CHAPTER ONE

INTRODUCTION AND LITERATURE

1.1 Introduction

1.1.1. Iron

1.1.1.1 The roles of iron in health and disease

Iron is vital for almost all living organisms by participating in a wide variety of metabolic processes, including oxygen transport, DNA synthesis and electron transport. However, iron concentrations in body tissues must be tightly regulated because excessive iron leads to tissue damage, as theresult of formation of free radicals. Disorders of iron metabolism are themost common diseases of humans and encompass a broad spectrum of diseases with diverse clinical manifestations, ranging from anemia to iron overload and, possibly, to neurodegenerative diseases and cancer (Lieu *et al.*, 2001).

1.1.1.2 Human iron status

The healthy adult human has a total body iron content of about 3500mg, of which 2000 mg is present as circulating hemoglobin, 300 mg is in the form of cell enzymes and pigments, and the remainder is stored in cells as ferritin or hemosiderin. Ferritin is a macromolecule composed of a protein shell within which up to 4500 atoms of iron can be stored as ferric oxhydroxide. Hemosiderin is probably a degraded form of ferritin that has lost part of its protein shell (Bebeshko *et al*., 2013).

Iron is stored mainly in the reticuloendothelial cells of the bone marrow, liver and spleen and in the parenchymal cells of the liver, which accept any excess of iron in the body.

When iron in these sites is needed by other tissues the stores release it into the blood, where transferrin carries it to the appropriate tissue; once the need has been met the stores are reconstituted (*Unal et al., 2*014).

Most of the iron in the blood is destined for the erythropoietic marrow, where it is incorporated into hemoglobin. Circulating erythrocytes are normally destroyed at the end of their life span by the reticuloendothelial cells in the spleen and liver. Most of the iron from degraded hemoglobin returns to the plasma, but small part first exchanges slowly with the iron stores in the reticuloendothelialcells (*Unal et al.,* 2014).

1.1.1.3 Ferritin

Ferritin is a ubiquitous intracellular protein that stores iron and releases it in a controlled fashion. The protein is produced by almost all living organisms, including algae, bacteria, higher plants, and animals. In humans, it acts as a buffer against iron deficiency and iron overload. Ferritin is found in most tissues as a cytosolic protein, but small amounts are secreted into the serum where it functions as an iron carrier. Plasma ferritin is also an indirect marker of the total amount of iron stored in the body; hence serum ferritin is used as a diagnostic test for iron deficiency anemia (Wang *et al.*, 2010).

1.1.1.3.1 Function

1.1.1.3.1 Iron storage

Ferritin serves to store iron in a non-toxic form, to deposit it in a safe form, and to transport it to areas where it is required. The function and structure of the expressed

ferritin protein varies in different cell types. This is controlled primarily by the amount and stability of mRNA. mRNA concentration is further tweaked by changes to how it is stored and how efficiently it is transcribed. The presence of iron itself is a major trigger for the production of ferritin (Andrews *et al.*, 1992).

1.1.1.3.2 Diagnostic uses

Serum ferritin levels are measured in medical laboratories as part of the iron studies workup for Iron-deficiency anemia. The ferritin levels measured usually have a direct correlation with the total amount of iron stored in the body. However, ferritin levels may be artificially high in cases of anemia of chronic disease where ferritin is elevated in its capacity as an inflammatory acute phase protein and not as a marker for iron overload (Tran *et al.*, 2013).

1.1.2 Leukemia

1.1.2.1 Leukemia definition and incidence

Leukemia describes a wide range of clonal hematological disorders with heterogeneous features. It embraces acute and chronic forms of neoplasms of the myeloid and/or the lymphoid cell lineage. It is one of the most diseases and occurs worldwide in about 50 of 100,000 of the population. Males are up to twice as often affected as females. The diversity of leukemia is determined by the origin of the malignant cell clone from different cell types (Swerdlow *et al.*, 2008).

1.1.2.2 Leukemia: unregulated proliferation of hematopoietic cells

A malignant transformation can happen at any stage of blood cell development. These abnormal blood cells are characterized by abnormal unregulated proliferation of one or more cells of the hematopoietic lineage. This abnormal behavior is due to the generation of somatic mutations which confer the affected cells a proliferative or survival advantage over the normal cells. The mutations include translocations, deletions and insertions that usually affect oncogenes or tumor suppressors (Rowley *et al.*, 1998).

