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STUDY THE SOME LIVER AND KIDNEY IN IRAQI PATIENTS WITH LEUKAEMIA

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STUDY THE SOME LIVER AND KIDNEY FUNCTIONS IN IRAQI PATIENTS WITH LEUKAEMIA

By Saif Hammood Khudhur ALLAWEE

August 2021

We certify that we have read this thesis and that in our opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Science

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ABSTRACT

STUDY THE SOME LIVER AND KIDNEY FUNCTIONS IN IRAQI PATIENTS WITH LEUKAEMIA

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The purpose of this research is to assess certain liver and kidney functions in leukemia patients from Iraq. After collecting 120 blood samples from patients enrolled in the research at Ibn Al-Atheer Teaching Hospital, the samples were divided into age groups ranging from 8 to 75 years. Laboratory tests were performed on the samples. Where the highest rate of infection was recorded (34.26%) out of the total number in a chronic form. While the lowest rate of patients was (0.186%) for the age group (1-15) years, sharply. The total of these cases are: (70) a case of chronic leukemia, (30) a case of acute leukemia, and (20) a case of healthy (control). The current results showed that there is a statistical significance for half of the variables, with the exception of the other half.

2021, 89 pages

Keywords: Iraqi patients, Liver function, Renal function, Leukemia

ÖZET

IRAK LÖSEMI HASTALARINDA BAZI KARACIĞER VE BÖBREK FONKSIYONLARININ INCELENMESI

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Kimya, Yüksek Lisans
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Ağustos 2021

Çalışmanın amacı Irak lösemili lösemili hastalarda yapılan bazı karaciğer ve böbrek fonksiyonlarının değerlendirilmesidir. İbn Al-Atheer Eğitim Hastanesi'nde çalışmaya dahil edilen hastalardan 120 kan örneği alındıktan sonra, numunelerin 8 yaşından başlayarak 75 yaşına kadar yaş gruplarına ayrılması sürecinden sonra üzerlerinde laboratuvar testleri yapıldı. En yüksek enfeksiyon oranı (%34,26) kronik formda toplam sayı içinde kaydedildi. En düşük hasta oranı (1 - 15) yaş grubunda ise keskin bir şekilde (%0,186) idi. Bu vakaların toplamı: (70) kronik lösemi vakası, (30) akut lösemi vakası ve (20) sağlıklı (kontrol) vakadır. Mevcut sonuçlar, diğer yarısı hariç, değişkenlerin yarısı için istatistiksel bir anlamlılık olduğunu göstermiştir.

2021, 89 sayfa

Anahtar Kelimeler: Iraklı hastalar, Karaciğer fonksiyonu, Böbrek fonksiyonu, Lösemi

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The reason I am who I am now is because of your support and unwavering caring.

I am grateful to my sisters, brothers, and all of my friends for their support.

Saif Hammood Khudhur ALLAWEE

Çankırı -2021

CONTENTS

LIST OF ABBREVIATIONS

%	Percent
±	Plus Minus
FDA	Food And Drug Administration
6-MP	6-Mercaptopurine
ALL	Acute Lymphoblastic Leukemia
CLL	Chronic Lymphocytic Leukemia
AML	Acute Myelogenous Leukemia
CML	Chronic Myelogenous Leukemia
HTLV	Human T-Lymphotropic Virus
HCL	Hairy Cell Leukemia
T-PLL	T-Cell Prolymphocytic Leukemia
KKLF	Kay Kendall Leukaemia Fund
DS	Down Syndrome
BCP	B-Cell Precursor
ML-DS	Myeloid Leukemia İn Down Disorder
HPA	Hypothalamic-Pituitary-Adrenal
OSHA	Occupational Safety And Health Administration
MDS	Myelodysplastic Syndrome
CBC	Complete Blood Count
BMT	Bone Marrow Transplantation
CNS	Central Nervous System
6-MP	6-Mercaptopurine
SDS	Safety Data Sheet
BCG	Bromocresol Green
DMSO	Dimethyl Sulfoxide
CPC	Cresolphtalein Complexone
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ALP	Alkaline Phosphatase
LDH	Lactate Dehydrogenase
Ca+	Calcium
°C	Degrees Celsius
dk	Minute
g	Gram
kg	Kilogram
m^2	Square meters
mg	Miligram
mL	Mililiter
ng	Nanogram

nm	Nanometer
μg	Microgram
μL	Microliter

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1. INTRODUCTION

Leukemia is a kind of cancer that starts in the tissues responsible for the production of blood cells. Typically, this kind of cancer begins in white blood cells, which are capable of fighting infections and other diseases. In general, these cells grow and divide in response to the body's requirements. However, leukemia causes the body's bone marrow to generate an abnormally high number of white blood cells that are unable to function normally. Leukemia affects individuals of various ages, not just children. There are four distinct kinds of leukemia, as well as a variety of other illnesses, only a subset of which impact children. Leukemia is an uncommon disease, with fewer than ten new instances diagnosed per 100,000 people each year. Nonetheless, the disease has gotten a lot of attention more than some other more prevalent diseases because it is extremely deadly, especially in youngsters, where it usually takes an acute form. Since the introduction of chemotherapy, childhood leukemia survival has improved little, yet it seldom lasts more than a year. The genesis of leukemia is not well understood. According to certain studies, one of the causes of leukemia is exposure to radiation. Some individuals believe that leukemia is brought on by a virus because certain demographic trends of leukemia mimic those of poliomyelitis. Several studies have revealed that leukemia may have a seasonal occurrence (Hayes 1961).

Around 281,500 individuals died of leukemia worldwide in 2010 (Koren and Lishner 2010). Around 256,000 children and adults were diagnosed with leukemia globally in 2000, with 209,000 dying as a consequence. This represents about 3% of the nearly seven million cancer-related fatalities that occur each year, as well as 0.35 percent of all deaths. Leukemia was the 12th most frequent kind of neoplastic illness and the 11th most common cause of cancer-related mortality among the sixteen different locations where the body was compared. Leukemia is more prevalent in richer nations (Dimas *et al.* 1999).

In 1827, surgeon and anatomist Alfred-Armand-Louis-Marie Velpeau published the first description of leukemia. Rudolf Virchow, a pathologist, provided a more comprehensive account in 1845. Ten years after Virchow's findings, pathologist Franz Ernst Christian

Neumann found that the bone marrow of a dead person with leukemia was tinted "dirty green-yellow" rather than the usual red. This discovery led Neumann to the conclusion that abnormal blood in persons with leukemia was caused by a bone marrow issue.

By 1900, leukemia had evolved into a group of diseases rather than a single illness. Based on prior studies, Boston researcher Sidney Farber believed that aminopterin, a folic acid replacement, may potentially treat leukemia in children by 1947.

Although the majority of the children with ALL who were tested showed evidence of improvement in their bone marrow, none of them were cured. However, this prompted more research. Emil J. Freireich, Jr. and Emil Frei III utilized a mix of chemotherapy to try to cure leukemia in 1962. The tests were successful, and some patients lived long after the exams were completed (Patlak 2002).

The leukemias have long served as model diseases for cancer biology and treatment. The ability to repeatedly and safely sample malignant cells in peripheral blood and bone marrow contributed to fortuitous and seminal discoveries such as the 1960 observation of the Philadelphia chromosome in chronic granulocytic (myeloid) leukemia (Nowell and Hungerford 2004). Creation of useful experimental systems such as leukemia cell lines (Drexler and MaCleod 2010), and murine models (Fortier and Graubert 2009) enhanced biologic understanding, and early treatment successes with antifolates (Farber *et al.* 1948) and antimetabolites (Skipper *et al.* 1954).

Leukemias have been at the forefront of most key advances Clinical oncology in the 21st century. By 1964, when the American Society of Clinical Oncology was established, physicians and leukemia patients had access to the most effective therapies available, some of which had previously been authorized by the US Food and Drug Administration (FDA): Methotrexate, a folate inhibitor; synthetic corticosteroids; the antimetabolites 6-mercaptopurine (6-MP) and 6-thioguanine; vincristine, a vinca alkaloid; and a range of DNA alkylating agents (busulfan, cyclophosphamide, and chlorambucil). In 1964, clinical trials for the antimetabolite hydroxyurea (first chemically produced in 1869 but not FDA approved for leukemia therapy until 1967) and the first anthracycline, daunorubicin (originally created as an antibiotic), began (Fishbein *et al.* 1964). Despite the availability of a wide range of interesting and clinically viable new medicines, cures were still uncommon.

In 2017, the number of new instances of leukemia has increased and discovered (about 62,130). Resulting in a considerable number of individuals who needed to be diagnosed. Leukemia is categorized into four basic types based on clinical and pathological characteristics. Acute lymphoblastic leukemia is the most prevalent form of leukemia in young children (ALL). Adults, particularly those 65 years and older, are also impacted. Chemotherapy and radiation are two frequently utilized therapies. Acute biphenotypic leukemia, Burkitt's leukemia, and precursor B acute lymphoblastic leukemia are the three subtypes of acute lymphoblastic leukemia. While children make up the bulk of ALL cases, adults make up 80% of ALL fatalities (Carlson *et al.* 2019).

Adults over the age of 55 are most commonly affected by chronic lymphocytic leukemia (CLL). It affects young adults from time to time, but it practically never affects youngsters. Men account for two-thirds of those affected. The five-year survival rate is estimated to be around 85% (Tiwari 2019). Although it is incurable, there are numerous effective therapies available. B-cell prolymphocytic leukemia is one of the more aggressive subtypes.

Adults are significantly more likely than children to get acute myelogenous leukemia (AML), and men are significantly more likely than women to have the disease. Chemotherapy is used to treat it. The survival rate after five years is 20%. AML has three subtypes: “acute promyelocytic leukemia, acute myeloblastic leukemia, and acute megakaryoblastic leukemia”. Adults are the majority of those affected by chronic myelogenous leukemia (CML), however a small minority of youngsters are also affected. Imatinib (Gleevec in the US, Glivec in Europe) or other medications are used to treat it. Ninety percent of people survive five years. Chronic myelomonocytic leukemia is one of the subtypes.

ALL and AML are known to be the most deadly of them. As a consequence, early diagnosis and treatment of ALL and AML are essential for substantially decreasing malignant cell growth. Cancer Treatment Centers of America, a publication of the American Cancer Society (Tran *et al.* 2018). AML and ALL are both types of acute leukemia. Classification is based on the kind of cell involved and how the cells look under a microscope. Are very vague and varied. Clinical signs of acute leukemia patients, such as Acute Lymphoblastic Leukemia (ALL) and Acute Myeloid Leukemia (AML) (AML), include hyperleukocytosis and cytopenias (Deeg 2001). Splenomegaly and hepatomegaly are common in acute leukemia patients, LnfiltratLon of leukemic cells, which is prevalent in some kinds of leukemia, could be the source of this (Elbossaty 2017). Acute liver failure is the first symptom of acute leukemia, and it is highly unusual. Because of its rapid progression, it is difficult to diagnose. Due to the occurrence of blasts LnfiltratLon in ALL rather than AML, it has been described substantially more commonly in acute lymphoblastic leukemia than in acute myeloid leukemia. Acute renal failure has also been documented as a complicating factor in several leukemia patients (Bakst *et al.* 2011). Due to the proliferation and overgrowth of malignant cells, which increases the rate of nucleic acid turnover, the creation of urate ions, which can be deposited in renal tubules and cause blockage, might cause acute renal failure (Keating *et al.* 1982). Lactate dehydrogenase levels may also be raised as a result of rapid cell turnover. However, patients with leukemia who have infection and LnflammatLon may have an increased risk of erythrocyte sedimentation.

As with other cancers, leukemia is caused by DNA mutations. By activating oncogenes or deactivating tumor suppressor genes, some mutations may result in leukemia by disrupting the control of cell death, differentiation, and proliferation. These mutations may arise spontaneously or as a consequence of exposure to radiation or carcinogenic substances (Radivoyevitch *et al.* 2016).

Viruses have also been connected to leukemia in some cases. Adult T-cell leukemia is caused by the human T-lymphotropic virus (HTLV-1) (Mohapatra *et al.* 2016).

There have been a few instances of transmission between mother and fetus (when a baby gets leukemia because its mother had leukemia during pregnancy). Children whose mothers take reproductive medications to induce ovulation are more than twice as likely to develop leukemia throughout their childhoods as other children (Rudant *et al.* 2013).

2. LITERATURE REVIEW

2.1 History

Leukemia is one of the most prevalent forms of human cancer and one of the most frequent, and some sources say that the first instance of this illness was found in the nineteenth century by a European physician, and this sickness is termed leukemia. It is a composite term composed of two Greek words: leukos, which means white, and haima, which means blood; therefore, the combination of these two words is referred to as leukemia (Verleyen *et al.* 2016).

