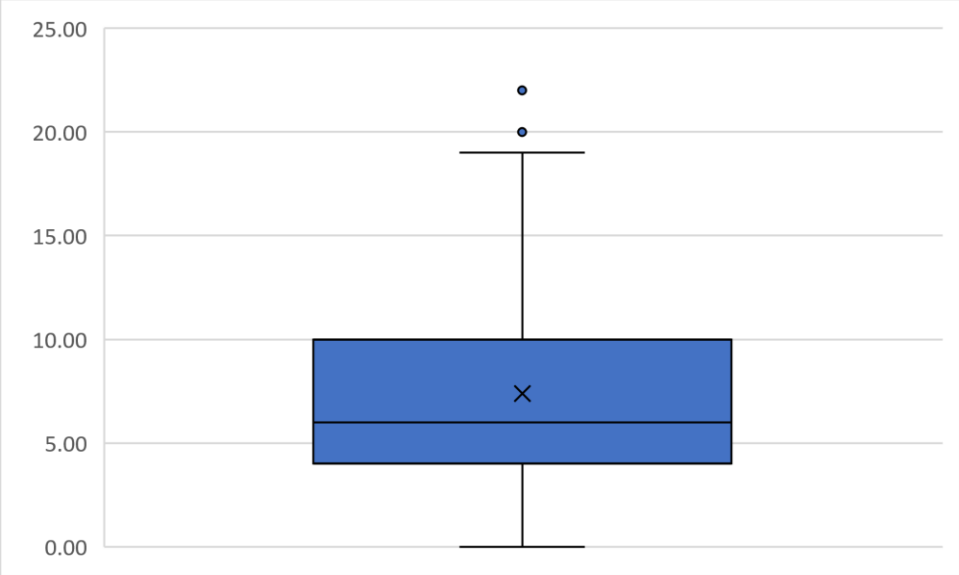


Figure 37: Box and Whisker plot of clinical hepatomegaly in all conditions

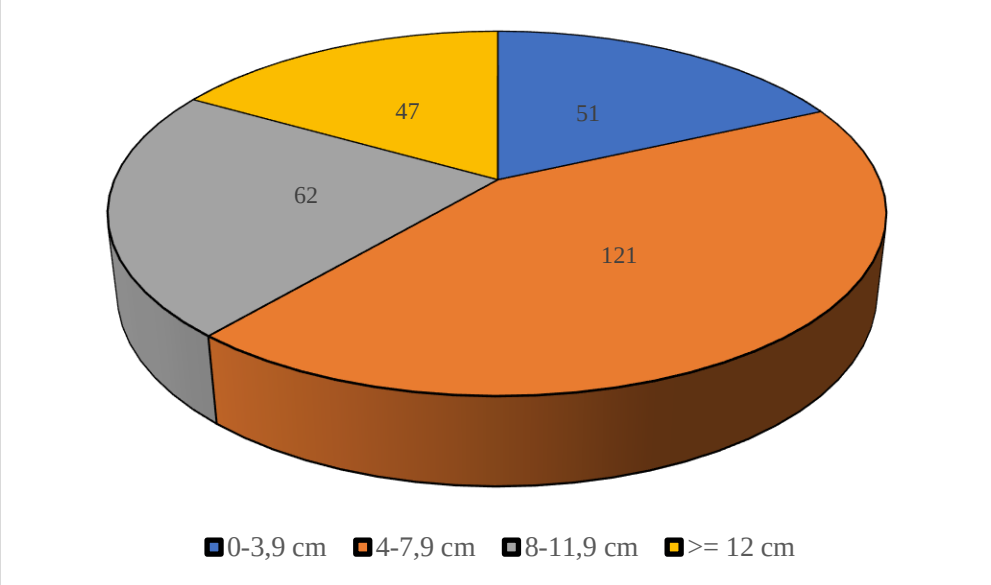


Figure 38: Breakdown of hepatomegaly associated with clinical splenomegaly in all conditions

3.4 Overall Results of Laboratory Parameters

The laboratory parameters that were investigated in the study included: haemoglobin, red cell count, white cell count and platelet count.

The aim was to correlate any abnormalities in laboratory findings with associated splenomegaly, and to investigate whether the degree of splenomegaly influenced the degree of laboratory abnormality. Increasing spleen sizes are plotted below against the average of the haematological parameter associated with the corresponding spleen size.

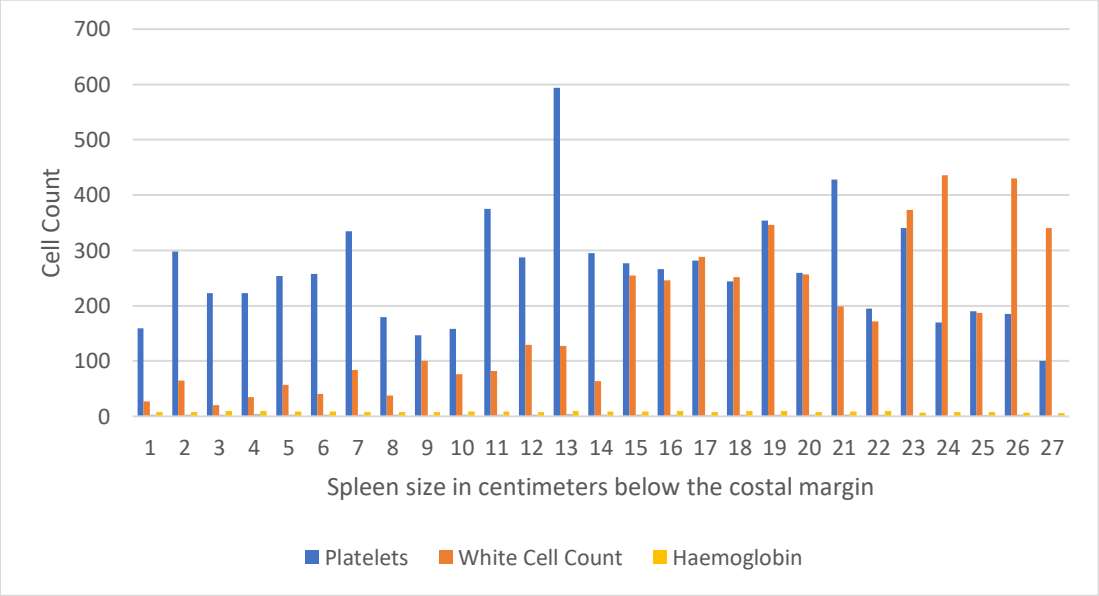


Figure 39: Degree of splenomegaly versus corresponding cell counts for all conditions

A similar study was taken to determine if the degree of hepatomegaly was associated with any significant laboratory abnormalities. Again, increasing hepatic sizes are plotted below against the average of the haematological parameter associated with the corresponding liver size.

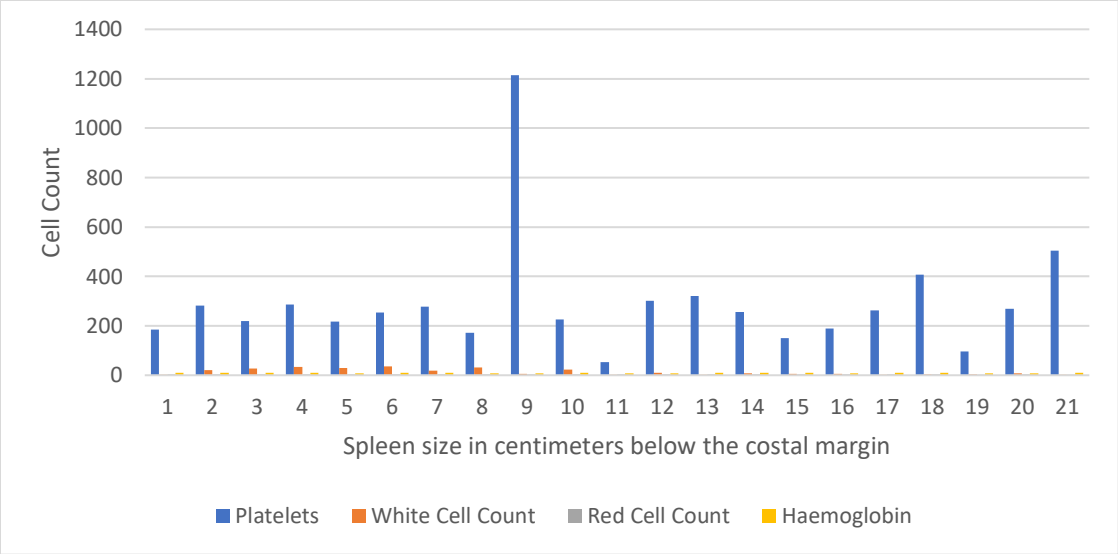


Figure 40: Degree of hepatomegaly versus corresponding cell counts for all conditions

p- values were calculated from the above data by multiple regression analysis to investigate whether there was any independent association between laboratory investigations and all haematological conditions that were encountered. The results are displayed below (as p-values):

Table 11: Significance of laboratory findings for all conditions

	Haemoglobin	Red cell count	White cell count	Platelets
All conditions (372 patients)	0,146	< **0,0001**	0,270	0,519

3.5 Overall Results of Imaging Parameters

3.5.1 Comparison of the clinical and ultrasound measurement of splenomegaly

Of the 127 patients (34,6 % of the total number in the study) in which data for both clinical and ultrasonography measurements existed for the same patient, 52 (40,9 %) had measurements that were accurate to within 20 % (this equated to a difference in measurement of less than 2 cm).