1.1.1.3 Subtypes of leukemia

Most leukemias fall into one of two general groups: myeloid leukemia(about60% of the cases) and lymphocytic leukemia(about 40%). patientsalso classifyleukemias according to whether they are acute(55%) or chronic(45%). In acute leukemias, the malignant cells, or blasts, are immature cells that areincapable of performing their immune system functions. The onset of acuteleukemias is rapid (weeks), and, in most cases, fatal unless the disease istreated quickly. Chronic leukemias develop in more mature cells, which can perform some of their duties but not well. These abnormal cells also increase at a slower rate (years). Hence, there are four main types of leukemia: AcuteLymphocytic Leukemia (**ALL**), Chronic Lymphocytic Leukemia (**CLL**), AcuteMyelogenous Leukemia (**AML**), Chronic Myelogenous Leukemia (**CML**) (Rowley *et al.*, 1998).

1.1.1.4 Acute lymphocytic leukaemia (ALL)

ALL is a neoplastic disease that results from multistep somatic mutations in a single lymphoid progenitor cell at one of several discrete stages of development. It is an acute

form of leukemia, or cancer of the white blood cells, characterized by the overproduction and accumulation of cancerous, immature white blood cells, known as lymphoblasts (Greer *et al.*, 2013).

It is the commonest pediatric cancer in industrialized countries. With an incidence expected to reach up to 4.75 cases per 100.000 people worldwide, ALL represents f 80% of leukemia diagnoses. Whereas ALL accounts for 23% of cancers among children younger than 15 years, it is responsible for up to 20% of all adult leukemia's, which are characterized by a worse prognosis with a decreased long-term survival (Redaelli *et al.*, 2005).

1.1.1.5 Etiology of ALL

ALL is not one homogenous disease and can be due to several causes. These include chromosome translocations, resulting in the generation of chimeric or fusion genes and change in chromosome number (hyperdiploidy or hypodiploidy). Genes involved in these abnormalities have very diverse functions, but it seems that most of them are involved in some critical stage of cell growth, development, or survival. Epidemiological evidence suggests that ionizing radiation and certain chemicals (such as benzene) may play a part in the development of some subtypes of leukemia and lymphoma in adults and children (*Bebeshko et al., 2013*).

1.1.2.3.8 Ferritin in cancer

While iron is an essential micronutrient for DNA synthesis in addition to respiratory and oxidative cell metabolism, its pro-oxidative properties can render it carcinogenic. Free

iron can catalyze the formation of mutagenic hydroxyl radicals that, in turn, can cause increased oxidative stress, DNA damage, and oncogene activation. Iron also suppresses host defenses, thereby permitting cancer cell proliferation, and acts as a nutrient for unrestricted tumor cell multiplication. Iron has been carcinogenic in animal models, and in several studies iron stores were positively associated with risks of certain human cancers, including colorectal and liver. Heme iron is of particular concern given that the body continues to absorb it even if stores are adequate (Weinberg *el al*., 1996).

Serum ferritin is elevated in many malignancies. In some cases, this overall increase in circulating ferritin is also associated with a shift in the composition of ferritin to more H-rich species. For example, serum ferritin in malignant histiocytosis consists mainly of ferritin H. Mechanisms underlying these changes are unclear. However, in neuroblastoma, an increase in serum ferritin has been directly linked to secretion of ferritin by the tumor. In these studies, human ferritins were detected in the sera of nude mice transplanted with human neuroblastoma. However, no difference in the ratio of acidic (H-rich) to basic (L-rich) isoferritins was detected in the sera of patients with neuroblastoma, suggesting that the amount or composition of ferritin secreted by tumors is not sufficient to change the overall composition of serum ferritin (Selig *et al.,* 1998).