Initially, leukemia was reported. In 1845, anatomist and surgeon Alfred-Armand-Louis-Marie Velpeau recognized it as a systemic disease for the first time. In 1845, pathologist Rudolf Virchow offered a more comprehensive explanation. Ten years after Virchow's discovery, pathologist Franz Ernst Christian Neumann noticed that the bone marrow of a deceased person with leukemia was tinted "dirty green-yellow" rather than the usual red. Neumann was able to determine that abnormal blood in persons with leukemia was caused by a bone marrow abnormality as a result of this discovery. The origins of leukemia can be traced back 200 years (Kampen 2012). In 1811, Peter Cullen classified a case of splenitis acutus with incomprehensible milky blood as a case of splenitis acutus with unexplained milky blood. Alfred Velpeau identified in 1825 the symptoms of leukemia and discovered pus in the blood vessels. Alfred Donné discovered in 1844 a halt in the maturation of white blood cells. Based on the microscopic buildup of purulent leucocytes, John Bennett called the disease leucocythemia (1845). Rudolf Virchow defined a reversed white and red blood cell equilibrium the same year. In 1847, he coined the term Leukämie to describe the sickness. Henry Fuller in 1846 was the first person to make a microscopic diagnosis of a leukemic patient while still alive. We arrived at our current understanding of this complex disease as a result of this long process.

2.2 Definition

Leukemia is a type of cancer that affects the tumor or abnormal proliferation of white blood cells and bone marrow. Leukemia differs from other types of cancer in that it does not form a mass of abnormal cells but rather increases the production of abnormal blood cells, specifically white blood cells.

Leukemia is a disease that impairs the development of white blood cells, while saline is composed of a different kind of cell (red blood cells, white blood cells and platelets). These cells are mostly produced in the bone marrow, but certain kinds of white blood cells are also produced in the lymph nodes, spleen, and thymus. After white blood cells are manufactured and they reach maturity, they enter the blood circulation to perform their vital functions as an essential part of the immune system, as they fight infection and defend the body from various germs.

Leukemia develops when abnormal white blood cells grow in the bone marrow (which is the fragile part inside the bone). Because these aberrant cells do not develop and mature properly, they lose their capacity to fulfill their main job of combating infection as a consequence of this imbalance. These abnormal cells increase in number and continue to divide until they fill the bone marrow, affecting the bone marrow's ability to manufacture other types of blood components.

Millions of cells are synthesized daily from the bone marrow, but when abnormal white blood cells are present, it will affect the production of red blood cells (anemia) and platelets (lack of platelets), and thus other symptoms appear accompanying the lack of normal white blood cells.

2.3 Types and Classification of Leukemia

Leukemia is split into several main groups based on clinical and pathological characteristics. The first distinction is between acute and chronic types of the disease:

- Acute leukemia is defined by an abnormally fast growth of immature blood cells. As a consequence of the congestion caused by these cells, the bone marrow is unable to generate healthy blood cells, resulting in insufficient hemoglobin and platelets. Acute leukemia requires prompt treatment owing to the fast development and concentration of malignant cells in the circulation, which ultimately spread to other organs of the body. The most prevalent kind of leukemia in children is acute leukemia.

- Chronic leukemia is distinguished by an abnormal accumulation of white blood cells that are somewhat mature but nonetheless aberrant. The cells are created at a far higher rate than usual, leading in many aberrant white blood cells, which might take months or years to advance. Chronic leukemia is occasionally monitored for a length of time before treatment to ensure that the medication is as effective as possible, unlike acute leukemia, which must be treated correctly just once. Chronic leukemia is more common in older persons, but it can strike anyone at any age. In addition, diseases are classified based on the type of blood cell that is affected. This distinguishes between lymphoblastic and lymphocytic leukemias, as well as myeloid and myelogenous leukemias.

The malignant transformation in lymphoblastic or lymphocytic leukemias occurs in a type of marrow cell that typically forms lymphocytes, which are infection-fighting immune system cells. The B cell is a kind of lymphocyte, is involved in the majority of lymphocytic leukemias. The malignant transformation in myeloid or myelogenous leukemias occurs in a type of marrow cell that typically forms red blood cells, some other types of white cells, and platelets. When these two classes are combined, four main groupings result. There are usually multiple subcategories within each of these primary groups. Finally, several rarer species are frequently excluded from this classification system.

Acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia are the four types of leukemia (CML). ALL and AML are the most lethal of them. As a consequence, ALL and AML must be identified and treated early to significantly decrease the rate of malignant cell growth. The American Cancer Society's Cancer Treatment Centers of America asserts that (Tran *et al.* 2018). AML and ALL are two different kinds of acute leukemia. Classification is based on the kind of cell involved and how the cells look under a microscope. The normal white blood cell, shown in purple in Figure 2.1 (a), is comparable in size to the surrounding red blood cells, while the leukemia blood cell, depicted in red in Figure 2.1 (b) and (c), is twofold bigger (c).

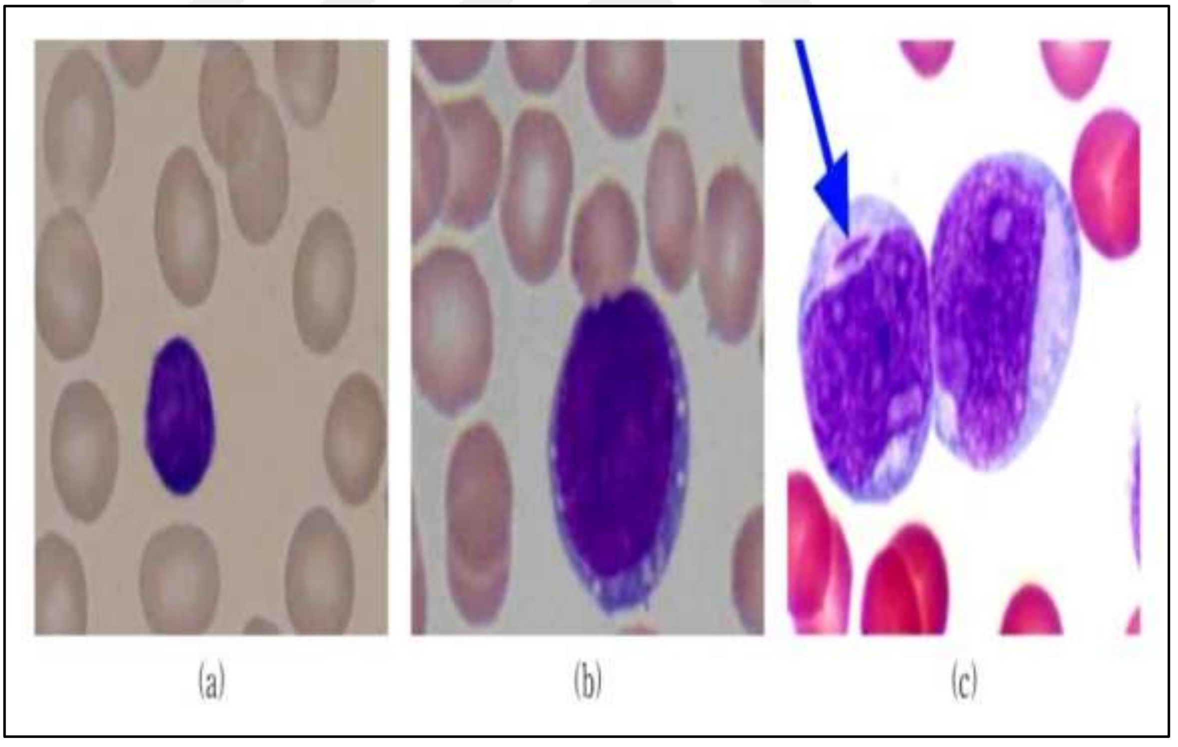

Figure 2.1 (a) Healthy white blood cell non-Leukemia, (b) ALL image, (c) AML image (the blue arrow indicates an Auer rod)

This is a useful feature for telling the difference between normal cell photos and ALL and AML photos. The nucleus of most ALL cells takes up roughly 80-90 percent of the total cell volume, whereas the nucleus of an AML cell takes up roughly 50-60 percent. Furthermore, an ALL cell's surface is smooth, Auer rods are found in the cytoplasm of AML cells, but not in the cytoplasm of normal cells, which are small purple stripes as shown in Figure 2.1 (c) which represented the physical exam, blood testing, and a bone marrow examination are the three basic approaches for diagnosing leukemia. Prior to the onset of symptoms, leukemia can be recognized through standard blood tests. If the patient has signs or symptoms, a physical exam may be undertaken to look for swollen or enlarged lymph nodes in the neck, axillary, or inguinal region. A variety of blood tests can be used to determine the quantity of white blood cells, red blood cells, and platelets in the body. Because leukemia results in a large number of aberrant white blood cells and a low number of red blood cells and platelets, a blood count check can identify these alterations, allowing leukemia to be diagnosed. Bone marrow examination is another method for detecting leukemia. A tissue sample collected from a human hipbone or other big bone is utilized to detect cancer markers and genetic markers using a technique called flow cytometer. These diagnostic approaches must be properly followed by doctors in a laboratory setting using dedicated and specialized equipment. Furthermore, the outcomes of these difficult examinations are heavily reliant on the talents and expertise of professionals.

The majority of leukemia classification research uses the ALL-IDB1 dataset to distinguish between normal cell and ALL images. We present a method for categorizing ALL, AML, and normal cell images using a unique CNN architecture called Leukemia Net in this paper. In comparison to the three rigorous examinations outlined above, this proposed method demonstrates a similarly exact procedure for leukemia diagnosis. Furthermore, this methodology is completely independent of technician expertise, which is one of the major drawbacks of traditional exams. An experiment is carried out to assess the suggested CNN architecture's correctness. The results show that Leukemia Net can classify ALL and AML with a 97.2 percent accuracy. As a result, this research presents a promising early clinical leukemia detection approach for detecting leukemia and categorizing it.

2.3.1 Subtypes of leukemia that are less prevalent than the primary subtypes

- Hairy cell leukemia is a subtype of leukemia that is characterized by hair loss (HCL), although it is often referred to as a subtype of chronic lymphocytic leukemia, it does not fit well into this classification. Adult males make up more than 80% of those afflicted. There have been no reports of incidents involving children. HCL is an incurable yet treatable illness. Survival rates vary from 96 to 100 percent after ten years (Else *et al.* 2005).

- T-cell prolymphocytic leukemia is a type of leukemia that affects T cells (T-PLL). Adults are affected by this exceedingly Leukemia is a rare and aggressive blood cancer that affects somewhat more males than women (Matutes 1998). Despite its rarity, it is the most common kind of adult T cell leukemia. B cells are involved in practically all other leukemias. Treatment is difficult, and patients' median survival times are in months measured.

- Large-scale granular lymphocytic leukemia is a form of granule leukemia. A non-aggressive (indolent), T- and NK-like leukemia which attacks B-cells exclusively is an indolent leukemia (Deeg 2001).

- Human T-lymphotropic virus (HTLV), a virus similar to HIV, causes adult T-cell leukemia. HTLV infects and replicates CD4+ T cells, similar to HIV, but does not destroy them. HTLV on the other hand "immortalizes," enabling it to abnormally multiply, infected T-cells. Human lymphotropic virus (HTLV-I/II) Type I and II are common in certain areas of the globe.

2.4 Causes of Leukemia

There is no single cause for this cancer; nevertheless, there are a few factors that contribute to the development of different varieties of it (Ross *et al.* 2002). The etiology of most cancer kinds is unclear; however, the causes may include ionizing radiation, chemotherapy, and family history of the disease are all factors, and the etiology varies by cancer type. A mutation in the genetically modified material produces leukemia via the activation or interruption of the tumor suppressor genes, cell death disruption, differentiation, or control of division. These processes may take place naturally or via ionizing radiation and/or cancer exposure (No external influence). In adults, natural and artificial ionizing radiation is the most common cause, but viruses such as the human virus that affects the tissue of lymph and chemical substances such as benzene and the treatment of chemical bases may also produce cancer (Radivoyevitch *et al.* 2016, Martinez-Torres *et al.* 2014).

Adults who smoke have a slightly higher risk of getting acute myeloid leukemia. Exposure to various petroleum compounds and hair dyes has been related to leukemia in "various studies, such as the Cohort and Case-Control studies". Although diet has little bearing on the virus, eating veggies may help to protect you. The viruses that have been discovered assigned to this cancer, which includes human cancer T-lymphoid a disease, which T-cell leukemia in adults is caused by (Mohapatra *et al.* 2016).

Family history and Twin research have been revealed that certain people have a genetic factor for leukemia development. Affected individuals share one or more common genes. Individuals in some families develop the same type of leukemia, whereas others have different types of blood cancers. People with chromosomal abnormalities are more likely to acquire this cancer (Ross *et al.* 2002). Individuals with Down syndrome, for example, are predisposed to leukemia (especially acute leukemia). Additionally, pediatric leukemia is associated with a mutation in the spred1 gene (Pasmant *et al.* 2009).