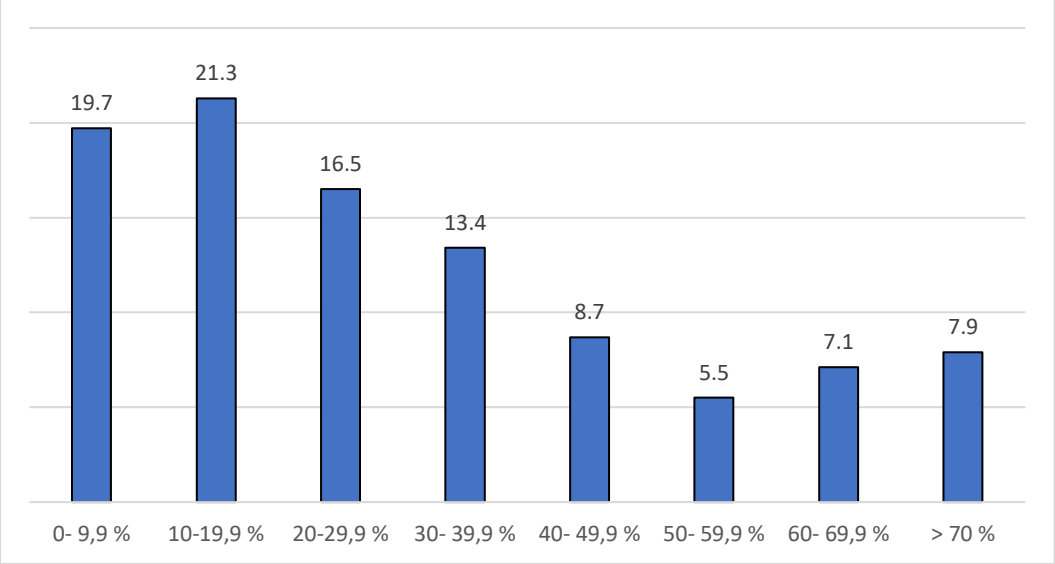


Figure 41: Accuracy of measurements between clinical and ultrasound measurements of splenomegaly

3.5.2 Comparison of the clinical and CT scan measurement of splenomegaly

Of the 89 patients (24,2 % of the total number in the study) that were eligible for this comparison, 52 (58,4 %) had measurements that were accurate to within 20 % (this equated to a difference in measurement of less than 2 cm).

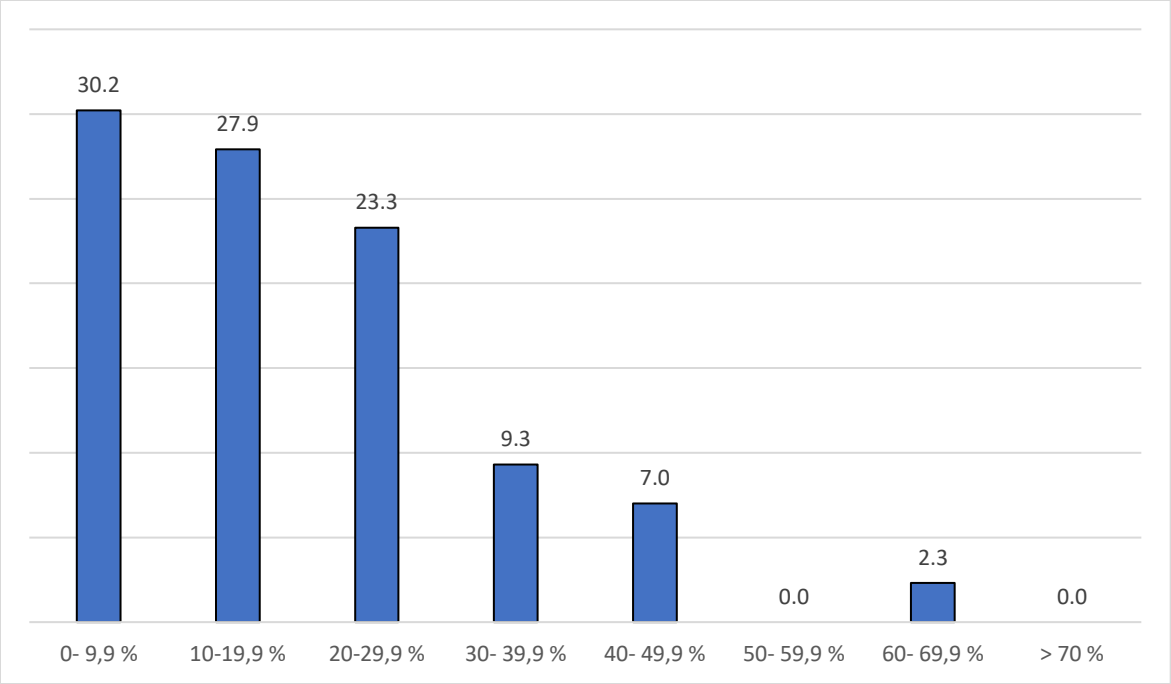


Figure 42: Accuracy of measurements between clinical and CT scan measurements of splenomegaly

3.5.3 Comparison of the ultrasound and CT scan measurement of splenomegaly

Thirteen patients (3,5 % of the total number in the study) were eligible for this comparison. Seven (53,8 %) had measurements that were accurate to within 20 % (this equated to a difference in measurement of less than 1 cm). No measurements showed differences greater than 49,9 % (measurements of greater than 2,5 cm).

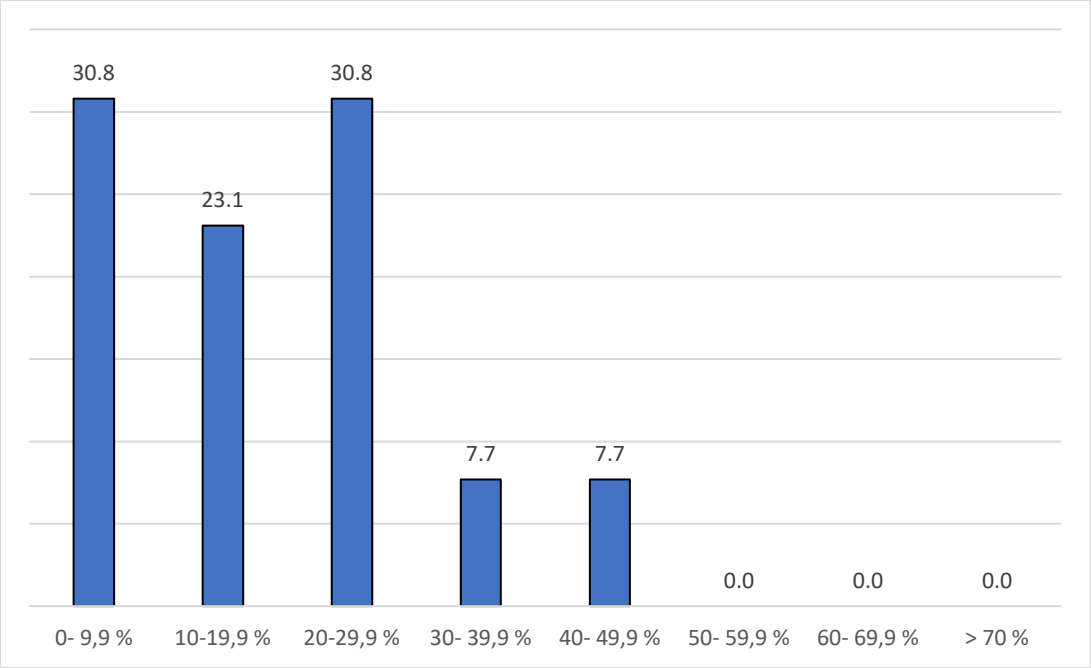


Figure 43: Accuracy of measurements between ultrasound and CT scan measurements of splenomegaly

CHAPTER 4: DISCUSSION

"Is it not a little remarkable that the ductless gland, to which for several centuries the attention of the profession has been specially directed, is the one of whose functions we are mostly ignorant" – W. Osler 1904 (Osler 1904).

4.1 Demographics of Included Patients

This study represents the largest cohort of patients with a clinical or radiological finding of splenomegaly in adult haematology patients carried out in South Africa to date. Previous similarly designed studies in the United States have evaluated splenomegaly in the setting of a referral hospital, and have not restricted their findings to the sub-speciality of Haematology alone (O'Reilly 1996, O'Reilly 1998).

Gender demographics across all conditions were evenly spread. Chris Hani Baragwanath Academic Hospital is a large, tertiary, public sector, University-associated hospital that is based in Soweto, Johannesburg. Because the hospital is based in the township of Soweto, Johannesburg, most patients who were included in this study were of black African descent. The predominantly black African population included in the study explains why the more traditional aetiologies of splenomegaly such as Thalassaemia and hereditary haemochromatosis were infrequently encountered.