Preoperative serum ferritin levels were elevated in with newly diagnosed breast cancer, locally recurrent, and metastatic disease. Tissue ferritin in cytosol extracts from mammary carcinomas showed up to a 10-fold increase from benign breast tissues, and electron microscopy showed that the ferritin was abundant in malignant epithelium, but was sparse in benign epithelium and connective tissue. However, another study detected

ferritin primarily in stroma and in histiocytes surrounding neoplastic cells, suggesting that raised serum ferritin concentrations in breast carcinoma patients might be attributed to stromal reaction rather than to tumor synthesis (Rossiello *et al.,* 1984).

It is known that excess iron alters the distribution of T-lymphocyte subsets and suppresses the action of helper T (CD4) cells, as well as the tumoricidal action of macrophages and monocytes. In hereditary hemochromatosis patients, iron overload increases the numbers and activities of suppressor T (CD8) cells and decreases the numbers and activities of CD4 cells resulting in increased CD8:CD4 ratios. Thus, it is thought that the excess iron may impair surveillance for cancer cells by these mechanisms. However, two cohort studies of malignancy in hemochromatosis patients showed no increased risk of breast cancer, though the number of women with hemochromatosis was quite small (Kabat *et al.,* 2007).

Kabat and Rohan (2007) have pointed out that the higher risk of breast cancer in women who are post-menopausal is consistent with the hypothesis that increased iron storage may contribute to carcinogenesis. They proposed that iron overload and the disruption of iron homeostasis may contribute to the development of breast cancer, and reviewed the evidence for this hypothesis (Kabat*et al.,* 2007). Oxidative stress is induced by a reactive oxygen species, the formation of which is mediated by free iron. Ferric iron (Fe3+) released from ferritin and hemosiderin is reduced to ferrous iron (Fe2+) which, in the presence of super oxide and hydrogen peroxide (H2O2), can catalyze the formation of the hydroxyl radical (*OH). The hydroxyl radical is a powerful oxidizing agent which can promote lipid peroxidation, mutagenesis, DNA strand breaks, activation of oncogenes,

and tumor suppressor gene inhibition. Conflicting evidence exists regarding the contribution of lipid peroxidation products in breast cancer. It is postulated that iron interacts with known agents in breast carcinogenesis, particularly estradiol, ethanol and ionizing radiation. Iron overload favors the production of reactive oxygen species, lipid peroxidation, and DNA damage (Wang *et al.*, 2010).

patients with a variety of hematologic malignant neoplasms were studied by (Patel et al, 1980) to determine the relation between changes in serum ferritin concentration and the clinical status of the patients. Patients with Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, blastic crisis of chronic myelocytic leukemia, acute myeloblastic leukemia and ALL were found to have significantly elevated serum ferritin levels. The serum ferritin level reflects acute phase reactions and is usually associated with iron storage. Other recent studies have suggested that ferritin is a surrogate for advanced disease and has an impact on relapse, because elevated serum ferritin predicts overall survival (OS) and relapse-free survival following autologous stem cell transplantation for lymphomas (Armand *et al*., 2007; Mahindra *et al.*, 2008).

1.2 **Literature review**

In patients with ALL the mean serum ferritin concentration showed a thirteen-fold increase compared with normal people. The high concentration of circulating ferritin seemed to be related to increased synthesis by leukaemic cells. The return of serum concentrations to normal in ALL patients after successful chemotherapy suggested that ferritin concentration may be a useful index of active disease and may help in prognosis (Parry *et al.*, 1995).

Serum ferritin was significantly elevated in leukemia patients. Transferrin iron saturation rose abruptly during the first week of chemotherapy with a gradual return to normal by the end of induction. TIBC appropriately decreased in response to high iron saturations. Thirteen subjects required between 2 and 5 transfusions of packed red blood cells during the study period. The increase in iron saturation was not related to iron transfused as packed red cells. Bone marrows stained for hemosiderin iron within the lymphoblast revealed a few small particles in 5/1000 cells in only one patient (Deborah *et al.*, 1997).

Serum levels of ferritin were in patients with hematologic malignancies. Of 473 patients with hematologic malignancies, 262 patients were diagnosed with acute leukemia. Serum ferritin levels of newly diagnosed and recurrent patients were significantly higher than those entering complete remission stage or in the control group ($P<0.001$). Serum ferritin levels in patients with hematologic malignancies at early stage and recurrent stage are significantly increased, so that detection and surveillance of changes of serum ferritin could be helpful in assessing conditions and prognosis of this patient cohort (Zhang *et al.*, 2014).