Non-ionizing radiation's potential to induce leukemia has been studied for decades. The World Organization for Cancer Research's working group reviewed all available data on static and low-frequency electromagnetic fields that naturally occur when creating, transmitting, and utilizing electrical energy and concluded that there is scant evidence that large amounts of low-frequency magnetic waves cause cancer. They have been linked to some kinds of leukemia in children, but not to other types of leukemia or neoplasms in adults. On the other hand, exposure to such amounts (If proven as a causative factor) is unusual. According to the World Health Organization, such radiations cause between 100 and 2400 instances of leukemia in children each year, accounting for between 0.2 and 4.9 percent of all leukemia cases in children and between 0.03 and 0.9 percent of all leukemia cases overall.. Cases of leukemia in children as a result of transmission from the mother to the fetus if the mother is diagnosed with leukemia while pregnant. Children born to moms who use fertility medicines to accelerate ovulation had a higher risk of infection, according to a study done by the Center for Research in In France, epidemiology and population health are important. Children with leukemia are twice as likely as other children to get leukemia during their childhood (Rudant *et al.* 2013). There are a number of factors that can make someone more susceptible to leukemia than others, including:

- Exposure to radiation. Whereas, it has been observed that radiologists, including physicians and technicians, and patients treated for inclosing spondylitis using compared to patients who received therapy other than radiotherapy as well as atomic bomb survivors in Hiroshima and Nagasaki in Japan all showed a higher incidence of leukemia.

- Certain chemical chemicals, such as chloramphenicol, benzene, and some pesticides, can cause cancer. Several medications are used to treat cancer, such as phenylalanine, which is used to treat multiple myeloma, as well as some basic compounds that are used to treat Hodgkin's disease and immunosuppressive medications.

- Certain genetic diseases such as Down syndrome and Bloom syndrome.

- Some viruses, such as the Human T-Lymphocyte Virus (HTLV-1) and its two forms, HTLV-1 and HTLV-2, cause cancer in human cells by introducing a gene and tumor (Oncogene) into the cells.

2.5 Basic Signs and Symptoms

In youngsters, the most frequent symptoms are easy bruising, pale skin, fever, and an enlarged spleen or liver (Hostmeyer *et al.* 2019). Damage to the bone marrow results in a deficiency of cells. Blood platelets are required for the coagulation process to occur. By increasing the amount of immature white blood cells and displacing normal bone marrow cells. This implies that those who have leukemia are more prone to bruise quickly, bleed excessively, or have pinprick bleeding (Petechiae) (Jyothi *et al.* 2017).

White blood cells, which aid in the fight against infections, may be suppressed or dysfunctional. This may render the individual's immune system incapable of combating a basic infection, or it may cause the immune system to focus on other bodily cells. Because leukemia impairs the immune system's capacity to function properly, some individuals have infections on a frequent basis. These infections may vary from infected tonsils, mouth sores, or "diarrhea" to potentially fatal pneumonia or opportunistic infections. Finally, anemia is produced by a red blood cell shortage, which may manifest as dyspnea and pallor. Other flu-like symptoms include malaise, fever, chills, night sweats, and exhaustion. Certain individuals experience nausea or a sense of fullness as a result of splenic and liver enlargement, which may result in unintentional weight loss. Affected blasts The disease may cause cells in the liver or lymph nodes to clump together and grow, resulting in discomfort and nausea (Moise 2003).

If leukemic cells reach the central nervous system, neurological symptoms (particularly headaches) may develop. Pressure on the brain stem may result in a variety of odd neurological symptoms, including headaches, seizures, and coma. All of the signs of leukemia are contagious. As a consequence, leukemia is detected via medical testing. The word "leukemia" is derived from the fact that the majority of individuals with leukemia had an increased white blood cell count prior to initiating treatment. When a blood sample is examined under a microscope, a high number of immature or defective white blood cells may be observed. Additionally, an abnormally high number of cells may disrupt the equilibrium of other cells, resulting in a hazardous blood count imbalance.

Certain individuals with leukemia may not have elevated white blood cell counts after routine blood testing. Leukemia is a less frequent kind of cancer. In the bone marrow, cancerous white blood cells persist, interfering with normal blood cell formation. They do not, however, reach the circulation, where they would be detected by a blood test. White blood cell counts in the circulation may be normal or low in individuals with leukemia. A leukemia may occur in any of the four different kinds of leukemia, but hairy cell leukemia is the most common (Runowicz *et al.* 2016).

2.6 Mechanisms

Researchers at the University of Sussex have uncovered a mechanism that drives leukemia cell proliferation, and they believe their discoveries may assist to inspire new cancer treatment tactics. Acute myeloid leukemia (AML) is a deadly blood malignancy that affects roughly 3,000 people in the UK each year. Despite significant improvements in patient survival over the previous 50 years, the prognosis for many subgroups of adults and children with the condition remains poor. Current chemotherapies are extremely toxic, and they frequently fail to cause long-term remissions, necessitating the development of better tolerated, highly targeted medicines that generate long-term remissions. A protein termed -catenin, which can drive cancer formation, is known to be hyperactive in leukemia cells. This protein can help activate genes involved in leukemia development once it enters the nucleus of cells, where DNA is stored. The contacts that -catenin creates with other proteins in the cell are crucial to its functioning. The migration of Catenin's entry into the nucleus of leukemia cells was previously unknown in blood cells. Thanks to funding from the Kay Kendall Leukaemia Fund (KKLF) and Bloodwise, researchers from the University of Sussex, Bristol, and Cardiff have discovered a protein companion accelerates this process and hence supports leukemia cell development. Their findings may lead to the development of new AML treatment techniques. Dr Rhys Morgan, Lecturer in Biomedical Science, in a paper published in the journal Haematologica, researchers showed that the protein LEF-1 can actively modulate the quantity of -catenin in the nucleus of myeloid leukemia cells. This is the first study to show that such a mechanism exists in leukemia cells (See Figure 2.2), as well as the first to identify the contact partners of -catenin in blood cells. While scientists have known for a long time that -catenin plays a role in cancer progression, no drugs directly targeting the protein or its partners have yet to reach the clinic, said Dr. Rhys Morgan of the University of Sussex. Based on our findings, we believe that preventing -catenin's translocation into the nucleus via a partner like LEF-1 by pharmaceutical means could be a potential leukemia treatment option. He went on to say: This research is still in its early stages, and inhibiting -catenin activity will not be a cure for all leukemia cases and subtypes, However, research indicate that high levels of this molecule are present in 20-80% of AML cases, justifying further exploration in this situation. Dr. Morgan and his team are now seeking to learn more about the biological importance of many of the new interacting proteins revealed in the study, in the hopes of finding more that could be used to block -catenin levels and activity in leukemia. This essay was reposted with permission from the University of Sussex (Morgan *et al.* 2019).

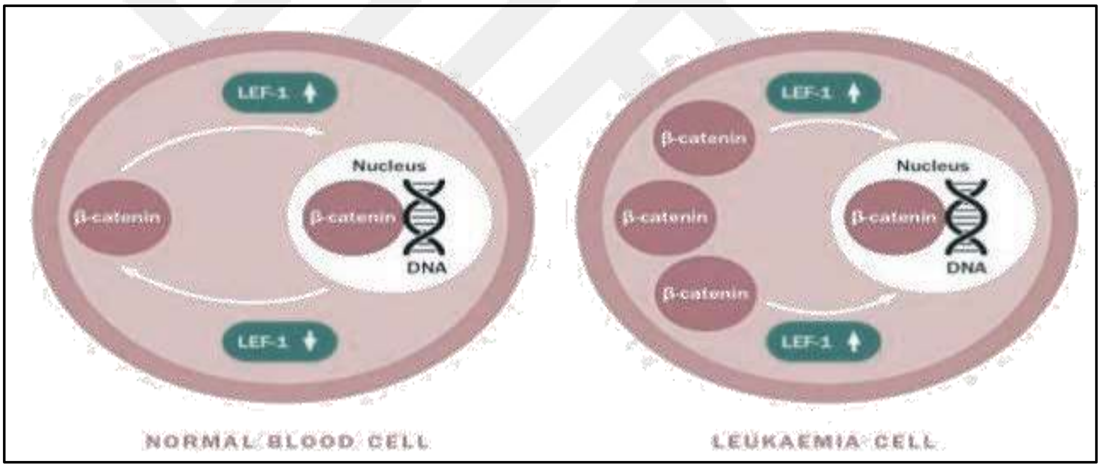

Figure 2.2 Mechanism for Leukemia Cell Growth

2.7 Epidemiology

Leukemia claimed the lives of around 281,500 persons worldwide in 2010 (Lozano *et al.* 2012). In 2000, 256,000 children and adults worldwide were impacted. 209,000 people were diagnosed with leukemia and died as a consequence. This was the reason why the illness was responsible for about 3% of the approximately seven million cancer-related fatalities that year, and 0.35 percent of all deaths. Leukemia was the 12th most frequent kind of neoplastic illness and the 11th most common cause of cancer-related mortality among the sixteen different locations where the body was compared. Leukemia is more prevalent in richer nations (Siraj 2012).

2.8 Etiology

The investigators cited several types of causes on this cancer. Although, dramatic biologic advances have expanded understanding of leukemogenesis. There is still a great uncertainty on the causes that develop leukemia. In most patients, leukemia develops because of accidental errors during the blood cells formation. There are multiple hypotheses of the reason behind leukemia. No single acknowledged cause for various leukemias exists. Debatable hypotheses was planned to suggest the role of physical factors (i.e., high dose ionizing radiation, electromagnetic fields), and chemical factors (i.e. benzene, formaldehyde), genetical (endogenous) factors (i.e., Down's syndrome, mutations in bone marrow), familial (hereditary) factors (i.e., Fanconi anemia), lifestyle factors (i.e. smoking, obesity, dietary intake), biological factors (i.e., adrenal hormones, animal sources), autoimmune disorders'factors (i.e., rheumatoid arthritis, autoimmune haemolytic anemia, ulcerative colitis), chemotherapeutics factors, (i.e., Chlorambucil, Melphalan, Cyclophosphamide), blood disorders' factors (i.e., Myelodysplastic syndrome and Myeloproliferative disorders) and even infectious factors (i.e., viruses) as being answerable for leukemia incidents. The real cause of leukemia is continues to be underneath scrutiny has been found that the risk of developing this cancer is increased when malignant diseases have occurred often in the family. This indicates that a genetic predisposition may play a role in leukemia development. Certain genetic abnormalities may raise the chance of developing leukemia. A subset of this is what is known as Down syndrome, which is caused by an inherent genetic mutation.

Down's syndrome: For most leukemic sufferers, there's no familial defect of the genetic material. "Children with Down syndrome disorder" (DS) have an increased risk of promoting acute lymphoblastic leukemia (ALL) characterized by an additional heterogeneous pattern of hereditary findings. These highlights feature the role of Down syndrome in leukemogenesis (Rai *et al.* 2014).

They have an expanded risk of B-cell precursor (BCP) acute lymphoblastic leukemia (ALL) (Bruwier and Chantrain 2012). Myeloid leukemia in down disorder (ML-DS) is observed as retrogradation with distinct clinical and organic features. There are few studies focusing on the clonal cytogenetic differences amongst the progress of ML-DS. “The molecular cytogenetic” examinations performed, permitted the description of novel chromosomal irregularities in ML-DS and potential candidate genes concerned within the leukemogenic process (Buitenkamp *et al.* 2014).

On the opposite hand, Amorim and his team have conducted a study to find out whether “677C-->T” and/or “1298A-->C” polymorphisms of MTHFR gene would play an extra role within the status of acute myelocytic leukemia (AML) in DS youngsters. The study revealed none association between these polymorphisms and so the risk of AML in DS youngsters. The data likewise prove that it does not relate MTHFR polymorphisms to the chance of being a DS child (De Souza *et al.* 2017).

Familial (hereditary) factors: Leukemia has been found to occur more often in particular families than in the general population over a lengthy period of time. The first evidence for genetic mechanisms governing familial leukemia was discovered in 1990, when Li-Fraumeni syndrome was linked to TP53 mutations. Since this finding, scientists have identified many genes associated with a genetic proclivity for leukemia (Porter *et al.* 2017). An investigator compared the demographics of households with a single case of pediatric cancer versus those with numerous instances. The large percentage of children diagnosed with leukemia who had a childhood relative with the same illness indicates a genetic component. Tawana and his team described a novel RUNX1 family in three sisters who were diagnosed with acute myelomonocytic leukemia (AML) at the age of five due to a germline nonsense RUNX1 variation. Exome sequencing of tumor tissues showed that the three siblings had myeloproliferative neoplasms separately (Tawana *et al.* 2017). The clinical and molecular homogeneity over these three young siblings provides the principal prominent example of convergent AML evolution in a RUNX1 pedigree giving rise to high-risk AML. Archer and his team have conducted an exome-wide association study of childhood (ALL) among Hispanics to affirm and recognize novel variants associated with disease risk in this ethnic group. A case-parent trio study design was used to avoid issues with population stratification bias among this at-risk ethnic group. The assessment uncovered none potent novel hereditary genetic risks of (ALL) among this ethnic group.