The adult population at Chris Hani Baragwanath Academic Hospital include those individuals who are older than 14 years of age. Thus, all patients over the age of 14 years were included in this study. The distribution of ages seen over the 10-year period is skewed towards the 31 to 40-year age group (median age of presentation 44 years of age; IQR= 34-58 years)

This relatively younger age demographic possibly reflects the association between the relatively higher burden of HIV in this younger population, coupled with the association that exists between HIV and haematological abnormalities in the South African setting (Patel, Philip et al. 2011) (Patel, Philip et al. 2015).

The number of people who were HIV seropositive at enrolment into the study agrees with national statistics which show a similar prevalence rate for this period. Two thirds of patients enrolled in this study had a CD_4 count that was below 200 cells/ µL, indicative of a state of severe immunocompromise at presentation. The relatively high proportion of patients with CD_4 counts above 500 cells/ µL may be partially explained by the fact that patients with underlying lymphoproliferative diseases (specifically CLL) and concomitant HIV disease had a median CD_4 count of 961 cells/ µL at presentation. The timing of the retrospective review encompassed a period when access to antiretroviral drugs was initially not legislated, to a period where individuals with a CD_4 count below 200 cells/ µL (and eventually 350 cells/ µL) were granted access to antiretroviral drugs. This shift in policy may account for the low numbers of patients on antiretroviral therapy at the time of the diagnosis of their haematological abnormality.

4.2 Underlying Aetiologies of Included Patients

Over half of the patients included in this study had neoplasms of the lymphoid lineage. Together with the myeloid neoplasms, these two groups of conditions constitute a total of 89 % of the underlying aetiologies of all patients included in the study. This is in accordance with previous studies which have demonstrated a similar overall picture of the lymphoid and myeloid neoplasms which dominated the list of causes of splenomegaly (Swaroop and O'Reilly 1999).

Within this study, the most common lymphoid malignancies were Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). The most common subtypes of HL were the nodular sclerosis and mixed cellularity subtype. Within the NHL group, diffuse large B cell lymphoma and Burkitt's lymphoma together accounted for 67 % of cases.

The association with underlying retroviral disease in these specific conditions remained stronger for NHL with 71 % of patients having underlying retroviral disease; in the HL group, the percentage of patients who were found to be HIV seropositive was 41 %. Further discussion of splenomegaly with respect to lymphoid neoplasms appears later.

4.2.1 Myeloid neoplasms

Within the group comprising the myeloid neoplasms, the single largest entity of haematological disorders encountered was Chronic Myeloid Leukaemia (CML) which made up 64 % of included patients in this group. When combined with Acute Myeloid Leukaemia (AML) and Primary Myelofibrosis (PMF), this proportion increased to 80 % overall.

The prevalence of retroviral disease in the myeloid neoplasm group overall remained low at 14 %. It is well known that the association of the myeloid neoplasms with HIV is only coincidental, and this is borne out by the low association in this study.

The mechanism of splenomegaly in the acute and chronic myeloid leukaemias is due to the infiltration of the spleen by leukaemic cells. The pathogenesis of splenomegaly in CML and Primary Myelofibrosis (PMF) is also thought to be due to extramedullary hematopoiesis.

Acute Myeloid Leukemia

Splenomegaly, per se, is not considered a poor prognostic indicator in AML (Ferrara and Schiffer 2013). Splenomegaly has been associated with the t (9;22) subtype of AML, which is rare (approximately 1 % of all AML cases) and is postulated to arise from the transformation of unrecognized CML (Hassan, Qureshi et al. 1993, Lowenberg, Downing et al. 1999).

In a study by Sultan et al conducted in Pakistan in a cohort of 125 patients with AML, splenomegaly and hepatomegaly were detected in 16 % and 12 % of patients, respectively (Sultan, Zaheer et al. 2016). In the current study, 7,8% of patients with AML had evidence of splenomegaly.

The reason for the relatively lower number of patients presenting with splenomegaly in our cohort compared to cohorts in the developed countries may be because very few patients in our setting have a prior myelodysplastic syndrome (MDS).

Chronic Myeloid Leukaemia

In contrast to AML, 89,4 % of patients with CML had splenomegaly and 100 % of the patients with PMF had splenomegaly. The presence of an enlarged spleen remains the most common clinical abnormality detected in CML patients (Savage, Szydlo et al. 1997). Splenomegaly occurs traditionally in 50-70% of cases of CML in the chronic phase, and hepatomegaly is typically present in 10-20% of cases (Savage, Szydlo et al. 1997). In a retrospective study by Jonte et al, of 134 patients diagnosed with CML, splenomegaly was present in 73,8% of patients, and hepatomegaly in 37,6% at the time of diagnosis (Jonte, Barez et al. 1992).

Splenomegaly in the setting of CML is commonplace, as was documented in a cohort of 430 patients who were undergoing allogeneic bone marrow transplants at the Hammersmith Hospital. Symptoms attributable to an enlarged spleen were present in 18,6% of patients on questioning. A palpable spleen was present in 75,8% of patients, with 36,9% of those having a spleen that was >10 cm, with a median length of 15 cm (range 0 cm to 28 cm) below the costal margin (Savage, Szydlo et al. 1997). Massive splenomegaly has been quoted as being present in 61% of patients with CML (Yang, Rickman et al. 1991). In an earlier study of 40 patients with CML at CHBAH, splenomegaly was present in 93% of patients at presentation, with over half of the patients having massive splenomegaly (Patel 1994).

The findings from the current study revealed a much higher proportion of patients with massive splenomegaly, with 84,7% of patients with splenomegaly in the setting of CML meeting the criteria for massive splenomegaly (range 1 cm to 32 cm, median length of 16 cm). This discrepancy may be due to the late presentation of patients at Chris Hani Baragwanath Academic Hospital. This finding was echoed by the significantly higher proportion of patients with CML who presented with hepatomegaly (72,9% of patients, median size 6,25 cm below the costal margin, IQR 5 cm to 13,5 cm).

The presence of splenomegaly constitutes a criterion for patients who have a poorer prognosis in some classification systems (Hasford, Pfirrmann et al. 2003, Jabbour and Kantarjian 2012, Pfirrmann, Baccarani et al. 2016).

Primary Myelofibrosis

The presence of splenomegaly constitutes a cardinal clinical finding in underlying Primary Myelofibrosis (PMF) (Rupoli, Da Lio et al. 1994). The finding of splenomegaly has been postulated to confer a poorer prognosis (Wang, Xu et al. 2014). Splenomegaly accounts for severe disability, irrespective of the underlying cause (whether primary myelofibrosis or secondary myelofibrosis due to Polycythaemia Rubra Vera or Essential Thrombocytosis). Splenomegaly in the setting of PMF is associated with poorer prognosis and survival (Randhawa, Ostojic et al. 2012). In a study of 72 patients with PMF, the incidence of splenomegaly was 97,1% and that of massive splenomegaly was 26,4% (Borosi 2011). In the data collected in this study, 100% of patients with PMF had splenomegaly and 81,8% of included patients met the criteria for massive splenomegaly. Again, this discrepancy in splenomegaly recorded at diagnosis between previous studies and this study may be accounted for by the late presentation and subsequent advanced disease of patients on presentation.

Polycythaemia Rubra Vera

Splenomegaly constitutes a minor criterion for the diagnostic criteria of Polycythaemia Rubra Vera (PRV) (Pearson and Messinezy 1996). In a retrospective review of 70 patients with confirmed PRV, splenomegaly was found in 48 patients (68,6%) (Ren, Fu et al. 2015).

Massive splenomegaly was found in 23% of patients with PRV in previous series (O'Reilly 1996, O'Reilly 1998). In the current study, 61,5% of patients with PRV (a total number of 8 patients) had splenomegaly and were included. The small number of patients with PRV and splenomegaly obviated any possible statistical analysis in this study.

Essential Thrombocytosis

Splenomegaly (usually not exceeding >3 cm below the left costal margin) occurs in 10-20% of patients at diagnosis (Andriani, Latagliata et al. 2016). This finding was confirmed in the retrospective review by Mayet done at Chris Hani Baragwanath Academic Hospital, where the median spleen size of the spleen was under 4cm (Mayet 2015). Splenomegaly confers a poor prognosis, thought to be due to the increased risk of thrombosis (Andriani, Latagliata et al. 2016, Haider, Gangat et al. 2016). In this study, 32,3% of the patients with ET had evidence of splenomegaly, with a median spleen size of 4 cm (IQR= 2cm to 6,5 cm). A correlation between spleen size and platelet number was significant (p=0,04), however the small numbers of patients included with ET may confound any positive findings.

In a retrospective review of Philadelphia chromosome negative myeloproliferative neoplasms done over a 10-year period at Chris Hani Baragwanath Academic Hospital's Clinical Haematology Unit, PMF was found to be the most common subtype (42 patients), followed by ET (35 patients) and PV (17 patients) (Mayet 2015). Splenomegaly in this setting was present in 80% of patients overall. Ninety-eight percent of patients with PMF had splenomegaly clinically. The size of the spleen was as follows: <4cm below the costal margin 27%, 4-8cm below the costal margin 34%, and >8cm below the costal margin 39%. In patients with ET, 80% of patients had splenomegaly and in PV this proportion was 76%.