Production of reactive oxygen species (ROS) in which serum ferritin is incorporated is an inevitable result in cells that use aerobic metabolism for energy production. ROS are known to play a dual role in biological system, since they may be either harmful or beneficial to living systems. Accumulation of such molecules causes noxious effects on individuals, resulting in diseases such as hematopoietic malignancies (Masutani,*et al*., 2000).

Artzet *et al.,* (2016) reported that transplant-related mortality was associated with the pre-specified thresholds of C-reactive protein more than 10 mg/L (P=0.008) and albumin less than 3.5 g/dL (P=0.01) but not ferritin more than 2500 ng/mL. Only low albumin independently influenced overall mortality. Optimal thresholds affecting transplant-related mortality were defined as: C-reactive protein more than 3.67 mg/L, log (ferritin), and albumin less than 3.4 g/dL. A 3-level biomarker risk group based on these values separated risks of transplant-related mortality: low risk (reference), intermediate (HR=1.66, P=0.015), and high risk (HR=2.7, P<0.001).

Chuaet *et al.*, (2016) reported that After adjustments for age, smoking, drinking, anthropometric and biochemical variables, or menopausal status (breast cancer), higher serum iron concentrations and transferrin saturation were associated with increased risks of incident nonskin cancer [HR for iron: 1.83 (95% CI: 1.21, 2.76; P < 0.01); HR for transferrin saturation: 1.68 (95% CI: 1.18, 2.38; P < 0.01)] including breast cancer [HR for iron: 2.45 (95% CI:1.12, 5.34; P < 0.05); HR for transferrin saturation: 1.90 (95% CI:1.02, 3.56; P < 0.05)] in women. Transferrin saturation was also associated with a greater risk of cancer death (HR: 2.48; 95% CI: 1.28, 4.82; P < 0.01). In men, higher iron concentrations were associated with reduced risks of incident nonskin cancer (HR: 0.65; 95% CI: 0.42, 0.99; P < 0.05) including colorectal cancer (HR: 0.34; 95% CI: 0.12, 0.95; P < 0.05). There was no association between serum iron and colorectal cancer risk in women. Serum ferritin was not associated with cancer risk or cancer death.

Yuan et al., (2016) showed the levels of serum Cyfra21-1, SCCAg, ferritin, and CEA in patients with OSCC/OPSCC were significantly higher than those of benign tumor and

healthy control group ($P<0.05$). The levels of CA19-9 and AFP showed no significant difference between patients with OSCC/OPSCC, benign tumor, and healthy group ($P>0.05$). The level of serum Cyfra21-1 in patients with early OSCC/OPSCC (stage I + II) was significantly higher than that of benign tumor and healthy control group ($P<0.05$). However, the levels of serum SCCAg, ferritin, CEA, CA19-9, and AFP showed no significant difference between patients with early OSCC/OPSCC, benign tumor, and healthy control group ($P>0.05$). The levels of serum Cyfra21-1, SCCAg, ferritin, and CEA in the middle-late stage of patients with OSCC/OPSCC (stage III + IV) were significantly higher than those of patients with the early OSCC/OPSCC, benign tumor, and healthy control group ($P<0.05$). The diagnostic cutoff levels of Cyfra21-1, SCCAg, ferritin, and CEA were 2.17, 0.72, 109.95, and 1.99 ng/mL, respectively. The sensitivities were 60.36%, 73.37%, 81.66%, and 66.27%, respectively. The specificities were 81.03%, 68.10%, 40.52%, and 61.21%, respectively.

1.3 Justification

ALL is one of the most common neoplasms particularly among children. Leukemic cells, due to their rapid proliferation, have increased iron needs and large numbers of transferrin receptors. Although patients with many forms of malignancy are known to have increased serum ferritin, other iron indices have not been examined. As there is no previous study evaluated the association of serum ferritin with ALL, so we analyze variability and clinical significance of iron status by the evidence of serum ferritin levels in Sudanese patientswith ALL.