Obesity: Obesity is related to an increased incidence of the many cancers, as well as leukemia, though it's unknown whether malignant neoplastic diseases incidence is augmented directly by fatness (Yun *et al.* 2010). Animal models were developed to test whether obesity is correlated with acute lymphoblastic leukemia (ALL). Thus, the determined associations between fatness and leukemia incidence are possible to be directly associated with biological effects of obesity. Other research works offer many evidences that the association with obesity is a risk issue for hematologic malignancy (Lichtman 2010).

Smoking: The results of earlier researches on the "influence of smoking on the risk of leukemia" are not evident. However, "evidence that smoking increases the risk of developing acute myeloid leukemia". Several studies have been directed in leukemic smoker's subjects to identify the association of smoking with leukemia. The scientists look at the chance that smoking cigarettes can increase the risk of developing acute myeloid leukemia. Since cigarette smoke (tobacco) has benzene and radioactive matter that may induce leukemia (Bonaventure *et al.* 2012). It is known cigarette smoking induces leukocytosis and enhanced genetic instability in normal healthy individuals. Many epidemiological studies have conducted in smokers patients provides no proof that smoking bears any major relationship to the incidence of leukemia (Adami *et al.* 1998). Other studies showed it was potential that fag smoke might act as a promoter or co-carcinogen within the transformation of chronic myelogenous leukemia. There are many studies that explored interactions between antepartum exposure to maternal smoking and polymorphisms in metabolic genes within the risk of childhood cancer of the blood (ALL). Assuming, smoke smoking habits are the activating agent of antepartum malignant neoplastic diseases. The studies did not prove the interaction between

CYP1A1*2A/2B and maternal smoking. The association with NAT2*5 and so the gene-gene interactions ought to be duplicated (Brondum *et al.* 1999).

Adrenal hormones: The corticosteroid has a unique role in the fetus in inducing a wide range of enzymes before birth on which survival after birth is dependent. Viral infections increase corticosteroid levels through activation of the hypothalamic-pituitary-adrenal (HPA) axis by cytokines (Silverman *et al.* 2005). Interpretation of the adrenal hypothesis proposes that the chance of childhood ALL is reduced once infancy infections induce qualitative and quantitative changes within the hypothalamuspituitary-adrenal axis that increases plasma corticoid levels.

Benzene: Benzene was employed as a solvent, and these chemicals were considered unsafe. Leukemia induced by the proven professional handling of benzene as an occupational disease. Benzene is a leukemogenic, and thus the Occupational Safety and Health Administration (OSHA) is trying to limit exposure to it. There's still no agreement of the role benzene in chronic varieties of cancer of the blood. Benzene elevated risks of chronic lymphatic leukemia even though with wide confidence intervals (Costantini *et al.* 2008).

Radioactive rays and X-rays: radiologists who were exposed to high doses of radiation for a prolonged period became much more likely to develop leukemia than would be expected from the normal chance risk. The higher the radiation dose exposure to the person, meaning the higher the disease risk (Calvente *et al.* 2010).

Viruses: Three theories exist about the infectious processes underlying the genesis of juvenile leukemia:

1. Exposure to the uterus or around the time of birth.
2. Delayed exposure to frequent infections beyond the early year of life.
3. Population mingling in an unusual way.

No specific virus has been identified with childhood leukemia and no evidence up to now of viral genomic inclusions within leukemic cells (See Figure 2.3). There is unsatisfied evidence from studies on early childhood infectious exposures, vaccination, and social mixing (McNally and Eden 2004).

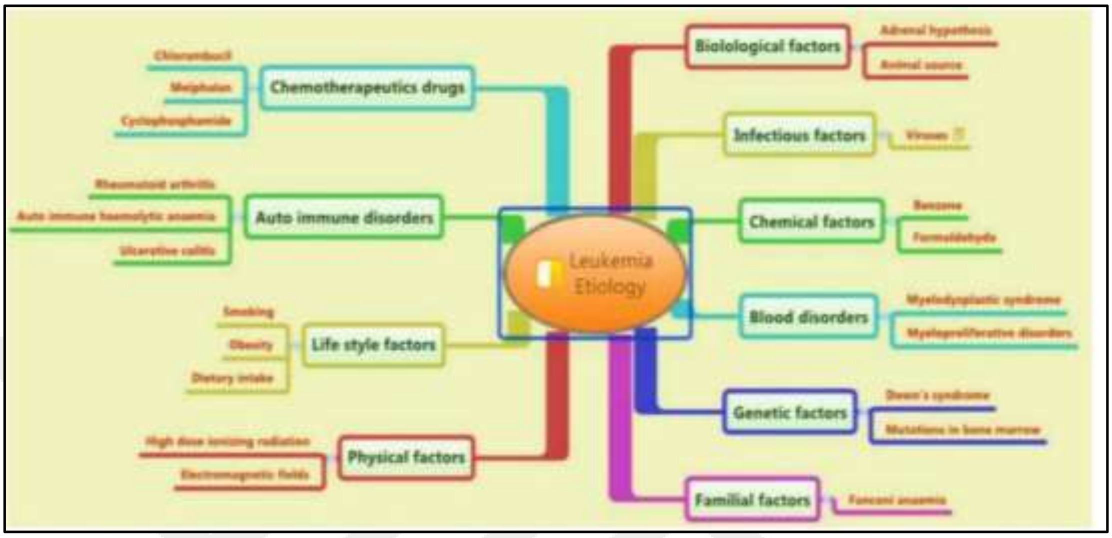

Figure 2.3 Several varied factors are potential to cause Leukemia (Elawad *et al.* 2019)

Human T-lymphotropic (HTLV) viruses cause a rare T cell leukemia: Human T-lymphotropic virus (HTLV), found mainly in Japan, the Caribbean, and certain parts of Africa and South America, affects human T cells and, in rare cases, can cause a particular form of T cell leukemia. The risk of suffering from HTLV in this particular leukemia is 1-2%. For other human leukemias, still insufficient evidence that viruses or other pathogens are involved in the disease. These leukemias are considered non-contagious or transferable (Tezuka *et al.* 2018).

2.9 Morphology

The next significant development in 1869, both blood and bone marrow were inspected under a microscope, which led to the discovery of leukaemia morphology. Franz Ernst C. Neumann (1834-1918), a German pathologist born in Königsberg and a student of Hermann Ludwig F. von Helmholtz (1821-1894) and Virchow, was a student of Hermann Ludwig F. von Helmholtz (1821-1894) and Virchow, By analyzing bone fragments, he was the first to show that haematopoiesis occurs in the bone marrow. He claimed that blood is made up of a common precursor called a stem cell (German: Stammzelle). Neumann claimed that, in addition to the lymphatic and splenic leukemias described by Virchow, there was another type of leukemia that originated in the bone marrow. He coined the term "myeloid leukaemia" and Bizzozero later confirmed his notion. Paul Ehrlich was responsible for the most recent discovery in this brief history of leukaemia morphology (1854-1915). While still a medical student, Ehrlich invented cell staining and discovered for the first time the cytoplasmic components and distinct types of nuclei in blood cells, giving rise to the terms acidophils and basophils (See Figure 2.4).

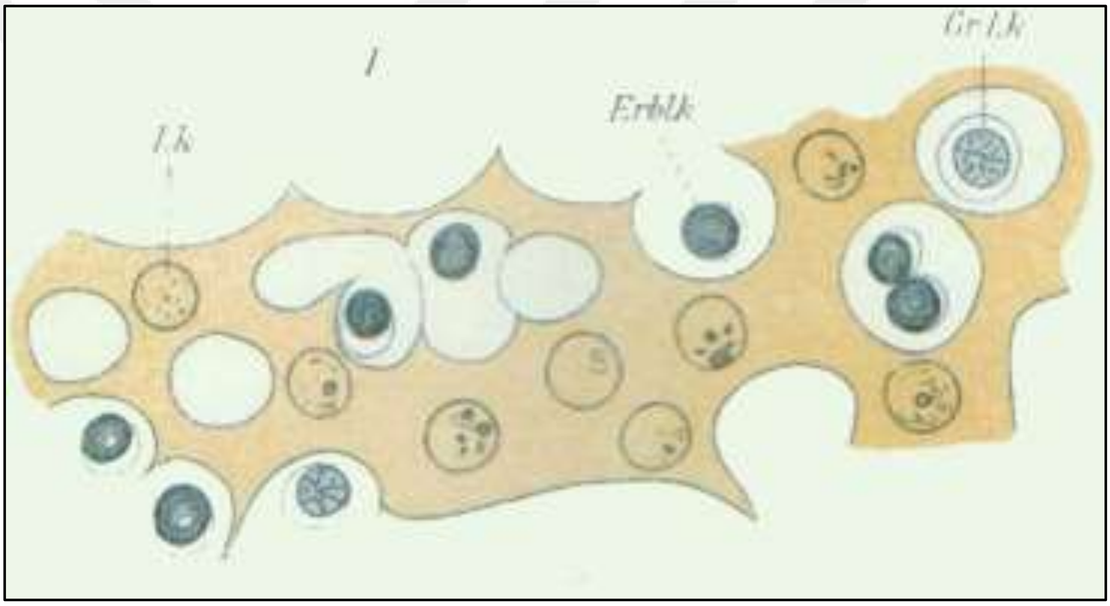

Figure 2.4 Sketch of the origin of leukaemic cells (Qiu 2010)

2.10 Clinical Presentation

Acute Lymphoblastic Leukemia: Acute lymphoblastic leukemia (ALL) patients have signs and symptoms related to leukemic cells directly infiltrating the marrow or other organs, or “signs and symptoms related to decreased production of normal marrow elements”. Temperature is one of the most prevalent symptoms of ALL, and people with ALL frequently have a fever while having no other indicators of infection. However, until shown otherwise, all fevers in these patients must be assumed to be caused by infections, because failing to treat infections promptly and aggressively can be fatal. Infections are still the leading cause of death in individuals receiving ALL therapy.

CLL (Chronic Lymphocytic Leukemia) is a type of leukemia that affects: Patients with chronic lymphocytic leukemia (CLL) experience a wide range of symptoms and signs. CLL develops slowly, and it's not unusual for it to be identified by accident after a blood cell count is performed for another reason, 25 - 50 percent of patients will be asymptomatic when they first appear. The most common presenting symptom is enlarging lymph nodes, which are seen in 87 percent of patients who are symptomatic at the time of diagnosis. It's possible to notice a proclivity for infections including pneumonia, herpes simplex labialis, and herpes zoster. An enlarged spleen might cause early satiety and/or abdominal discomfort. Thrombocytopenia can cause mucocutaneous hemorrhage and/or petechiae. Tiredness and weariness may be present as a result of anemia; 10% of CLL patients will I'm suffering with autoimmune hemolytic anemia. In around 3 - 10% of instances, Richter syndrome, also known as Richter transformation, occurs when CLL evolves into an aggressive large B-cell lymphoma. Symptoms include weight loss, fevers, night sweats, muscle atrophy (i.e. B symptoms), and developing hepatosplenomegaly and lymphadenopathy.

Acute Myeloid Leukemia: The signs and symptoms of acute myeloid leukemia (AML) are caused by bone marrow loss, organ invasion with leukemic cells, or both. The duration of the event is vary. Some individuals, particularly those who are younger, have acute symptoms that last for a few days to a week. Others have a longer time to recover, with fatigue or other symptoms lasting weeks or months. A preceding hematologic condition, such as myelodysplastic syndrome, may be indicated by a lengthier course (MDS).

Chronic Myelogenous Leukemia: Chronic myelogenous leukemia (CML) has subtle clinical symptoms. During the chronic phase, the disease is frequently identified by chance when a routine blood check reveals an elevated white blood cell (WBC) count or when a general physical examination reveals an enlarged spleen. Long after the commencement of the disease, nonspecific symptoms such as weariness and weight loss may appear. After a few months in the chronic phase, you may notice a loss of energy and a reduction in your exercise tolerance. Patients frequently experience symptoms due to spleen, liver, or both enlargements. The big spleen may press against the stomach, resulting in early satiety and reduced food intake. Spleen infarction can cause "gripping" stomach pain in the left upper quadrant. A hypermetabolic condition, fever, weight loss, and persistent weariness may also be linked to an enlarged spleen. The patient's weight loss could be due to an enlarged liver. Hypermetabolism causes low-grade fever and profuse perspiration in some CML patients. Bleeding, petechiae, and ecchymoses may be important symptoms in some patients who come in the accelerated, or acute, phase of the disease (skipping the chronic phase). Fever is generally connected with infections in these cases. The blast phase is marked by bone pain and fever, as well as a surge in bone marrow fibrosis.

2.11 Diagnostic Criteria

The disease is diagnosed laboratory by performing a series of tests, the most essential of which is which is:-

1- A complete blood count (CBC). As a result of this investigation, preliminary indications can be mentioned as a possibility developing leukemia is a type of cancer.

2- An enlarged liver, spleen, or lymph nodes are detected during a clinical examination.

3- A bone marrow biopsy is a procedure that involves taking a sample of the patient's by examining that after staining it with special chemicals that indicate the presence of leukemia, the biopsy was examined under a microscope.