Myelodysplastic Syndromes

Myelodysplastic syndromes (MDS) encompass a wide variety of clinical processes which are classified according to the French-American-British (FAB) criteria introduced in 1982 as 5 distinct morphological categories: refractory anaemia (RA), refractory anaemia with excess of blasts (RAEB), refractory anaemia with excess of blasts in transformation (RAEB-t), refractory anaemia with ringed sideroblasts and chronic myelomonocytic leukaemias (Bennett, Catovsky et al. 1982). Splenomegaly in the setting of MDS is an uncommon finding (around 11%) and does not confer a survival prognosis (van der Weide, Sizoo et al. 1988, Mereuta and Turtureanu-Hanganu 1990, Takahashi, Koike et al. 1990). Four patients out of 20 with MDS were included in the study. This small number of patients precludes any statistical analysis.

4.2.2 Lymphoid neoplasms

The spleen is involved in one-third of HL and in 30-40% of NHL at presentation. Splenic infiltration is considered nodal in HL and extranodal in NHL (Paes, Kalkanis et al. 2010).

Acute Lymphocytic Leukaemia

Acute lymphocytic leukaemia is the most common leukaemia in childhood. Forty-one patients aged 15-44 years (mean age of 32 years) with ALL were noted in this adult haematology cohort, of whom 7 had splenomegaly (7/41=17%). Interestingly, 6/7 patients (85.7%) with splenomegaly, presented with massive splenomegaly.

Chronic Lymphocytic Leukaemia

CLL accounts for approximately 30% of adult leukaemias and remains the most common form of leukaemia in the Western hemisphere (Maurer and Hallek 2013). The pathogenesis of splenomegaly in CLL is thought to be due to infiltration of the spleen by malignant cells.

The associated clinical finding of splenomegaly is incorporated into the staging system for CLL (Rai classification), and the finding of a palpable spleen classifies the patient as having intermediate-risk disease (Rai stage II) (Rai, Sawitsky et al. 1975). Previous studies indicate that approximately 30-54% of patients have splenomegaly at diagnosis of CLL, and that 10-20% of cases have hepatomegaly at diagnosis (Zwiebel and Cheson 1998). The Binet scoring system also takes the presence of splenomegaly into account, which classifies the patient as a Binet “B” stage (intermediate prognosis) (Binet, Auquier et al. 1981).

Almost half (45,9%) of the 111 patients assessed with CLL had splenomegaly, and 90,2% had hepatomegaly on presentation. The significantly increased number of people with hepatomegaly may be explained by a possible later presentation of underlying disease (as hepatomegaly also forms part of the scoring systems) and is then associated with an intermediate outcome.

Hairy cell leukaemia

Hairy cell leukaemia is an uncommon B-cell lymphoproliferative disorder that involves the blood, bone marrow and the spleen. In the spleen, it characteristically involves the red pulp (Wotherspoon, Attygalle et al. 2015). Because of the relative rarity of this condition, retrospective analyses in the literature are limited by small patient numbers.

The incidence of splenomegaly in these analyses at the time of diagnosis is quoted at between 45% and 93,5% (Konkay, Uppin et al. 2014, Venkatesan, Purohit et al. 2014, Hacioglu, Bilen et al. 2015, Payandeh, Sadeghi et al. 2015). Five percent of patients with HCL had massive splenomegaly in the largest cohort of 71 patients (Golomb, Catovsky et al. 1978).

The rarity of this entity was echoed in our study by the small number of included patients (3 patients seen with HCL in a 10-year period, 3 with clinical splenomegaly, i.e. 100% at the time of diagnosis).

Hodgkin lymphoma

The background picture of Hodgkin lymphoma (HL) suggests an increasing association with HIV/ AIDS (Patel, Philip et al. 2011, Spina, Carbone et al. 2011) . In our study, 21,1% of patients with HL had splenomegaly on presentation, and there were no patients with massive splenomegaly. Half (50%) of the patients included had nodular sclerosis subtype of HL.

It is understood that HIV is an independent risk factor for the development of HL, with an estimated risk that is 10-fold higher than in the general population (Hessol, Katz et al. 1992, Carbone, Gloghini et al. 2009).

In a retrospective review at Chris Hani Baragwanath Academic Hospital that assessed HIV seroprevalence and HL, the HIV seroprevalence rate in a 2-year period (43 consecutive patients) was 67% (Patel, Philip et al. 2015). In the same study, 28% of patients had splenic involvement. Interestingly, the mixed cellularity subtype was most frequently encountered in the HIV seropositive population (in contrast to the HIV seronegative population), followed by the nodular sclerosis subtype (Thompson, Fisher et al. 2004).

Non-Hodgkin's Lymphoma

The incidence rate for NHL among people with HIV is increased by 113-fold (Goedert, Cote et al. 1998). NHL is the commonest haematological malignancy seen in adults at CHBAH (40% of the total number of patients with haematological malignancies). The impact of the HIV/AIDS pandemic is clearly illustrated by the relative increase in cases from 24% 10 years previously.

This increase in prevalence coincided with an increase in HIV seropositivity of 34% to 74% in the same cohort (Patel, Philip et al. 2015).

Splenic marginal zone lymphoma

Splenic marginal zone lymphoma is an exceedingly rare variant of NHL, accounting for approximately 2% of NHL, and is almost universally characterized by splenomegaly (Thieblemont, Felman et al. 2002, Xing, Kahlon et al. 2015). The splenomegaly results from the progressive replacement within the spleen's red and white pulp by small lymphocytes (Thieblemont, Felman et al. 2002). Massive splenomegaly is common in the setting of splenic marginal zone lymphoma and splenectomy is often required for remediation of the associated cytopaenias. Only 3 patients (75% of all splenic marginal zone lymphomas – 1 patient was excluded due to lack of initial spleen measurement) with this condition were included in this study. The median spleen size was 22 cm in these 3 patients.

Mantle cell lymphoma

Mantle cell lymphoma is a subset of B-cell NHL with a distinctive morphological, immunophenotypic and characteristic cytogenetic abnormality, the t (11;14) (q13; q32). This is associated with overexpression of cyclin D1. Splenomegaly has been reported in 53,8% to 81% of patients (Duggan, Weisenburger et al. 1990, Bosch, Lopez-Guillermo et al. 1998, Papajik, Raida et al. 1999, Roy, Kar et al. 2013). It accounts for 6% of all NHL in the United States. However, data in South Africa is lacking (Rosen, Link et al. 2013). Splenomegaly is associated with a poorer outcome in patients with mantle cell lymphoma (Norton, Matthews et al. 1995, Bosch, Lopez-Guillermo et al. 1998).

Six patients (from a total of 15 patients seen over the 10-year period with mantle cell lymphoma) were included in the study. The median spleen size in the patients who were included was 19cm.

T- cell lymphoma

Splenomegaly has been noted to be present in 12% to 43% of the patients with an underlying T-cell lymphoma (Greer, York et al. 1984, Weisenburger, Linder et al. 1987). In our cohort, splenomegaly was detected in 3 of 16 files assessed (18,75%), with a median length of 19 cm.

Multiple myeloma

The presence of splenomegaly in the setting of multiple myeloma is an uncommon finding. In a case series of 2 patients who presented with massive splenomegaly as the presenting complaint and were subsequently diagnosed with multiple myeloma, splenectomy failed to reveal infiltration by lymphoid cells, as might have been expected (Jacobs, Wood et al. 1998). The possibility that the 3 patients in our series may have had alternative or concomitant diagnoses such as amyloidosis or Waldenstrom's macroglobulinaemia, or have been a component of the POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes) syndrome remains a consideration.

Another possible confounder is the fact that all 3 patients who had multiple myeloma associated with splenomegaly were HIV seropositive. The possibility therefore exists that there may be a secondary pathology (such as concomitant tuberculosis, for example).

Waldenstrom's macroglobulinaemia

Waldenstrom's macroglobulinaemia is a rare immunoproliferative disorder. The common clinical features encountered in Waldenstrom's macroglobulinaemia include: anaemia, abnormal bleeding and hyperviscosity (due to an IgM paraprotein-macroglobulin). 20%-40% of patients are reported in the literature to present with lymphadenopathy or splenomegaly (McDermott and Bell 1999).

In a retrospective review of 22 patients with WM, the presence of splenomegaly has been postulated to confer a poorer prognosis (Andriko, Aguilera et al. 1997). Four patients were seen at Chris Hani Baragwanath Academic Hospital over a 10-year period, of which 3 had splenomegaly.

4.2.3 Bone marrow failure syndromes, haemolytic anaemias and haemostatic abnormalities

Hypoplastic and aplastic anaemia: In our study, splenomegaly was encountered in 4 out of 15 cases (26,7%) of patients with hypoplastic anaemia, and in 1 out of 52 cases (1,9%) of patients with aplastic anaemia.