1.4 Objectives

1.4.1 General objective

To assess and determine prognosis of serum ferritin among ALL Sudanese patients.

1.4.2 Specific objectives

- To compare serum ferritin levels between ALL patients and apparently healthy controls.
- To correlate the results of serum ferritin levels with TWBC count and blast%
- To compare serum ferritin levels with possible risk factors gender and age in all study volunteersmales and females.

CHAPTER TWO

MATERIALS & METHODS

2.1 Study design

This was a prospective case control study.

2.2 Study population

One hundred Sudanese patients diagnosed and confirmed to have ALL according to WHO criteria and age and hundred age- and gender- matched apparently healthy individuals were included in this study.

2.3 Study area

The study was conducted in Khartoum state, Fedail Hospital.

2.4 Study duration

This study was conducted during the period from September 2015 to March 2016.

2.5 Inclusion and exclusion criteria:

Inclusion criteria: Sudanese patients with ALL, both male and female, at any age.

Exclusion criteria: Those on iron supplementation or in drugs affecting iron metabolism.

2.6 Sampling:

26.1 Sample collection:

Five ml of venous blood was collected with aseptic precautions from antecubital vein, 3 ml was dispensed into EDTA container and 2 ml was poured into plain container. Blood mixed with EDTA was used for full blood count.

The blood sample in the plain container was left at room temperature for two hours and centrifuged at 3200 rpm for three minutes to obtain sera. Sera obtained were then collected in 1.5 ml eppendorf tubes and frozen at (-20c) for performance of serum ferritin.

2.6.2 Data collection

Questionnaires were designed to provide personal and medical information about the patients (appendix I). Questionnaires were filled by asking the patients about personal information. Medical information was collected from medical file with the help of treating doctors.

2.7 laboratory investigations

2.7.1 Full blood count (CBC) and peripheral blood picture

CBC was measured using a Sysmex KX21 autoanalyzer that uses aperture-impedance technology. CBC will be performed within 1 hour of collection to minimize variations due to sample aging by exactly following manufacturer instructions. CBC was done following these steps:

The whole blood mode (WB) was selected to analyze the whole blood sample without pre-dilution. The sample number was entered before each sample. This procedure was followed:

A well-mixedanticoagulated sample was set to the sample probe, and the start switch was pressed till the aspirating process was finished. (Volume aspirated approx. 50µL).

The sample was removed straight down and the sample probe was automatically cleaned.

The aspirated sample was then automatically suspended into the different detector blocks and different parameters were measured.

The results of parameters were then viewed on the screen and subsequently printed out.

For examination of (PBP) 2 thin blood films were stained: one with rapid diff quick stain and the others with MGG from RAL. The examination of PBP was used to get the microscopic differential count of white cells, the validation of platelet count and the morphology of red cells.

2.7.2Serum ferritin

Serum ferritin levels were determined by Immunoassay based on ECL for the in vitro quantitative determination of ferritin in human serum and plasma (roche- Germany)

2.8 Ethical consideration of the Study

The study was revised and ethically approved by the Ethical Committee of the Faculty of Medical Laboratory Sciences, Sudan University of Science and Technology. Samples were taken with verbal consent from patients or their relatives.

2.9Statistical analysis

The statistical analysis was performed using statistical package for social sciences (SPSS) version 20.0. Frequencies, independent- Sample T Test and Pearson Correlations.All reported P values were considered significant at a level of $P<0.05$.

CHAPTER THREE

RESULTS

3.1 Results

One hundred patients with ALL (54 male, 46 females; mean age ±STD = 22.6 ± 18.8 years) and 100 healthy subjects (55 male, 45 female; mean age±STD = 19.9 ± 19.7 years) comprised the study group, Table 3.1.

Serum levels of ferritin were higher in patients with ALL [M±STD = 870 ± 2.18 ng/dl] when compared with controls [M±SD = 210.0 ± 45.25 mg/dl]. This difference was statistically significant [*P = 0.0001*], Table 3.1.