In some cases, blood tests do not reveal that the patient has leukemia, particularly during the development or latency of the disease, i.e. when there are no symptoms. In some types of cancer, a lymph node biopsy may be used (See Figure 2.5). After diagnosis, blood chemistry tests can be performed to determine the kidney and liver damage and the effect of chemotherapy on the patient. It is possible to use x-ray, which is an x-ray image, ultrasound, or an MRI. These tests are used to diagnose damage to the bones (X-ray), brain (MRI), kidneys, spleen, and liver (liver biopsy) (ultrasound). The lymph nodes in the chest can be examined using computerized tomography (LCT), however this technology is rarely employed. Although these methods are used to diagnose the patient if he is injured or healthy, some people have not been diagnosed, and the reason for this is the wrong diagnosis of the similarity of symptoms with other diseases. It is for this reason that the American Cancer Society estimates that at least five of people with leukemia have not been diagnosed with the disease (Smith *et al.* 2010).

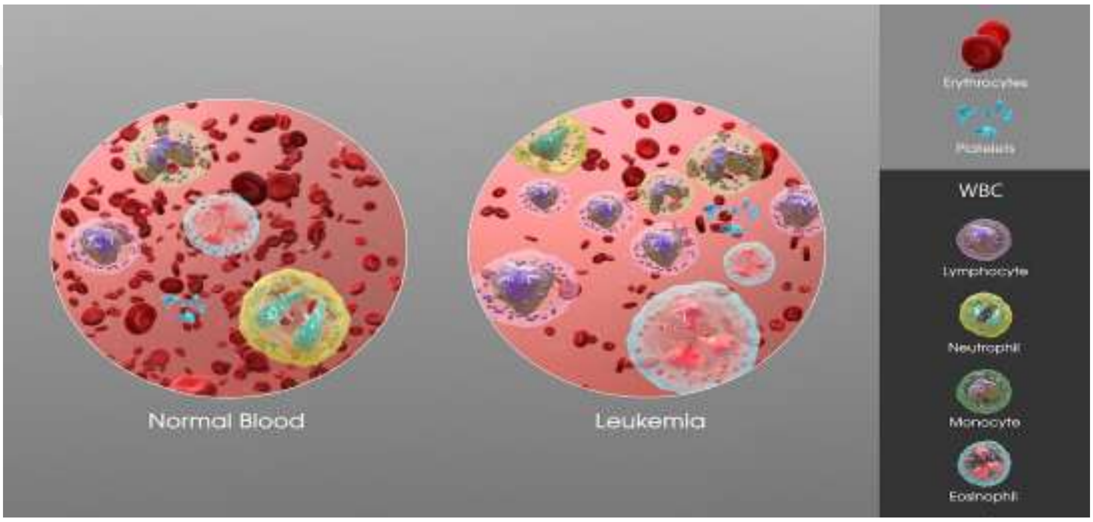

Figure 2.5 The increase in white blood cells in leukemia

2.12 Recent Advances

Although the outlook for children with leukemia has improved significantly, these advancements are only available to a small percentage of the world's youngsters. In traditional chemotherapy, there is still opportunity for advancements, which must be tested in randomized trials. As chemotherapy becomes more successful, the function of bone marrow transplants in initial remission changes. New drugs are being developed. Patients who have relapsed require new therapy. Although molecular diagnosis has improved prognosis, the added value provided by measuring minimal residual disease is unclear. Treatment for uncommon subtypes of leukemia will require international collaboration. Lessons learnt about the biology of leukemia have begun to have an impact on patient management in the recent decade. The prognosis for children with leukemia has progressively improved, with at least 60 – 70% of youngsters now achieving long-term survival and cure (Chessells 2000). Recent advancements in the treatment of uncommon leukemias have increased survival rates to around 50%. Although high-dose therapy and bone marrow transplantation (BMT) have grown safer and more widely available, treatment for relapsed youngsters remains inadequate.

2.13 Treatments

Pharmaceutical medications are used to treat most types of leukemia, which are usually integrated into a multi-drug chemotherapy treatment. Radiation therapy is also used in some cases. A bone marrow transplant can help in some circumstances.

Acute lymphoblastic: The goal of ALL treatment is to keep the Controlling bone marrow and systemic (whole-body) sickness Monthly lumbar punctures show that treatment is keeping leukemic cells from migrating to other parts of the body, particularly the central nervous system (CNS). In general, ALL treatments are divided into several steps:

- Bone marrow remission is achieved with induction chemotherapy. Prednisone, vincristine, and an anthracycline medication are common induction programs for adults; additional medication programs may include L-asparaginase or cyclophosphamide. For the first month of treatment, typical therapy for children who are at low risk ALL is usually made up of three medications (prednisone, L-asparaginase, and vincristine).

- To remove any remaining leukemia cells, consolidative or intensification therapy is used. Consolidation can take a variety of forms, but it usually involves a high-dose, multi-drug treatment that lasts a few months. Antimetabolite medicines such as methotrexate and 6-mercaptopurine are used to treat people with low- to moderate-risk

ALL (6-MP). High-risk people are given greater doses of these treatments, as well as extra medications.

- In high-risk persons, CNS prophylaxis (preventive therapy) is used to prevent cancer from spreading to the brain and nervous system. Prophylaxis can include head radiation and/or medications injected directly into the spine.

- Maintenance therapy using chemotherapeutic drugs are used to prevent illness recurrence once remission has been achieved. Maintenance therapy usually consists of decreasing medication dosage and can last up to three years.

- Transplantation of allogeneic bone marrow, on the other hand, may be appropriate for high-risk or relapsed patients (Manisha 2012).

Chronic lymphocytic: Because with current treatments, the majority of CLL patients are incurable; treatment focuses on keeping the disease from progressing for a long time rather than treating it. Chemotherapy with chlorambucil or cyclophosphamide, as well as a corticosteroid like prednisone or prednisolone is the preferred chemotherapeutic strategy. Corticosteroids also have the added benefit of reducing several autoimmune disorders, such as immunohemolytic anemia and immune-mediated thrombocytopenia. In resistant cases, single-agent therapy based on nucleoside medications such as fludarabine are employed (Eichhorst *et al.* 2006). It's possible that cladribine or pentostatin will help. Younger and healthier people may choose allogeneic or autologous bone marrow transplantation in the hopes of a permanent cure (Gribben 2009).

Acute myelogenous: Treatments differ slightly depending on the patient's age and the individual AML has a subtype. The general strategy is to treat bone marrow and systemic (whole-body) illness, as well as “the central nervous system (CNS)” if it is involved. In the early stages of chemotherapy, called induction, most physicians rely on medication combinations. Early remission and a lesser chance of disease resistance are usually two advantages of this type of combination chemotherapy. The goal of consolidation and maintenance therapy is to keep the disease from recurring. In many cases, consolidation treatment entails repeating or strengthening induction chemotherapy with additional drugs. Maintenance treatment, on the other hand, involves a lower pharmaceutical dosage than induction treatment (Sung *et al.* 2009).

Chronic myelogenous: CML can be treated in a variety of ways, although imatinib (Gleevec) therapy is the gold standard for newly diagnosed patients. It has low negative effects compared to most anti-cancer medications It's easy to take and can be done at home. Using this therapy, more than 90% of people will be able to keep their disease under control for at least five years (Fausel 2007). CML will become a chronic, manageable disease. When a person cannot tolerate imatinib or wants to attempt for a lasting cure, an allogeneic bone marrow transplantation can be done at a more advanced, uncontrolled state. Following the infusion of bone marrow from a suitable donor, high-dose chemotherapy and radiation are employed. Approximately 30% of people die as a result of this treatment.

Hairy cell: People who need therapy are usually given one week of cladribine, which is given daily via intravenous infusion or a simple injection underneath the skin, or six months of pentostatin, which is given every four weeks via intravenous infusion. The majority of patients will experience a long-term remission after just one session of treatment. Self-injection with Interferon-alpha or Rituximab infusion are two alternative alternatives. In certain cases, a splenectomy may be beneficial (removal of the spleen). These drugs are rarely utilized as first-line treatments since their success rates are lower than cladribine or pentostatin (Saven *et al.* 1999).

T-cell prolymphocytic: The majority of individuals with T-cell prolymphocytic leukemia, a rare and aggressive leukemia with a median survival of less than one year, require immediate treatment. Treatment for T-cell prolymphocytic leukemia is complicated, and most chemotherapy drugs are ineffective. Many various treatments have been tried, with varying degrees of purine analogues (pentostatin, fludarabine, cladribine), chlorambucil, and a variety of chemotherapeutic combinations have had effectiveness in some persons (cyclophosphamide, doxorubicin, vincristine, prednisone CHOP, cyclophosphamide, vincristine, prednisone [COP], vincristine, doxorubicin, prednisone, etoposide, cyclophosphamide, bleomycin VAPEC-B).has proven to be more effective than earlier treatments (Dearden *et al*. 2001). Some persons who respond well to treatment have their response reinforced with stem cell transplantation.

2.14 Risk Factors

More than 60,000 people are diagnosed with leukemia each year. Leukemia is more likely to develop as people get older, although it can also strike persons under the age of 20. While the specific etiology of leukemia is unknown, certain risk factors have been linked to the disease, including radiation exposure. Leukemia has a number of known risk factors (Schwartz and Woloshin 2016):

- Gender: Leukemia is more common in men than in women.

- Age: The risk of most leukemias increases as people get older. The typical age of a patient with acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), or chronic myeloid leukemia (CML) is 65 years or older. People under the age of 20 are more likely to develop acute lymphocytic leukemia (ALL). The median age of an ALL patient at the time of diagnosis is 15.

- Blood disorders: People with persistent myeloproliferative diseases including polycythemia vera, idiopathic myelofibrosis, or essential thrombocytopenia are more prone to acquire AML.
- History of the family: The majority of the two types of leukemia are unrelated. If you are a first-degree cousin of a CLL patient or have an identical twin who has or has had AML or ALL, you may be at a higher risk of developing CLL.
- Syndromes that are present during birth: Down syndrome, Fanconi anemia, Bloom Congenital disorders such as syndrome, ataxia-telangiectasia, and Blackfan-Diamond syndrome all appear to raise the risk of AML.

- Exposition to specific substances Specific substances have been related to certain kinds of leukemia. For instance, benzene exposure is a risk factor for AML. Additionally, it may be associated with an increased risk of acute lymphocytic leukemia (ALL). Agent Orange exposure, a pesticide used during the Vietnam War, has been associated with an increased risk of developing chronic lymphocytic leukemia (CLL).

3. MATERIALS AND METHODS

3.1 Materials

3.1.1 Chemicals

The real photos of chemical laboratory material that used in the present study are illustrated in the Appendices.

3.1.2 Instrumentals

The real photos of medical laboratory instruments that used in the present study are illustrated in the Appendices.

3.2 Methods

3.2.1 Design of study

1- 120 cases were taken in Ibn Al-Atheer Teaching Hospital, Mosul / Iraq. These cases are divided into two parts.
   A- We take 80 cases of infected patients (the disease).
   B- Take 40 healthy controls.
2- Sterilizing hands and wiping the patient's hand with sterilization and a cotton ball to take a blood sample.
3- We take 5mm of blood from patients and leave 20 minutes inside the gel tube until it clots.
4- We take an autobahn and put it in the center fug at a temperature of 4000 for 10-15 minutes.

5- Take the serum blood serum after leaving the Center Fusion and put it in a tube with an airtight cover, then put it in the refrigerator for 20 minutes In this way, samples are collected from patients and healthy people.

3.2.2 Sample collection

Five milliliters of venous blood were collected into gel tubes from each men under study after the sterilization procedure (See Figure 3.1). The blood samples were allowed for 10 minutes on the rack to clots, then “centrifuged at 4000 rpm” for 10 minutes. Then serum was separated from the other cells by using micro pipet, and divided into 4 eppendorf, then frozen at -20 ºC until the use for assay.

Figure 3.1 Venous blood were collected into gel tubes after the sterilization procedure

3.2.3 Biochemical parameters

3.2.3.1 AST got

Principle

Karmen and Al devised the method, which Henry and others refined (accordance to IFCC recommendations that have been changed).
The following is the reaction scheme:-

$$\text{L-Aspartate} + \text{2-Oxoglutarate} \overset{\text{AST}}{\Longleftrightarrow} \text{Oxaloacetate} + \text{L-Glutamate} \qquad (3.1)$$

$$\text{Oxaloacetate} + \text{NADH} + H^{+} \overset{\text{MDH}}{\Longleftrightarrow} \text{L-Malate} + \text{NAD}^{+} \qquad (3.2)$$

The quantity of AST activity in the samples is evaluated by measuring the drop in absorbance at 340nm. Because P5P isn't present, the working reagent is more stable.

Reagents Composition

The reagents that used in the present study and its composition are illustrated in Table 3.1.