Aplastic anaemia associated with splenomegaly is a rare presentation, but has been described in a case series (Kaito, Otsubo et al. 1995). Aplastic anemia is the result of a lack of precursors to produce the constituents of blood. Therefore, no extramedullary haematopoesis occurs, as these precursors are globally lacking. Splenomegaly encountered in the setting of an aplastic anaemia may allude to a second pathological process (Kaito, Otsubo et al. 1995, Yoshioka, Kawamata et al. 1999). In keeping with this, is the higher proportion of splenomegaly seen in this study with hypoplastic anaemia, which is likely due to a secondary cause.

Haemolytic anaemia: hereditary spherocytosis (HS) was encountered in 2 out of 5 patients seen over a 10-year period. These low numbers reflect the ethnic population served by the hospital (over 90% of patients in this study were black Africans). HS remains an important cause of splenomegaly, and an indication for a possible splenectomy (Sandusky, Leavell et al. 1964, Jankulovski, Antovic et al. 2014, Comite Nacional de, Donato et al. 2015). The reported rate of splenomegaly in a cohort of 68 children with HS was 72,5% (Konca, Soker et al. 2015).

Thalassaemia was diagnosed in 5 patients in total, over a 10-year period. The low numbers correlate with the sample population, as described above. One of the 5 patients had splenomegaly clinically.

This figure is lower than figures reported in the literature, but is difficult to extrapolate due to the small numbers of patients. In heterozygote beta thalassaemia, a palpable spleen is found in 17.8% of patients (Tassiopoulos, Rombos et al. 1995). Both patients with persistence of foetal haemoglobin and sickle cell haemoglobin had splenomegaly clinically. Two of the 37 patients with autoimmune haemolytic anaemia

4.2.4 Miscellaneous conditions

Castleman's disease

The relatively high numbers of miscellaneous conditions included in this study are explained by the high number of patients with Castleman's disease (15/ 23 patients, 65,2% of the total number of miscellaneous conditions) that were included. Again, this may be a by-product of associated HIV infection, as all the patients with the multicentric variety of Castleman's disease were found to be HIV seropositive. In a study done at Chris Hani Baragwanath Academic Hospital, multicentric Castleman's disease was the most frequently encountered subtype of Castleman's disease (92,1% of all cases) (Patel, Philip et al. 2015). In a cohort of 38 patients in this study, 57% had splenomegaly. The splenomegaly encountered in Castleman's disease is thought to be associated with high levels of circulating IL-6 (Polizzotto, Uldrick et al. 2013).

The other miscellaneous conditions that were included were too small in number to be assessed.

4.3 Spleen Measurement of Included Patients

The clinical measurement of splenomegaly was documented on initial assessment of the patient by the attending doctor from the Clinical Haematology Unit. The attending doctors who completed the initial assessment of the patients ranged in expertise from community service medical officers to clinical haematology consultants. There was therefore a wide range of clinical experience of the attending doctors. Inter-observer reliability, although significant, has interestingly not been found to correlate with the clinical experience of the attending physician (Tamayo, Rickman et al. 1993).

The date on which the initial assessment of the patient was carried out as well as the date of any radiological assessments of splenomegaly were recorded in conjunction with the day of initiation of therapy for the underlying haematological condition. This was done to exclude the possibility of prior treatment resulting in a factitiously smaller spleen than initially encountered on presentation. There were no cases in which the clinical and radiological assessment of the size of the spleen were undertaken before the initiation of treatment for the underlying condition was commenced.

Within the myeloid group, the condition with the largest median spleen size was PMF (18cm clinically, 18,5cm radiologically), followed by CML (16,5cm clinically, 18cm radiologically) and then CMML (10,5cm clinically, 16,5cm radiologically). AML, PRV, ET, MDS and AUL had median spleen sizes that ranged from 12,5cm to 17cm clinically (and 13cm to 18,5cm radiologically). The numbers of included patients in these groups remained low, and so these results may not accurately reflect the degree of splenomegaly associated with them as the sample size was small. The population sampled may have had an effect on the incidence of these conditions, as mentioned previously.

The conditions in the lymphoid neoplasm group with the clinically largest median splenic sizes with enough data points so as to be statistically significant were: CLL (14cm clinically, 15cm radiologically), followed by NHL as a group (13cm clinically, 15cm radiologically), HL (12cm clinically, 14cm radiologically).

Although larger spleen measurements were found in other conditions in this group, the relatively small numbers within these groups preclude any extrapolation of the data. Within the HL group, patients with the nodular sclerosis subtype had the largest median spleen size (12cm clinically, 14cm radiologically). This was followed by the mixed cellularity subtype (11,5cm clinically, 14cm radiologically) and then by the unclassifiable (11cm clinically, 14cm radiologically).

On further assessment of the patients presenting with NHL, the subtype with the largest spleen size clinically was the mantle cell subtype (18cm clinically, 19cm radiologically). This was followed by the follicular subtype (15,5cm clinically, 19cm radiologically) and the Plasmablastic subtype (15cm clinically).

The numbers within these subtypes remain small and therefore data extrapolation remains problematic. The most common subtype encountered was the diffuse large B-cell lymphoma (13cm clinically, 14cm radiologically), and the median clinical size of splenomegaly overall in the NHL group was 13cm.

An interesting finding that was highlighted in this study was the pattern of discordant measurements between the clinical and ultrasound findings overall. As the spleen increased in size, so the proportion of discrepant results between the clinical and radiological measurements increased, such that 20,5% of patients had results that were over 50% discrepant between clinical and ultrasound measurement of the spleen. This equated to a measurement of approximately 4,5cm difference. Interestingly, this trend increased as the size of the spleen increased.

A possible explanation for this is that the spleen may be non-uniformly measured as it becomes massive. In previous studies, up to 20% of spleens with an estimated weight of 900g were not palpated at all.

The suggested correct measurement of an enlarged spleen is from the midpoint of the spleen, as it is palpated at the costal margin, to the edge of the spleen's furthest point in an oblique/ inferolateral direction, as shown below:

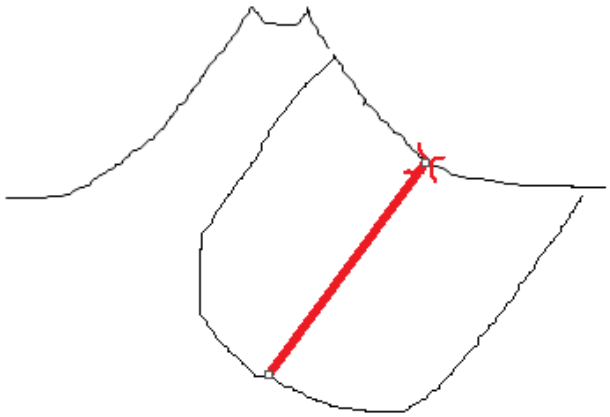


Figure 44: Suggested measurement of splenomegaly

If the spleen is massively enlarged, multiple non-uniform techniques may used to measure the spleen:

- The clinician may measure the spleen from the mid-clavicular line (green line)
- The measurement may not be made in a line parallel to the midpoint of the spleen (red cross)

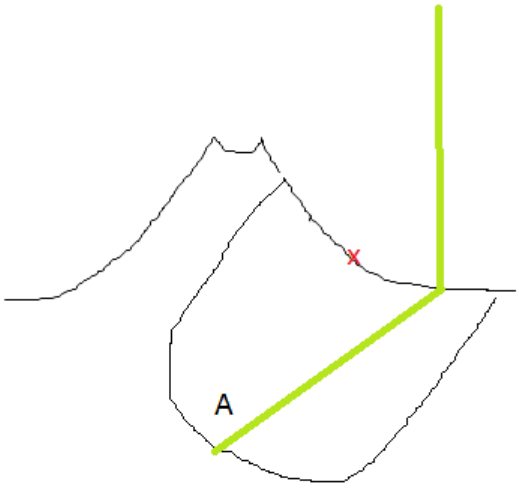


Figure 45: Measurement of splenomegaly

If the spleen is only mildly enlarged, these errors may be obviated, and thus clinical and radiological methods correlate more accurately,

The measurement of spleen sizes between ultrasound and CT scan correlated with a high degree of certainty.

4.4 Laboratory Findings of Included Patients

Radio-labelled studies show that the spleen contains approximately 25% of the exchangeable pool of B lymphocytes, and 10% of the exchangeable pool of T lymphocytes (Brox and Shustik 1993). Approximately one third of platelets are sequestered to the spleen in healthy states. These numbers may increase dramatically in the setting of an enlarged spleen, as sequestration within the spleen increases.

Laboratory variables were recorded for all conditions and assessed using a linear regression model to identify any possible associations between the degree of splenomegaly and baseline laboratory values.

Overall, white cell counts remained significantly associated with an enlarged spleen size ($p < 0,001$) for all conditions. The strongest association across all groups was that between the white cell count which was significantly associated with increasing spleen size within the myeloid neoplasms as a group ($p <0,0001$). There was no inversely proportional association between increasing spleen size and cell counts (i.e. a positive correlation between spleen size and the degree of sequestration could not be proven) in any of the conditions assessed in our study. In the study by Savage et al, in the setting of CML in particular, the white cell count correlated significantly with spleen size ($p <0,001$); neither white cell count nor spleen size correlated with platelet count (Jabbour and Kantarjian 2012). This finding was not corroborated in our study with regard to CML, with a p value that did not reach significance for an association between spleen size and either white cell count or platelet count ($p=0,237$ and $p=0,364$, respectively).