Table 3. 1: The distribution of gender age of participants

	Cases	Controls	*P* value
Male	54,54%	55,55%	
Female	46,46%	45,45%	
Mean ± SD age	22.6 ± 18.8	19.9 ± 19.7	
Mean ± ferritin	780± 401.8	210± 122.8	0.0001

The average of WBCs count and blast cells among cases were 176.3± 45.8 X^{10}/µl and 122± 39.9 X^{10}/µl respectively. Pearson correlation analysis among ALL, showed a highly significant direct correlation between serum ferritin levels and white blood cell counts (r = 0. 604, p = 0.002) as well as with the number of blast cells (r = 0.735, p< 0.001), table 3.2.

Table3.2: Correlation of serum ferritin with WBC and blast cell in ALL patients

	White cell count	Blast cell count
Mean ± SD	176.3± 45.8 X^{10}/µl	122± 39.9 X^{10}/µl
Pearson correlation (r)	0.604	0.735
P-value	< 0.0001	< 0.0001

The serum ferritin levels in males were 520 ± 288 mg/dl while in females were 470 ± 242 mg/dl. However this difference was statistically insignificant P > 0.05, figure, 3.2.

There was no statistically significant difference in serum levels of ferritin between adults (420 ± 277 mg/dl) and children (470 ± 293mg/dl) when comparing serum levels of ferritin between those who below 18 and those who above 18 years, P > 0.05, as illustrated in figure 3.3.

Table 3.3: Effect of age and gender on serum ferritin levels among all studied subjects

variables		Ferrin levels (mg/dl)	*P* value
Gender	Male	520 ± 288	0.101
	Female	470 ± 242	
Age	< 18	470 ± 293	0.116
	> 18	420 ± 277	

CHAPTER FOUR

DISCUSSION

4.1 Discussion

ALL is the most common cancer found in the pediatric population and it accounts for more than 50% of the hematopoietic malignancies in this age group. ALL is a disorder caused by an abnormal expression of genes, which is usually a result of chromosomal translocation .The disease can be originated from lymphoid cells of different lineages giving rise to B or T cell Leukemia or sometimes mixed –lineage leukemia (Gaynon *et al.,* 2005).

In recent years, researchers focus on effects of iron chelator such as anti-proliferation, cytotoxic effect, and inducing cell apoptosis, and suppose that iron-deprivation could control the proliferation of various tumor cells and induce apoptosis (Zhang *et al.* 2014).

Our results revealed that serum ferritin levels are significantly higher than in normal subjects. This is in agreement with previous studies (Parry *et al.,* 1995; Aulbert and Schmidt 1995; Zhang *et al.* 2014) and disagreed with study conducted by Chua et al (2016) who reported serum ferritin was not associated with cancer risk or cancer death. The differences between our result and other finding may due to differences in race, sample size and method used for measuring serum ferritin.

The present study showed that the role of ferritin contribution to the prognosis of ALL by the evidence of hematological prognostic markers. This in accordance with the study of Parry and his colleagues which found that there was no correlation between the serum

ferritin concentration and the total white cell count and the peripheral blood blast count (Parry *et al.*, 1995). Such association is not found in previous study of (Ahlawat *et al.*, 1994).

Contrary to our finding Artz *et al*., (2016) and (Ahlawat *et al.*, 1994) there was insignificant correlation between serum ferritin with age and gender.

4.2 Conclusion

Serum ferritin levels in patients with hematologic malignancies at early stage and recurrent stage are significantly increased; detection and surveillance of changes of serum ferritin could be helpful for assessing conditions and prognosis of this patient cohort.

4.3 Recommendations

Large sample size aiming an understanding the role of ferritin in ALL, this may therefore represent interesting target for designing new therapeutic strategies for patients with different hematological malignancies.

Serum ferritin should be used as prognostic factors.

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Questionnaire

1. Name:…….....2.date:……
3. Address:……
3.1 City,……3.2 state,……
4.1 Date of birth: YY/MM ☐ ☐ 5.1 Sex *(circle)*: Female Male

Laboratory data:

Full blood count (CBC)

Parameter	**Count**
TWBCs $X10^3$ /µl	
Blast $X10^3$ /µl	(%)

Serum ferritin

Parameter	**Measure**
Serum ferritin	levels
Blast $X10^3$ /µl	