Table 3.1 The reagents composition that used in the present study

R1 AST (GOT) IFCC	**Danger**
EDTA	5 mmol/L
2-Oxoglutarate	12 mmol/L
L-Aspartate	200 mmol/L
MDH	495 Ul/L
LDH	820 Ul/L
NADH	≤ 0.18 mmol/L
Tris Buffer	80 mmol/L
pH at 30°C	7.80 +0.1

Preservative

Toxic before reassembling: H300 is lethal if eaten. H412 (Aquatic Chronic 3) is toxic to aquatic life and has long-term effects. P264: Wash your hands thoroughly after handling. P270: While using this product, do not eat, drink, or smoke. If swallowed, immediately contact a poison center or a doctor/physician. P501: Rinse your mouth, P330: Rinse your mouth Dispose of the contents/container in line with the rules for the disposal of hazardous waste. Classification according to Sodium aside concentrations of less than 1%. Refer to the Safety Data Sheet for additional information (SDS)

Procedure

On request, a detailed Kenza 240TX process is available. 340 nm is the wavelength. The temperature is 37 degrees Celsius (See Table 3.2).

Table 3.2 Allow reagents and material to stand at room temperature

	Automated analyzer	Manual procedure
Reagent	200 µL	1000 µL
Standard / Control or Specimen	20 µL	100 µL
Mix. Record initial absorbance after 1 minute at 340 nm. Record the absorbance again every minute during 3 minutes.		
Calculate absorbance change per minute (ΔAbs/min).		

Calculation

Calculate the result as follows:

With serum multi calibrator:

$$\text{AST Activity} = \frac{(\Delta Abs/min)\ Assay}{(\Delta Abs/min)\ Calibrator} \times \text{Calibrator Concentration} \quad (3.3)$$

With theoretical factor:

Activity (IU/L) = ΔAbs/min x Factor (3.4)

$$\text{Factor} = \frac{VR \times 1000}{6.3 \times VE \times P} \quad (3.5)$$

With:

VR = Total reactional volume (mL)

VE = Specimen volume (mL)

6.3= Molar extinction coefficient for NADH at 340 nm

P = Pathlength (cm).

$$\frac{\text{Example,with manual Procedure.}}{\text{(Path length 1 cm,37°C,340 nm):}} \quad (3.6)$$

IU/L = (DAbs/min) x 1746 (3.7)

$$\mu\text{Kat/L} = \frac{IU/L}{60} \quad (3.8)$$

3.2.3.2 Alkaline phosphatase

Principle

Colorimetric measurement of ALP activity using the following reaction scheme:-

$$\text{Phenylphosphate} \xrightarrow{\text{Alkaline phosphatase}} \text{Phenol} + \text{Phosphate} \quad (3.9)$$

In the presence of alkaline potassium ferricyanide, free phenol liberated from the substrate interacts with 4-amino-antipyrine to form a red-colored complex with an absorbance at 510 nm that is proportional to the ALP activity in the specimen. By adding sodium arsenate to the reagent, further enzyme activity is eliminated and the color is not diluted as in prior methods.

Reagents

Vial. R1 : Substrate-Buffer

Disodium Phenylphosphate : 5 mmol/L

Carbonate-bicarbonate buffer pH 10 : 50 mmol/L Stabilizer

Vial. R2 Standard

Phenol corresponding to 20 U King and Kind, Vial. R3 and its blocking reagent are illustrated in Table 3.3.

Table 3.3 Vial. R3 and its blocking reagent

Vial. R3	Blocking Reagent
4-Amino-antipyrine	60 mmol/L
Sodium arsenate	240 mmol/L
R45 :	Could result in cancer
R23/25 :	Toxic when inhaled or consumed
S28 : With plenty of water	In the event of contact with the skin, thoroughly rinse
S45 :	Consult a physician if you are feeling ill (eventually, show him the label)

Vial. R4 **:** Dye Reagent

Potassium ferricyanide **:** 150 mmol/L

Manual Procedure

Table 3.4 illusrated the reagents and material that used in the present study.

Table 3.4 Allow reagents and material to stand at room temperature

Prepare tubes as follows :	Reagent blank	Specimen blank	Standard	Assay
Reagent R1	2 mL	2 mL	2 mL	2 mL
Incubate 5 minutes at 37°C.				
Specimen				50 µL
Reagent R2 (Standard)			50 µL	
Let stand **exactly 15 minutes at 37°C.**				
Reagent R3	0,5 mL	0,5 mL	0,5 mL	0,5 mL
Mix well.				
Reagent R4	0,5 mL	0,5 mL	0,5 mL	0,5 mL
Specimen		50 µL		
Demineralised water	50 µL			
Mix. Incubate 10 minutes at room temperature and away from light. Read absorbances of the blank specimen, standard and assay at 510 nm against reagent blank. Coloration is stable for 45 minutes away from light.				

Calculation

$$\text{ALP activity (Kind and King units/ 100mL)} = \frac{Abs\ Assay - Abs\ Specimen\ blank}{Abs\ Standard} \times 20 \quad (3.10)$$

Notes:

One Kind and King Unit is the amount of enzyme that liberates 1mg of phenol in 15 minutes at 37°C under reaction conditions.

Result (IU/L) = 7.09 x Result (Kind and King Unit/100 mL) (3.11)

3.2.3.3 Albumin

Principle

Albumin in a buffered solution at pH 4.2 is bound by the dye bromocresol green, producing in a colored compound with an absorbance of 630 nm (620-640) that is proportional to the quantity of albumin in the test solution. Table 3.5 illustrated the reagent and its composition.

Table 3.5 Reagent composition

R1 Albumin	**Reagent**
Succinic acid	83 mmol/L
Bromocresol green (BCG)	167 µmol/L
Sodium hydroxide	50 mmol/L
Polyoxyethylene monolauryl ether	1.00 g/L

Preservative

Attention, Met. Corr.1: H290 – Metals may be corroded. P234: Only keep in original container; P390: Absorb spills to avoid material damage. The following factors contributed to the classification: 1 percent sodium hydroxide Refer to the Safety Data Sheet for more information (SDS). Table 3.6 illustrated the Albumin and the standard concentration that used in the present study.

Table 3.6 Albumin and the standard concentration

R2 Albumin	**Standard**
Bovine albumin	5.0 g/dL (725 µmol/L)

According to 1272/2008 regulation, this reagent is not classified as dangerous.

Manual Procedure

Table 3.7 illustrated the let stand reagents and specimens at room temperature that used in the present study.

Table 3.7 Let stand reagents and specimens at room temperature

Reagent R1	1000 µL
Blank, Standard, Control or Specimen	5 µL
Mix well. Read absorbance at 630 nm (620-640), against reagent blank after exactly 1 minute or within 3 minutes (7)	

1. Performances with manual procedure should be validated by user.
2. Kenza applications and other applications proposal are available on request.

Calculation of Serum and plasma

$$\text{Result} = \frac{Abs\ (Assay)}{Abs\ (Standard)} \times \text{Standard concentration} \qquad (3.11)$$

3.2.3.4 Total and direct bilirubin

Principle

The interaction between bilirubin and diazotised sulfanilic acid results in the formation of azobilirubin, which may be colored in either acidic or basic conditions. According to the Malloy-Evelyn principle, as modified by Walters and colleagues, only DB interacts with other molecules in an aqueous solution. It is necessary to break the connection between unconjugated bilirubin and albumin in order to conduct a tuberculosis test. DMSO (Dimethyl sulfoxide) is the solvent of choice at this stage. The Using this method, the absorbance of azobilirubin, which is proportional to the bilirubin concentration, is measured at the wavelength of 550nm (530-580). Table 3.8 illustrated the reagents composition of the total bilirubin that used in the present study.

Table 3.8 Reagents composition of the total bilirubin

R1	**Total Bilirubin**
Sulfanilic acid	30 mmol/L
DMSO	7 mol/ L
Hydrochloric acid	130 mmol/L

EUH210: Safety Data Sheet available on request.

EUH208: Contains sulfanilic acid. May produce an allergic reaction.

Table 3.9 illustrated the reagents composition of the direct bilirubin that used in the present study.

Table 3.9 Reagents composition of the direct bilirubin

R2	**Direct Bilirubin**
Sulfanilic acid	30 mmol/L
Hydrochloric acid	130 mmol/L

EUH210: Safety Data Sheet available on request.

EUH208: Contains sulfanilic acid. May produce an allergic reaction.

Table 3.10 illustrated the reagents composition of the total and direct bilirubin that used in the present study.

Table 3.10 Reagents composition of the total and direct bilirubin

R3	Total and direct bilirubin
Sodium Nitrite	0.74 mmol/L

According to 1272/2008 regulation, this reagent is not classified as dangerous.

Table 3.11 illustrated the Let stand reagents and specimen at room temperature that used in the present study.

Manual procedure

Table 3.11 Let stand reagents and specimen at room temperature

	Assay	Blank
Reagent R1 (TB) or R2 (DB)	1000 µL	1000 µL
Distilled water		50 µL
Reagent R3	50 µL	
Mix and add		
Specimen, calibrator or control	100 µL	100 µL
Zero on distilled water and drain well the cuvette. Read first all blanks of one run then all the assays, well-draining cuvette between each tube. But DO NOT RINSE WITH WATER as it could produce streaks on the cuvette. Mix well and start a timer when adding specimen. Read absorbance at 550 nm (530-580) against blanks TB: reading after > 3 minutes at 37°C or > 5 minutes at room temperature DB: reading at exactly 3 minutes at 37°C or 5 minutes at room temperature		

1- Manual procedure performances should be verified by the user.
2- On request, Kenza applications and other application proposals are available.
3- Paediatric Specimen: divide sample volume by 5.

Calculation

With Seric Muticalibrator

$$\text{Result} = \frac{Abs\ (Assay - Blank)\ Specimen}{Abs\ (Assay - Blank)\ Calibrator} \times \text{x calibrator concentration} \quad (3.12)$$

With Factor (Path length 1 cm, 37°C, 550 nm)

mg/dL = Abs. assay – Abs. Blank x 11.4 (3.13)

$\mu mol/L$ = Abs. assay – Abs. Blank x 195 (3.14)

With Paediatric method: multiply the factor by 5 (sample volume). This factors should be used as a guide only

3.2.3.5 Uric acid

Principle

Uricase produces allantoin, carbon dioxide, and hydrogen peroxide when it reacts with uric acid. In the presence of peroxidase, hydrogen peroxide combines with a chromogen (amino-antipyrine and dichlorohydroxybenzene sulfonate) to produce quinoneimine, a red complex. The amount of uric acid in the material is proportional to the absorbance recorded at 505nm.
Table 3.12 illustrated the Reagents of Uricase produces allantoin that used in the present study.

Table 3.12 Reagents of Uricase produces allantoin

R1	**UA2 Buffer**
Tris pH 8.0 at 25°C	50 mmol/L
Dichloro-hydroxybenzene sulfonate	3 mmol/L
Potassium hexacyanoferrate (II)	53 µmol/ L
3-DDAPS	0.7 mmol/L
EDTA	2 mmol/L

Preservative

Table 3.13 illustrated the preservative of uricase produces allantoin that used in the present study.

Table 3.13 Preservative of uricase produces allantoin

R2	**UA2 Enzymes**
Peroxidase	≥ 2000 U/ L
Amino-antipyrine	750 µmol/ L
Uricase	≥ 500 U/ L

Preservative

According to 1272/2008/EC Regulation, these reagents are not classified as dangerous.

Procedure

Refer to validated application of the Kenza Analyzer used.

Calculation

The analyzer provides directly final result. Refer to the instruction of use of Kenza analyzer.

3.2.3.6 Calcium

Principle

The CPC (O-Cresol Phtalein Complexone) method developed by Moorehead and Briggs can be used to determine total Calcium concentration in serum, plasma, or urine. CPC interacts with calcium in alkaline solution to generate a dark-red colored complex whose absorbance at 570 nm is proportional to the amount of calcium in the material.

Reagents

EUH210: Material safety data sheet available on request.
P302+352: IF ON SKIN: Wash with soap and water.
P305+351+338: IF IN EYES: Rinse continuously with water for several minutes. Remove contact lenses if present and easy to do –continue rinsing.
Table 3.14 illustrated the reagents of Calcium that used in the present study.

Table 3.14 Reagents of Calcium

R2	**Calcium Dye**
0-Cresolphtalein complexone (CPC)	78 µmol/L
Hydroxy-8-Quinoline	3.36 mmol/L
Hydrochloric acid	25 mmol/L
R3	Calcium Standard
Calcium	10 mgram/dL (2.5 mmol/L)

According to 1272/2008 regulation, these reagents are not classified as dangerous

Procedure

Detailed Kenza 240TX procedure is available on request
Wavelength: 570 nm, Temperature: 37°C
Temperature should be held constant as the absorbance of the dye is temperature sensitive.

Calculation

Calculate the result as follows:

Serum or plasma:

$$\text{Result} = \frac{Abs(Assay)}{Abs(Standard)} \times \text{Standard concentration} \tag{3.15}$$

Urines:

Multiply the above result by dilution factor 3

3.2.3.7 Urea UV

Principle

Enzymatic approach based on the Talke and Schubert reaction, simplified by Tiffany and colleagues, who showed that urea concentration is proportional to the change in absorbance at 340 nm over a defined time interval. The following is the reaction scheme:

$$\text{Urea} + H_2O \xrightarrow{Urease} 2NH_3 + CO_2 \tag{3.16}$$

$$NH_3 + \text{Oxoglutarate} + \text{NADH} + H^+ \xrightarrow{GLDH} \text{Glutamate} + \text{NAD}^+ + H_2O \tag{3.17}$$

Table 3.15 shows Reagents composition of urea.