There were no statistically significant findings with regard to the degree of splenomegaly and laboratory abnormalities encountered within the PMF group (although the small sample set may obscure any possible associations).

In the lymphoid neoplasm group, the platelet count was significantly associated with increasing spleen size ($p=0,01$).

Hepatomegaly in the presence of an enlarged spleen was significantly associated with the haemoglobin ($p=0,03$) and more so with the white cell count ($p=0,002$). The association with platelet count did not reach statistical significance.

CHAPTER 5: CONCLUSION

5.1 Background

There remains a large, unknown element in the quantification of splenomegaly and the association with haematological disorders in South Africa. While the epidemiology in South Africa reflects both developed and developing problems, South Africa has an added burden of HIV/ AIDS which influences the local picture. The current haematological aetiologies which result in splenomegaly may not be an accurate representation of the complete picture in South Africa, as this study shows.

While the majority of haematological aetiologies resulting in splenomegaly comprise myeloid and lymphoid neoplasms, aetiologies associated with HIV seropositivity such as multicentric Castleman's disease is becoming more prevalent in the South African setting.

The South African setting provides a unique opportunity to explore the clinical manifestation of haematological disorders for a number of reasons:

There is a paucity of data of similar studies conducted in other countries, and those studies that have been done were done in the developed world.

5.2 Findings

Splenomegaly was present in (15.6%) of patients presenting to the Clinical Haematology Unit, Department of Medicine, Chris Hani Baragwanath Hospital over a 10-year period. Almost (89.3%) of these patients had underlying neoplasms of the myeloid and lymphoid lineage. The most common neoplasm of the myeloid lineage was CML (63.9%) of all myeloid neoplasms). The most common neoplasms of the lymphoid lineage were non-Hodgkin lymphoma (47%), CLL (26%) and Hodgkin lymphoma (17%).

The remaining 10% comprised of miscellaneous causes such as Castleman's disease, haemolytic anaemias, haemostatic abnormalities, and bone marrow failure syndromes.

HIV seropositivity was associated most frequently with multicentric Castleman's disease (100% seropositivity), followed by the non-Hodgkin lymphoma group (71% seropositivity) and then by the Hodgkin lymphoma group (41% seropositivity).

The findings of these studies can clearly not be extrapolated to the developing world, as the aetiology of splenomegaly that is encountered, although similar in some respects, remains distinctive due to the added burden of infectious diseases. This aetiological pattern was clearly shown in this study, with the most common aetiologies being myeloid and lymphoid neoplasms, with a definite slant towards the HIV seropositive-associated malignancies (Hodgkin lymphoma and non-Hodgkin lymphoma, as well as Castleman's disease). Traditional developing world aetiologies of splenomegaly such as thalassaemia and sickle cell anaemia were encountered infrequently, due to the setting of the study in Soweto, Johannesburg, and the infrequency of these conditions in the local setting.

The late presentation of many of the patients included in this study with advanced stage disease, was also shown to impact the degree of splenomegaly encountered at presentation locally versus in international studies. The results from this study suggest that the approach to splenomegaly in the South African setting may be unique, and that the traditional haematological aetiologies of splenomegaly may need to be rethought and that a local classification system may prove to be more relevant.

As this retrospective study was conducted in a Clinical Haematology setting, the conditions causing splenomegaly were predominantly of a haematological nature. Other causes of splenomegaly such as TB, schistosomiasis, portal hypertension, infiltrative disorders, storage diseases etc. that are encountered in a non-haematological setting were therefore, not seen in this study.

CHAPTER 6: LIMITATIONS OF THE STUDY

Files lost to follow up:

- Due to the large time period covered in this study, a proportion of files were unable to be located in the Clinical Haematology Unit.
- Files not opened for patients seen as consultations in the ward: a proportion of patients may have been seen in the ward without files being opened for long term follow up.
- Patients consulted on in the ward by the Clinical Haematology Unit may have demised before files were opened for them.

Files with incomplete information

- Some patient records (in particular the initial clinical assessment of splenomegaly) were incomplete and were thus unable to be included in the study
- Because of the retrospective nature of the study, some blood results were unable to be found on the laboratory system.

Small sample size in some haematological disorders

- Small groups of specific haematological aetiologies: in some groups, small numbers of included patients precluded the derivation of meaningful data outcomes without incurring bias.

Histological reporting

- The classification of histological findings of the underlying haematological disorders are dependent on inter-observer variability between pathologists and this may have affected the final histological diagnosis.

Limitations of a retrospective study

- Due to the retrospective nature of this study, selection and information bias may have negatively impacted on the validity of certain elements of the study.
- Patients with a primary diagnosis that was not haematological, may not have been included in the records of the Clinical Haematology Unit, even though the patients may have had an underlying secondary haematological disorder.

CHAPTER 7: REFERENCES

Andriani, A., Latagliata, R., Anaclerico, B., *et al.* 2016. Spleen enlargement is a risk factor for thrombosis in essential thrombocythemia: Evaluation on 1,297 patients. *Am J Hematol.* 91(3): 318-321.

Andriko, J. A., Aguilera, N. S., Chu, W. S., *et al.* 1997. Waldenstrom's macroglobulinemia: a clinicopathologic study of 22 cases. *Cancer*. 80(10): 1926-1935.

Barkun, A. N., Camus, M., Meagher, T., *et al.* 1989. Splenic enlargement and Traube's space: how useful is percussion? *Am J Med.* 87(5): 562-566.

Bashour, F. N., Teran, J. C. and Mullen, K. D. 2000. Prevalence of peripheral blood cytopenias (hypersplenism) in patients with nonalcoholic chronic liver disease. *Am J Gastroenterol*. 95(10): 2936-2939.

Bedu-Addo, G. and Bates, I. 2002. Causes of massive tropical splenomegaly in Ghana. *Lancet*. 360(9331): 449-454.

Bennett, J. M., Catovsky, D., Daniel, M. T., *et al*. 1982. Proposals for the classification of the myelodysplastic syndromes. *Br J Haematol*. 51(2): 189-199.

Bezerra, A. S., D'Ippolito, G., Faintuch, S., *et al*. 2005. Determination of splenomegaly by CT: is there a place for a single measurement? *AJR Am J Roentgenol*. 184(5): 1510-1513.

Binet, J. L., Auquier, A., Dighiero, G., *et al.* 1981. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. *Cancer*. 48(1): 198-206.
Blackburn, C. R. 1953. On the clinical detection of enlargement of the spleen. *Australas Ann Med*. 2(1): 78-80.

Borosi, G. 2011. Myeloproliferative Neoplasms: Biology and Therapy. Conventional and Investigational Therapy for Primary Myelofibrosis. New York, Humana Press.

Bosch, F., Lopez-Guillermo, A., Campo, E., *et al*. 1998. Mantle cell lymphoma: presenting features, response to therapy, and prognostic factors. *Cancer*. 82(3): 567-575.

Bowdler, A. 2001. The Complete Spleen. New Jersey, Humana Press.

Brox, A. and Shustik, C. 1993. Non-Hodgkin's lymphoma of the spleen. *Leuk Lymphoma*. 11(3-4): 165-171.

Carbone, A., Gloghini, A., Serraino, D., *et al*. 2009. HIV-associated Hodgkin lymphoma. *Curr Opin HIV AIDS*. 4(1): 3-10.

Chongtham, D. S., Singh, M. M., Kalantri, S. P., *et al*. 1997. Accuracy of palpation and percussion manoeuvres in the diagnosis of splenomegaly. *Indian J Med Sci*. 51(11): 409-416.

Comite Nacional de, H., Donato, H., Crisp, R. L., *et al*. 2015. Hereditary spherocytosis. Review. Part II. Symptomatology, outcome, complications, and treatment. *Arch Argent Pediatr*. 113(2): 168-176.

Doyle, D. 2006. William Hewson (1739-74): the father of haematology. *Br J Haematol*. 133(4): 375-381.

Duggan, M. J., Weisenburger, D. D., Ye, Y. L., *et al*. 1990. Mantle zone lymphoma. A clinicopathologic study of 22 cases. *Cancer*. 66(3): 522-529.

Ferrara, F. and Schiffer, C. A. 2013. Acute myeloid leukaemia in adults. *Lancet*. 381(9865): 484-495.

Furrer, H. 2000. Prevalence and clinical significance of splenomegaly in asymptomatic human immunodeficiency virus type 1-infected adults. Swiss HIV cohort study. *Clin Infect Dis*. 30(6): 943-945.

Gazin, P. 2004. Splenomegaly in Cambodia. *Med Trop (Mars)*. 64(5): 440.

Gielchinsky, Y., Elstein, D., Hadas-Halpern, I., *et al*. 1999. Is there a correlation between degree of splenomegaly, symptoms and hypersplenism? A study of 218 patients with Gaucher disease. *Br J Haematol*. 106(3): 812-816.

Goedert, J. J., Cote, T. R., Virgo, P., *et al*. 1998. Spectrum of AIDS-associated malignant disorders. *Lancet*. 351(9119): 1833-1839.