Table 3.15 Reagents composition of urea

R1	**Buffer enzyme and buf enz urea**
Tris pH 7.9 + 0.1 at 30°C	100 mmol/L
Urease	≥ 17000 IU/L
GLDH	≥ 700 IU/L
Oxoglutarate	6.5 mmol/L

Table 3.16 shows the preservative of urea.

Table 3.16 Preservative of urea

R2	**Coenzyme and coenz urea**
NADH	≥ 1.5 mmol/L

Table 3.17 shows the preservative of standard urea.

Table 3.17 Preservative of standard urea

R3	**Standard**
Urea	40 mg/dL

According to 1272/2008 regulation, these reagents are not classified as dangerous.

Procedure

A detailed method for the Kenza 240TX is provided upon request.

Wave length: 340 nanometer

"Temperature: 37°C "

Table 3.18 shows the allow reagents and specimens to stand at room temperature with more details that used in present study.

Table 3.18 Allow reagents and specimens to stand at room temperature

	Automated analyzer	Manual procedure
Working Reagent	300 µL	1000 µL
Specimen (1) or Standard/Controls	3 µL	100 µL
Mix. After 30 seconds, record initial absorbance A1 at 340 nm against distilled water. Record the absorbance A2 after 90 seconds.		

Calculation

Calculate the result as follows:

Serum and plasma:

$$\text{Result} = \frac{Abs\ (A1 - A2)\ Assay}{Abs\ (A1 - A2) Standard} \times \text{Standard concentration} \tag{3.18}$$

Urines

Multiply the result by dilution factor 20.

3.2.3.8 Creatinine

Principl*e*

The kinetics of the creatinine colorimetric reaction (Jaffe reaction) with alkaline picrate were measured without pretreatment at 490 nm (490-510). The development of an initial-rate method increased the reaction's specificity, speed, and flexibility.

3.2.3.9 L.D.H. (LDH-P)

Principle

UV Kinetic Method (DGKC)

$$\text{Pyruvate} + \text{NADH}^{+} + \text{H}^{+} \xrightarrow{LDH} \text{L - Lactate} + \text{NAD}^{+} \tag{3.19}$$

The decrease in absorbance due to the conversion of NADH to NAD^{+} , directly proportional to LDH activity in the specimen, is measured at 340nm.

Procedure

Refer to the application of the Kenza Analyzer that has been verified.

Calculation

The analyzer immediately displays the final value in IU/L. Refer to the Kenza analyzer's user manual.

3.2.3.10 Bilirubin

Principle

Bilirubin reacts with diazotised sulfanilic acid to form azobilirubin, which is colored in a strongly acidic or basic media. Only DB interacts in an aqueous solution, according to the Malloy-Evelyn principle as amended by Walters and colleagues. To perform a TB test, the link between unconjugated bilirubin and albumin must be broken. In this step, dimethylsulfoxide is utilized (DMSO). At 550nm, the absorbance of azobilirubin created this method is proportional to the bilirubin concentration (530.0 – 580.0).

Manual Procedure

Let stand reagents and specimens at room temperature.

Table 3.19 shows the procedure number 1 for total and direct bilirubin with some more details that used in the present study.

Table 3.19 Procedure number 1 for total and direct bilirubin

Pipette into well identified test tubes:	**Total Bilirubin**		**Direct Bilirubin**	
	Blank	**Assay**	**Blank**	**Assay**
Reagent R1	1mL	1mL		
Reagent R2			1mL	1mL
Distilled water	50µL		50µL	
Reagent R_3 (Nitrite)		50µL		50µL
Mix				
Specimen	100 µL	100 µL	100 µL	100 µL
When adding specimen, thoroughly mix and set a timer. Absorbance at 550 nm (530 - 580) should be compared to blanks. TB: after more than three minutes at 37°C or more than five minutes at room temperature. DB: take a reading after precisely three minutes at 37°C or five minutes at room temperature.				

Table 3.20 shows the procedure number 2 (Icteric or Pediatric Specimens) with some more details that used in the present study.

Table 3.20 Procedure number 2 (Icteric or Pediatric Specimens)

Pipette into well identified test tubes:	**TOTAL BILIRUBIN**		**DIRECT BILIRUBIN**	
	Blank	**Assay**	**Blank**	**Assay**
Reagent R1	1mL	1mL		
Reagent R2			1mL	1mL
Distilled water	50µL		50µL	
Reagent R3 (Nitrite)		50µL		50µL
Mix				
Specimen	20µL	20µL	20µL	20µL
When adding specimens, thoroughly mix and set a timer. Analyze absorbance at 550nm (530-580) in comparison to blanks. TB: after more than three minutes at 37°C or more than five minutes at room temperature. DB: take a reading after precisely three minutes at 37°C or five minutes at room temperature.				

Calculation

As follows, compute the outcome:

With calibrator (Procedure number 1 only):

$$\text{Result} = \frac{Abs\ (Assay - Blank) Specimen}{Abs\ (Assay - Blank)\ Calibrator} \times \text{calibrator concentration} \qquad (3.20)$$

With factor

Procedure number 1: mg/dL = [Abs. assay – Abs. Blank] x 11.4

$\mu mol/L = [Abs.\ assay – Abs.\ Blank] \times 195$

Procedure number 2: $mg/dL = [Abs.\ assay – Abs.\ Blank] \times 53.0$

$\mu mol/L = [Abs.\ assay – Abs.\ Blank] \times 906$

This factors should be used as a guide only and may vary with instrument and the batch of reagent used. It is recommended to verify with elevated control serum.

Procedure number 1: Use Biolabo Exatrol-P, Procedure number 2: Use Biolabo Paediatric Control.

3.3 Statistics Analysis

The unpaired t test was used to determine statistical differences between groups. The Pearson correlation test was used to evaluate the correlation research. P value of 0.05 was used to determine significance. The mean and standard error of the mean are used to represent all findings (SEM). GraphPad Prism 6 was used to conduct the statistical analysis and create the figures.

4. RESULTS AND DISCUSSION

4.1 Characteristics of the Studied Parameters

It was found after investigating the number of patients with leukemia and after collecting (120) blood samples from the patients included in the study, and laboratory tests were performed on them after the process of dividing the samples into age groups starting from 8 years to 75 years and in light of the tests and information taken in each sample, it was noticed that the age group (31- 40) years is the most vulnerable, as the highest rate of infection was recorded at 34.26% of the total number of injured, while the lowest rate of patients was 0.106 for the age group (1 - 15) years. Where the average age of the victim and the standard error in this study was 37.62 ± 1.27, and the average value was (34) years. And we noticed through this study that the infection rate increases with age, as the highest incidence rate was in the age groups after twenty years. It was found that the number of people with leukemia after fifty years of their age began to decrease due to death. As for most of the patients, and after performing a chi-square examination in order to find out whether the disease is related to the age of the patient, significant increases and statistical indications were found among the age groups (21 - 30), (31 - 40), (41 - 50).

4.2 Biochemical Parameters

4.2.1 ALT (alanine aminotransferase)

Table 4.1 and Figure 4.1 show a decrease in the significant difference between leukemia patients compared to control of ALT concentrations ($P \leq 0.05$).

4.2.2 AST (aspartate aminotransferase)

Table 4.1 and Figure 4.2 show that there is no significant difference between leukemia patients compared to control of AST concentrations ($P \geq 0.05$).

4.2.3 ALP (alkaline phosphatase)

Table 4.1 and Figure 4.2 show that there is no significant difference between leukemia patients compared to control of ALP concentrations ($P \geq 0.05$).

4.2.4 BR (bilirubin)

Table 4.1 and Figure 4.3 show that there is no significant difference between leukemia patients compared to control of bilirubin concentrations ($P \geq 0.05$).

4.2.5 Albumin

Table 4.1 and Figure 4.4 show that there is no significant difference between leukemia patients compared to control of albumin concentrations ($P \geq 0.05$).

Table 4.1 The results of biochemical parameters

Parameters	**Mean ± SD**		**t-test**
	Patient	**Control**	
ALT (U/L)	15.73 ± 7.75	26.38 ± 17.08	3.36
AST (U/L)	22.68 ± 9.05	25.43 ± 9.11	1.13NS
ALP (U/L)	250.73 ± 100.1	291.48 ± 170.4	1.17NS
Bilirubin (mg/dL)	0.55 ± 0.37	0.58 ± 0.31	0.26NS
Albumin (mg/dL)	36.64 ± 9.19	34.36 ± 5.73	1.03NS