Golomb, H. M., Catovsky, D. and Golde, D. W. 1978. Hairy cell leukemia: a clinical review based on 71 cases. *Ann Intern Med*. 89(5 Pt 1): 677-683.

Greer, J. P., York, J. C., Cousar, J. B., *et al*. 1984. Peripheral T-cell lymphoma: a clinicopathologic study of 42 cases. *J Clin Oncol*. 2(7): 788-798.

Hacioglu, S., Bilen, Y., Eser, A., *et al*. 2015. Multicenter retrospective analysis regarding the clinical manifestations and treatment results in patients with hairy cell leukemia: twenty-four year Turkish experience in cladribine therapy. *Hematol Oncol*. 33(4): 192-198.

Hackett, L. W. 1945. The malaria of the Andean region of South America. *Rev Inst Salubr Enferm Trop*. 6: 239-252.

Haider, M., Gangat, N., Hanson, C., *et al*. 2016. Splenomegaly and thrombosis risk in essential thrombocythemia: the Mayo Clinic experience. *Am J Hematol*. 91(5): E296-297.

Hasford, J., Pfirrmann, M., Hehlmann, R., *et al*. 2003. Prognosis and prognostic factors for patients with chronic myeloid leukemia: nontransplant therapy. *Semin Hematol*. 40(1): 4-12.

Hassan, K., Qureshi, M., Shafi, S., *et al*. 1993. Acute myeloid leukemia-FAB classification and its correlation with clinico-haematological features. *J Pak Med Assoc*. 43(10): 200-203.

Hessol, N. A., Katz, M. H., Liu, J. Y., *et al*. 1992. Increased incidence of Hodgkin disease in homosexual men with HIV infection. *Ann Intern Med*. 117(4): 309-311.

Jabbour, E. and Kantarjian, H. 2012. Chronic myeloid leukemia: 2012 update on diagnosis, monitoring, and management. *Am J Hematol*. 87(11): 1037-1045.

Jacobs, P., Wood, L. and Close, P. 1998. Myeloma Presenting with Massive Splenomegaly. *Hematology*. 3(5): 375-379.

Jankulovski, N., Antovic, S., Kuzmanovska, B., *et al*. 2014. Splenectomy for haematological disorders. *Pril (Makedon Akad Nauk Umet Odd Med Nauki)*. 35(1): 181-187.

Jonte, F., Barez, A., Soto, I., *et al*. 1992. Features of chronic myeloid leukemia at diagnosis. Study of a series of 134 cases. *Sangre (Barc)*. 37(5): 345-350.

Kaito, K., Otsubo, H., Ogasawara, Y., *et al*. 1995. Aplastic anemia with giant splenomegaly and myelofibrosis successfully treated with antilymphocyte globulin. *Rinsho Ketsueki*. 36(8): 786-791.

Kasper, D. L., Braunwald, E., Fauci, A. S., *et al*. 2005. Harrison's Principles of Internal Medicine. New York, McGraw-Hill. I**:** 343-348.

King, H. and Shumacker, H. B. 1952. Splenic studies. I. Susceptibility to infection after splenectomy performed in infancy. *Ann Surg*. 136(2): 239-242.

Konca, C., Soker, M., Tas, M. A., *et al*. 2015. Hereditary spherocytosis: evaluation of 68 children. *Indian J Hematol Blood Transfus*. 31(1): 127-132.

Konkay, K., Uppin, M. S., Uppin, S. G., *et al*. 2014. Hairy cell leukemia: clinicopathological and immunophenotypic study. *Indian J Hematol Blood Transfus*. 30(3): 180-186.

Lamb, P. M., Lund, A., Kanagasabay, R. R., *et al*. 2002. Spleen size: how well do linear ultrasound measurements correlate with three-dimensional CT volume assessments? *Br J Radiol* 75(895): 573-577.

Lowenberg, B., Downing, J. R. and Burnett, A. 1999. Acute myeloid leukemia. *N Engl J Med*. 341(14): 1051-1062.

Lowenthal, M. N., Hutt, M. S., Jones, I. G., *et al*. 1980. Massive splenomegaly in Northern Zambia. I. Analysis of 344 cases. *Trans R Soc Trop Med Hyg.* 74(1): 91-98.

Maurer, C. and Hallek, M. 2013. Chronic lymphocytic leukemia. *Dtsch Med Wochenschr*. 138(42): 2153-2166.

Mayet, Y. 2015. Philadelphia Chromosome Negative Myeloproliferative Neoplasms at Chris Hani Baragwanath Academic Hospital. Master of Medicine (MMed), University of the Witwatersrand.

McDermott, M. K. and Bell, E. M. 1999. A review of Waldenstrom's macroglobulinemia. *Clin J Oncol Nurs.* 3(3): 107-111.

Mereuta, A. and Turtureanu-Hanganu, E. 1990. Myelodysplastic syndromes. A clinico-biological analysis of 27 cases. *Rev Med Chir Soc Med Nat Iasi*. 94(1): 67-73.

Norton, A. J., Matthews, J., Pappa, V., *et al*. 1995. Mantle cell lymphoma: natural history defined in a serially biopsied population over a 20-year period. *Ann Oncol*. 6(3): 249-256.

O'Reilly, R. A. 1996. Splenomegaly at a United States County Hospital: diagnostic evaluation of 170 patients. *Am J Med Sci*. 312(4): 160-165.

O'Reilly, R. A. 1998. Splenomegaly in 2,505 patients in a large university medical center from 1913 to 1995. 1913 to 1962: 2,056 patients. *West J Med.* 169(2): 78-87.

Olson, A. P., Trappey, B., Wagner, M., *et al*. 2015. Point-of-care ultrasonography improves the diagnosis of splenomegaly in hospitalized patients. *Crit Ultrasound J*. 7(1): 13.

Osler, W. 1904. Chronic Cyanotic Polycythaemia with Enlarged Spleen. *Br Med J*. 1(2246): 121-122.

Paes, F. M., Kalkanis, D. G., Sideras, P. A., *et al*. 2010. FDG PET/CT of extranodal involvement in non-Hodgkin lymphoma and Hodgkin disease. *Radiographics.* 30(1): 269-291.

Papajik, T., Raida, L., Faber, E., et al. 1999. Mantle cell lymphoma as a diagnostic and therapeutic problem. *Vnitr Lek*. 45(1): 55-61.

Patel, M. 1994. Haematological Disorders. Baragwanath Hospital, 50 years, A Medical Miscellany. K. Huddle and A. Dubb. Johannesburg**:** 172-190.

Patel, M., Philip, V. and Fazel, F. 2011. Human Immunodeficiency Virus Infection and Hodgkin's Lymphoma in South Africa: An Emerging Problem. *Adv Hematol*. 2011: 578163.

Patel, M., Philip, V., Lakha, A., *et al.* 2015. Multicentric Castleman's disease. I*mmunopathology and Immunomodulation.* (11): 247-259.

Patel, M., Philip, V., Omar, T., *et al*. 2015. The Impact of Human Immunodeficiency Virus Infection (HIV) on Lymphoma in South Africa. *Journal of Cancer Therapy*. (6).

Payandeh, M., Sadeghi, M. and Sadeghi, E. 2015. Hairy cell leukemia: A retrospective study on 11 patients in the Western of Iran. *Int J Hematol Oncol Stem Cell Res*. 9(3): 133-137.

Pearson, T. C. and Messinezy, M. 1996. The diagnostic criteria of polycythaemia rubra vera. *Leuk Lymphoma*. 22 Suppl 1: 87-93.

Petzoldt, R., Lutz, H., Ehler, R., *et al*. 1976. Determination of splenic size by ultrasonic scanning (author's transl). *Med Klin*. 71(48): 2113-2116.

Pfirrmann, M., Baccarani, M., Saussele, S., et al. 2016. Prognosis of long-term survival considering disease-specific death in patients with chronic myeloid leukemia. *Leukemia*. 30(1): 48-56.

Picardi, M., Martinelli, V., Ciancia, R., *et al*. 2002. Measurement of spleen volume by ultrasound scanning in patients with thrombocytosis: a prospective study. *Blood*. 99(11): 4228-4230.

Polizzotto, M. N., Uldrick, T. S., Wang, V., *et al*. 2013. Human and viral interleukin-6 and other cytokines in Kaposi sarcoma herpesvirus-associated multicentric Castleman disease. *Blood*. 122(26): 4189-4198.

Pozo, A. L., Godfrey, E. M. and Bowles, K. M. 2009. Splenomegaly: investigation, diagnosis and management. *Blood Rev.* 23(3): 105-111.

Rai, K. R., Sawitsky, A., Cronkite, E. P., *et al*. 1975. Clinical staging of chronic lymphocytic leukemia. *Blood*. 46(2): 219-234.

Randhawa, J., A. Ostojic, R. Vrhovac, E. Atallah and S. Verstovsek (2012). "Splenomegaly in myelofibrosis--new options for therapy and the therapeutic potential of Janus kinase 2 inhibitors." J Hematol Oncol **5**: 43.

Ren, Y., Fu, R., Qu, W., *et al*. 2015. Clinical analysis of 70 cases of polycythemia vera. *Zhonghua Yi Xue Za Zhi*. 95(18): 1378-1381.

Robertson, F., Leander, P. and Ekberg, O. 2001. Radiology of the spleen. *Eur Radiol*. 11(1): 80-95.

Rosen, S. T., Link, B. K. and Fowler, N. H. 2013. Unmet needs in the treatment of mantle cell lymphoma. *Clin Adv Hematol Oncol*. 11(11 Suppl 18): 1-19.

Roy, A., Kar, R. and Basu, D. 2013. Nodal mantle cell lymphoma: a descriptive study from a tertiary care center in South India. *Indian J Pathol Microbiol*. 56(2): 94-97.

Rupoli, S., Da Lio, L., Sisti, S., *et al*. 1994. Primary myelofibrosis: a detailed statistical analysis of the clinicopathological variables influencing survival. *Ann Hematol*. 68(4): 205-212.

Sandusky, W. R., Leavell, B. S. and Benjamin, B. I. 1964. Splenectomy: Indications and Results in Hematologic Disorders. *Ann Surg*. 159: 695-710.

Savage, D. G., Szydlo, R. M. and Goldman, J. M. 1997. Clinical features at diagnosis in 430 patients with chronic myeloid leukaemia seen at a referral centre over a 16-year period. *Br J Haematol*. 96(1): 111-116.

Schloesser, L. L. 1963. The diagnostic significance of splenomegaly. *Am J Med Sci*. 245: 84-90.

Shisana, O., Rehle, T., Simbayi, L. C., *et al*. 2014. South African National HIV Prevalence, Incidence and Behaviour Survey 2012. Cape Town, HSRC Press.

Spina, M., Carbone, A., Gloghini, A., *et al*. 2011. Hodgkin's Disease in Patients with HIV Infection. *Adv Hematol*. 2011.

Sultan, S., Zaheer, H. A., Irfan, S. M., *et al*. 2016. Demographic and Clinical Characteristics of Adult Acute Myeloid Leukemia--Tertiary Care Experience. *Asian Pac J Cancer Prev*. 17(1): 357-360.

Swaroop, J. and O'Reilly, R. A. 1999. Splenomegaly at a university hospital compared to a nearby county hospital in 317 patients. *Acta Haematol*. 102(2): 83-88.

Takahashi, M., Koike, T., Kishi, K., *et al*. 1990. Prognostic Features in the Myelodysplastic Syndromes: Importance of Morphological Atypia in the Marrow Cell Lineages. *Leuk Lymphoma*. 1(2): 141-146.

Talbott, J. A. 1970. A Bibliographical History of Medicine: Excerpts and Essays on the Men and their Work. New York, Grunne & Stratton.

Tamayo, S. G., Rickman, L. S., Mathews, W. C., *et al*. 1993. Examiner dependence on physical diagnostic tests for the detection of splenomegaly: a prospective study with multiple observers. *J Gen Intern Med*. 8(2): 69-75.

Tassiopoulos, T., Rombos, Y., Konstantopoulos, K., *et al*. 1995. Spleen size in beta-thalassaemia heterozygotes. *Haematologia (Budap)*. 26(4): 205-209.

Thieblemont, C., Felman, P., Berger, F., *et al*. 2002. Treatment of splenic marginal zone B-cell lymphoma: an analysis of 81 patients. *Clin Lymphoma*. 3(1): 41-47.

Thipphavong, S., Duigenan, S., Schindera, S. T., *et al*. 2014. Nonneoplastic, benign, and malignant splenic diseases: cross-sectional imaging findings and rare disease entities. *AJR Am J Roentgenol*. 203(2): 315-322.

Thompson, L. D., Fisher, S. I., Chu, W. S., *et al*. 2004. HIV-associated Hodgkin lymphoma: a clinicopathologic and immunophenotypic study of 45 cases. *Am J Clin Pathol*. 121(5): 727-738.

van der Weide, M., Sizoo, W., Krefft, J., *et al*. 1988. Myelodysplastic syndromes: analysis of morphological features related to the FAB-classification. *Eur J Haematol*. 41(1): 58-61.

Venkatesan, S., Purohit, A., Aggarwal, M., *et al*. 2014. Unusual presentation of hairy cell leukemia: a case series of four clinically unsuspected cases. *Indian J Hematol Blood Transfus*. 30(Suppl 1): 413-417.

Wang, J., Xu, J., Gale, R. P., *et al*. 2014. Prognostic impact of splenomegaly on survival of Chinese with primary myelofibrosis. *Leuk Res.* 38(10): 1207-1211.

Weisenburger, D. D., Linder, J. and Armitage, J. O. 1987. Peripheral T-cell lymphoma: a clinicopathologic study of 42 cases. *Hematol Oncol*. 5(3): 175-187.

Wotherspoon, A., Attygalle, A. and Mendes, L. S. 2015. Bone marrow and splenic histology in hairy cell leukaemia. *Best Pract Res Clin Haematol*. 28(4): 200-207.

Xing, K. H., Kahlon, A., Skinnider, B. F., *et al.* 2015. Outcomes in splenic marginal zone lymphoma: analysis of 107 patients treated in British Columbia. *Br J Haematol*. 169(4): 520-527.

Yang, J. C., Rickman, L. S. and Bosser, S. K. 1991. The clinical diagnosis of splenomegaly. *West J Med*. 155(1): 47-52.

Yoshioka, Y., Kawamata, N., Sato, E., *et al.*1999. Primary splenic lymphoma with hypoplastic bone marrow. *Rinsho Ketsueki*. 40(2): 124-128.

Ziegler, J. L., Bragg, K., Abrams, D., *et al.* 1984. High-grade non-Hodgkin's lymphoma in patients with AIDS. *Ann N Y Acad Sci.* 437: 412-419.

Zwiebel, J. A. and Cheson, B. D. 1998. Chronic lymphocytic leukemia: staging and prognostic factors. *Semin Oncol*. 25(1): 42-59.

APPENDICES

Appendix A: Data Collection Sheet

ALLOCATED STUDY NUMBER: _____

A) Demographic Information:

a. Age: _____

b. Gender: Male □ Female □

c. Ethnic Group: African □ Caucasian □ Indian □ Coloured □

d. Retroviral Status:

i. Positive □ Negative □ Unknown □

ii. CD_4 count if known: _____

iii. Antiretroviral therapy: Yes □ No □ Unknown □

iv. Duration of therapy: 0-1 years □ 1-5 years □ > 5years □ Unknown □

B) Clinical Information

a. General: Pallor □ Jaundice □

b. Splenomegaly Confirmed:

i. Clinically: Size:_____ cm

ii. Radiologically: Ultrasound □ Size:_____ cm

CT Scan □ Size:_____ cm

c. Lymphadenopathy:

i. Extent: Localised □ Generalised □

ii. Sites:

_____

d. Hepatomegaly

i. Clinically: Size:_____ cm

ii. Radiologically: Ultrasound □ Size:_____ cm

CT Scan □ Size:_____ cm

C) Laboratory Information

a. Initial Blood Results

Test	Parameter	Patient Result
Full Blood Count	Haemoglobin	
	Red Cell Count	
	White Cell Count	
	Platelets	
Differential Count (%)	Neutrophils	
	Basophils	
	Eosinophils	
	Monocytes	
	Lymphocytes	
Liver Function Tests	Direct Bilirubin	
	Conjugated Bilirubin	
	Protein	
	Albumin	
	AST	
	ALT	
	ALP	
	GGT	

b. Bone Marrow Aspirate and Trephine Biopsy

Conclusion:_____

_____

_____

c. Other Histological Findings:

i. Biopsy Site_____

ii. Disease Stage:_____

d. Final Diagnosis (including histological subtype)

_____

Appendix B: Ethics Clearance Certificate

R14/49 Dr Michelle Venter

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150339

NAME: (Principal Investigator)	Dr Michelle Venter
DEPARTMENT:	Internal Medicine Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	A Description of Splenomegaly in a Hospital Haematology Setting
DATE CONSIDERED:	27/03/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof M Patel
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	20/04/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature

Date 09/06/2015

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix C: Turn-it-in Letter from Supervisor

Division of Haematology, Department of Medicine, Chris Hani Baragwanath Academic Hospital, University of the Witwatersrand, Johannesburg
Chris Hani Road, Diepkloof, Soweto. Tel: +27 11 9339377, Fax: +27 11 9339449, email: moosa.patel@wits.ac.za

15 March 2017

The Chair

Postgraduate Studies Committee

Faculty of Health Sciences

University of the Witwatersrand

Re: Turn-it-in report: Dr Michelle Venter – 0102016D. 'A description of splenomegaly in hospital haematology setting'

As the supervisor of Dr Venter's MMed, I have reviewed the Turn-it-in report of her MMed research report. The Turn-it-in report identifies a similarity index of 21%. Much of this similarity relates to definitions and terminology, which is standardized. The other information which bears a similarity has been appropriately referenced.

Thank you

Yours sincerely

Moosa Patel MBChB, FCP(SA), MMed(Wits), FRCP(Lond.), PhD(Wits)

Professor and Head of Clinical Haematology, Department of Medicine, Chris Hani Baragwanath Academic Hospital and the Faculty of Health Sciences, University of the Witwatersrand,