*Significant at $P \leq 0.05$, Non-significant at $P \leq 0.05$

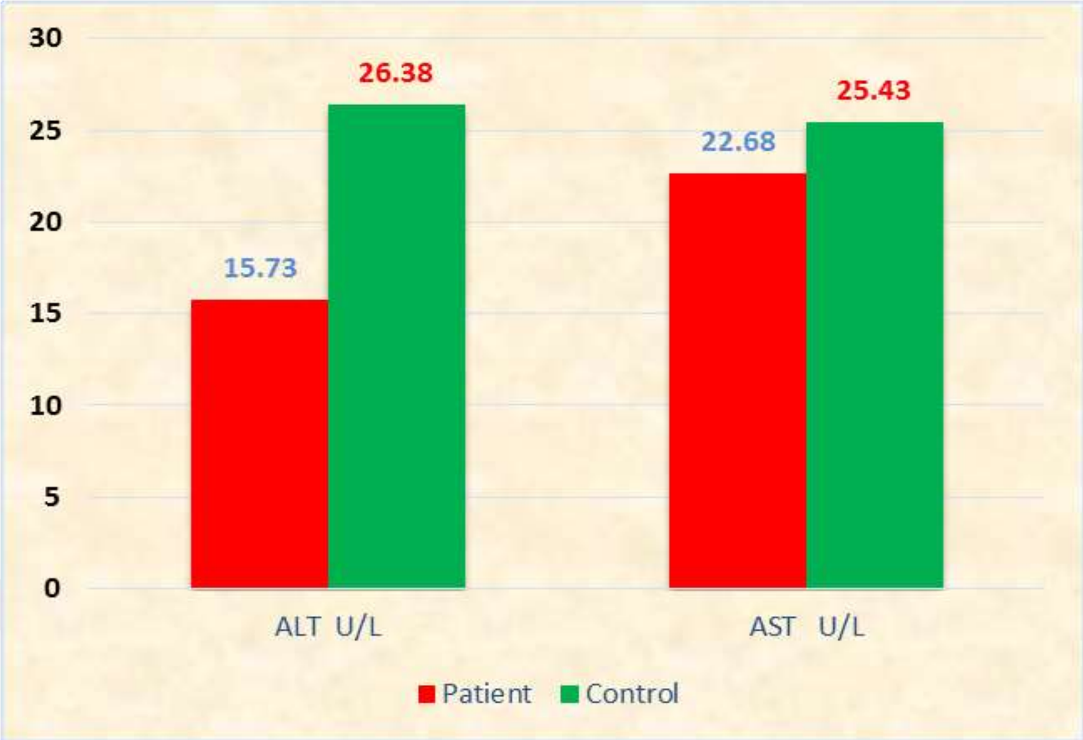

Figure 4.1 Comparison of ALT, AST in patients and control groups

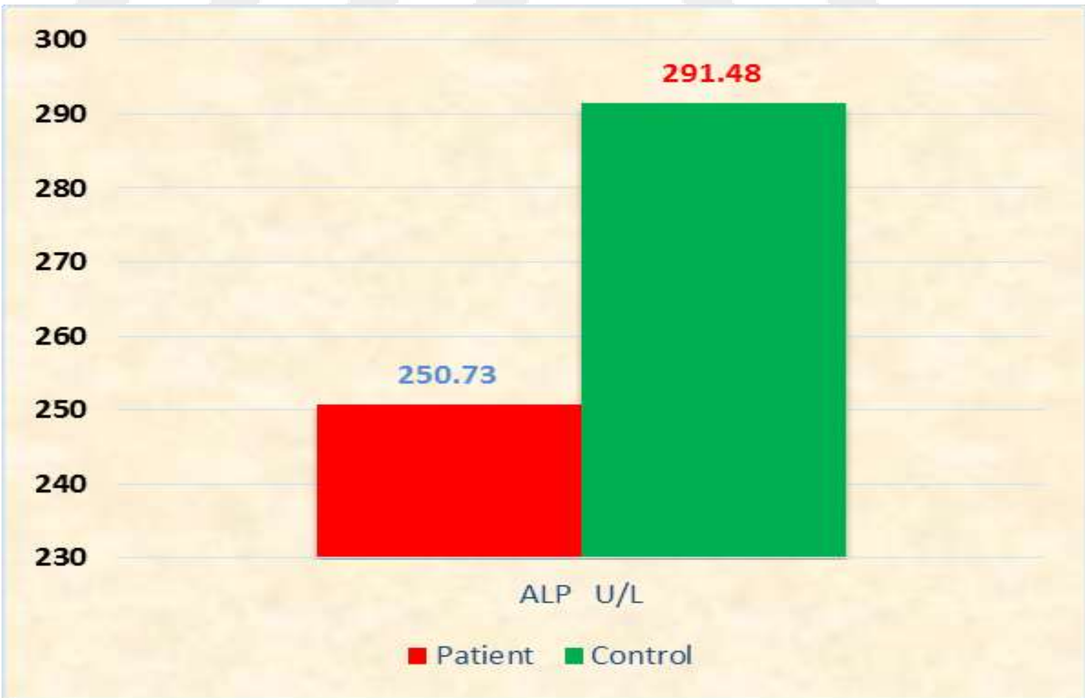

Figure 4.2 Comparison of ALP in patients and control groups

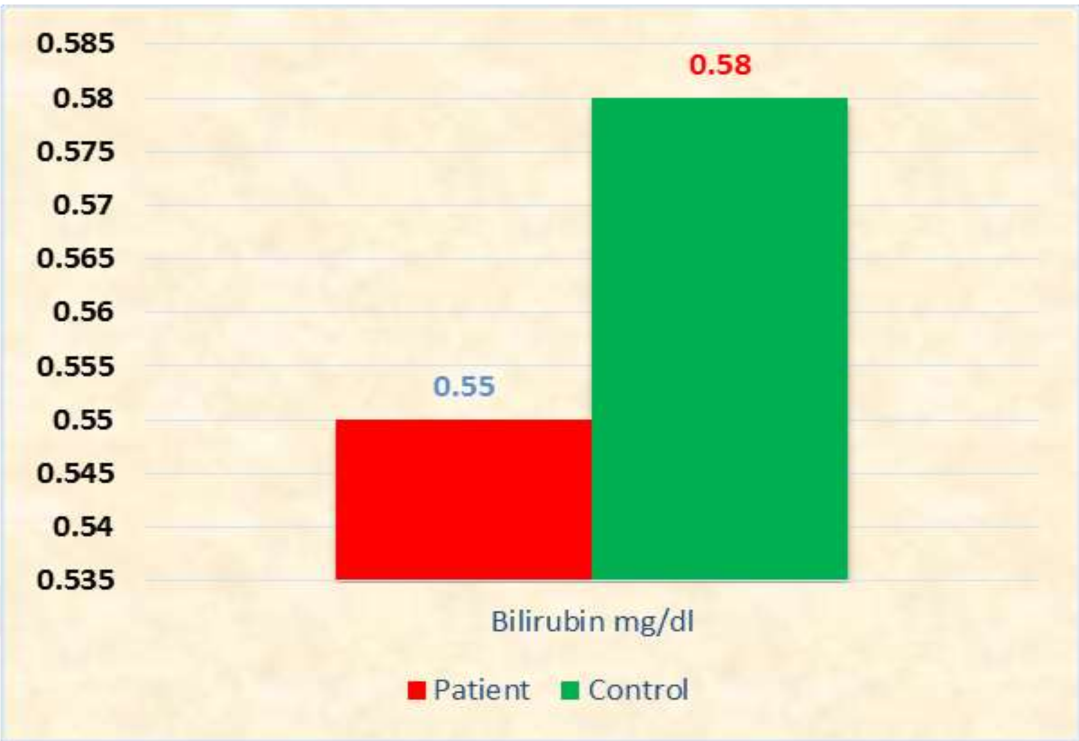

Figure 4.3 Comparison of bilirubin in patients and control groups

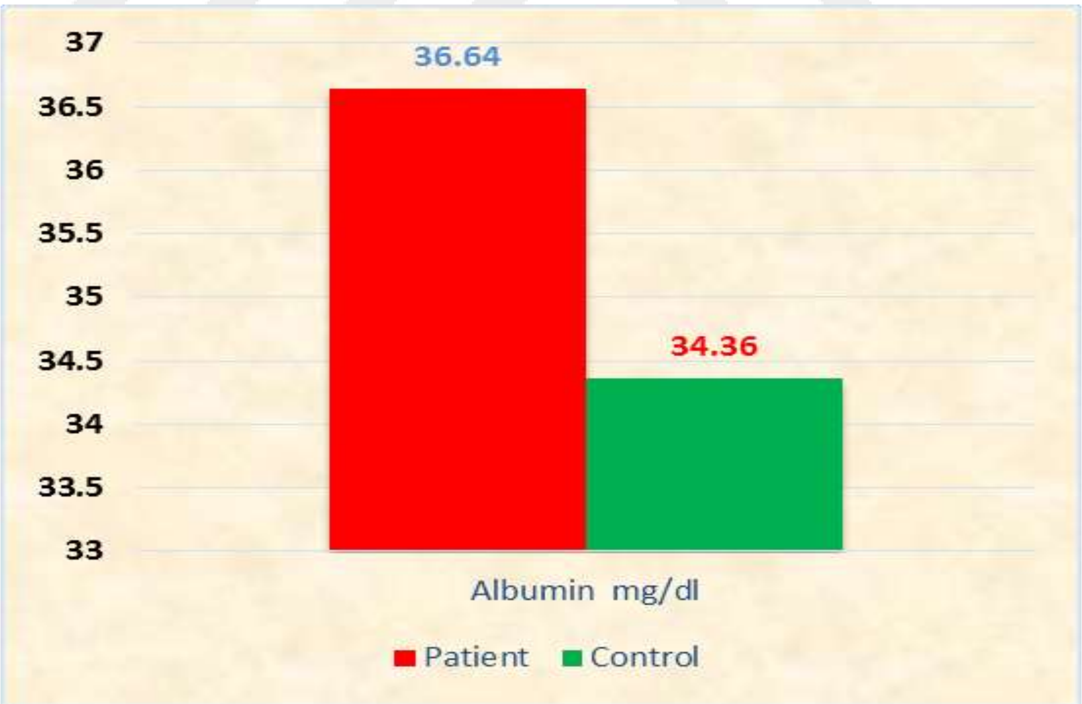

Figure 4.4 Comparison of albumin in patients and control groups

4.2.6 LDH (lactate dehydrogenase)

Table 4.2 and Figure 4.5 show a decrease in the significant difference between leukemia patients compared to control of LDH concentrations ($P \leq 0.05$).

Table 4.2 The values of LDH (lactate dehydrogenase)

Parameters	Mean ± SD		t-test
	Patient	Control	
LDH (U/L)	425.83 ± 99.38	333.33 ± 197.4	2.44

*Significant at P≤0.05

Figure 4.5 Comparison of LDH in patients and control

4.2.7 Blood urea

Table 4.3 and Figure 4.6 show a decrease in the significant difference between leukemia patients compared to control of blood urea concentrations ($P \leq 0.05$).

4.2.8 Creatinine

Table 4.3 and Figure 4.7 show a decrease in the significant difference between leukemia patients compared to control of creatinine concentrations ($P \leq 0.05$).

4.2.9 Uric acid

Table 4.3 and Figure 4.8 show a decrease in the significant difference between leukemia patients compared to control of uric acid concentrations ($P \leq 0.05$).

4.2.10 Serum calcium

Table 4.3 and Figure 4.9 show that there is no significant difference between leukemia patients compared to control of calcium concentrations ($P \geq 0.05$).

Table 4.3 The results of calcium concentrations

Parameters	Mean ± SD		t-test
	Patient	Control	
B. Urea (mg/dL)	19.12 ± 8.50	28.58 ± 7.30	4.33
S. Creatinine (mg/dL)	0.67 ± 0.29	0.89 ± 0.37	2.53
Uric acid (mg/dL)	3.73 ± 1.73	5.49 ± 1.69	3.81
Calcium (mg/dL)	9.97 ± 2.31	9.07 ± 0.80	1.73

Figure 4.6 Comparison of blood urea in patients and control groups

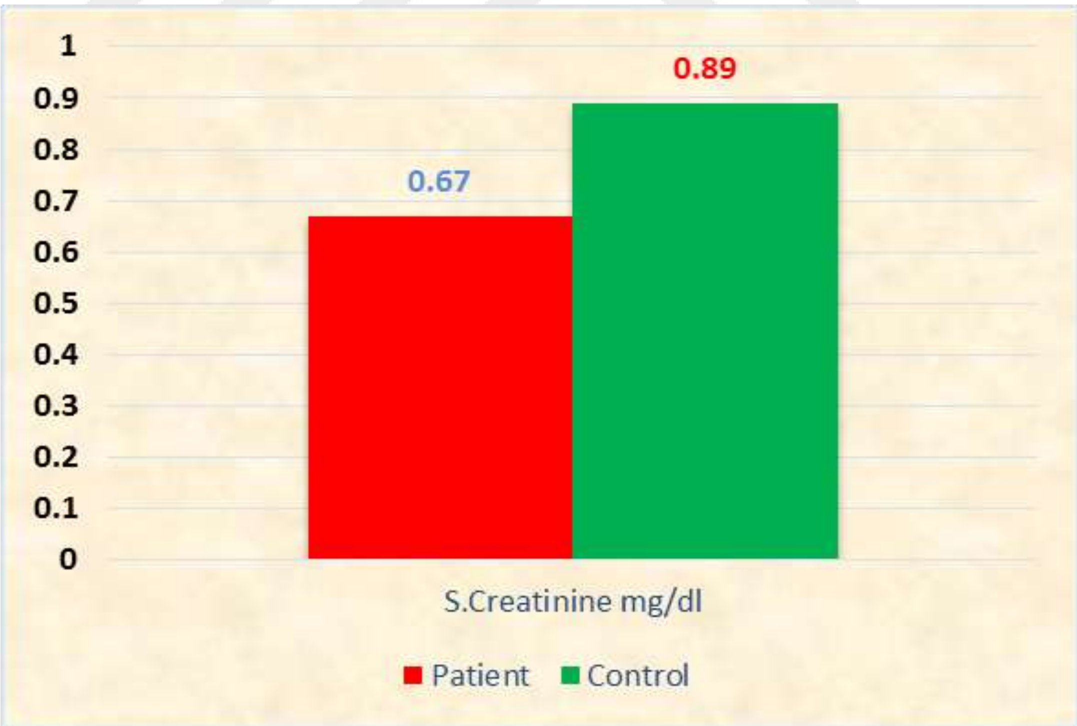

Figure 4.7 Comparison of S. creatinine in patients and control groups

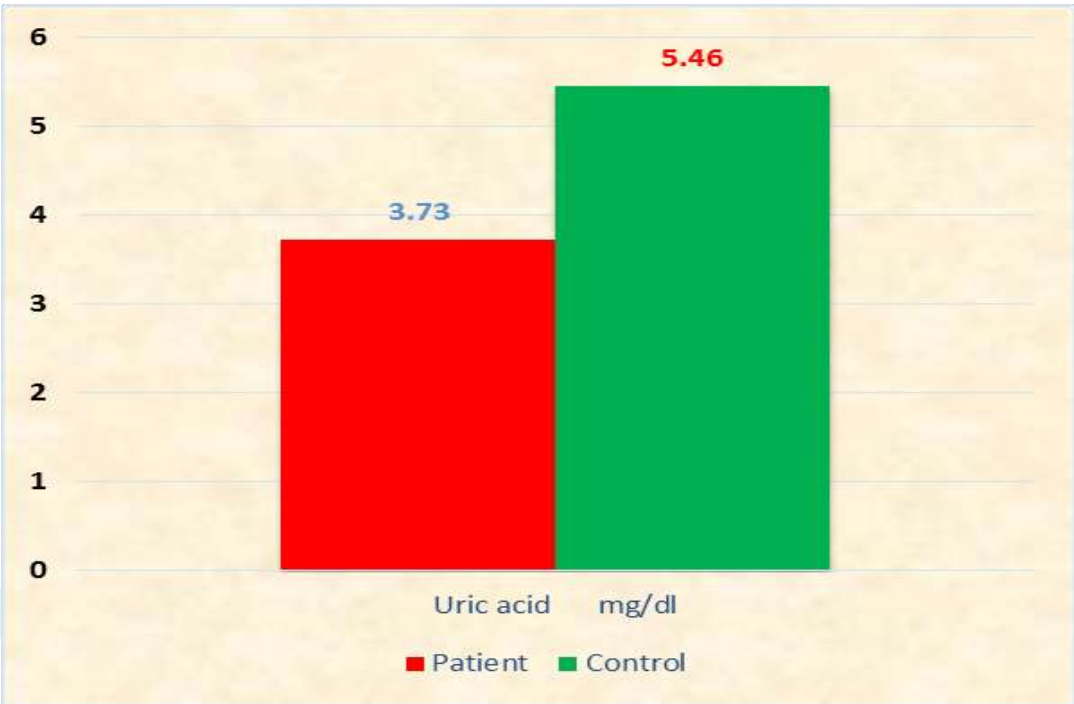

Figure 4.8 Comparison of uric acid in patients and control

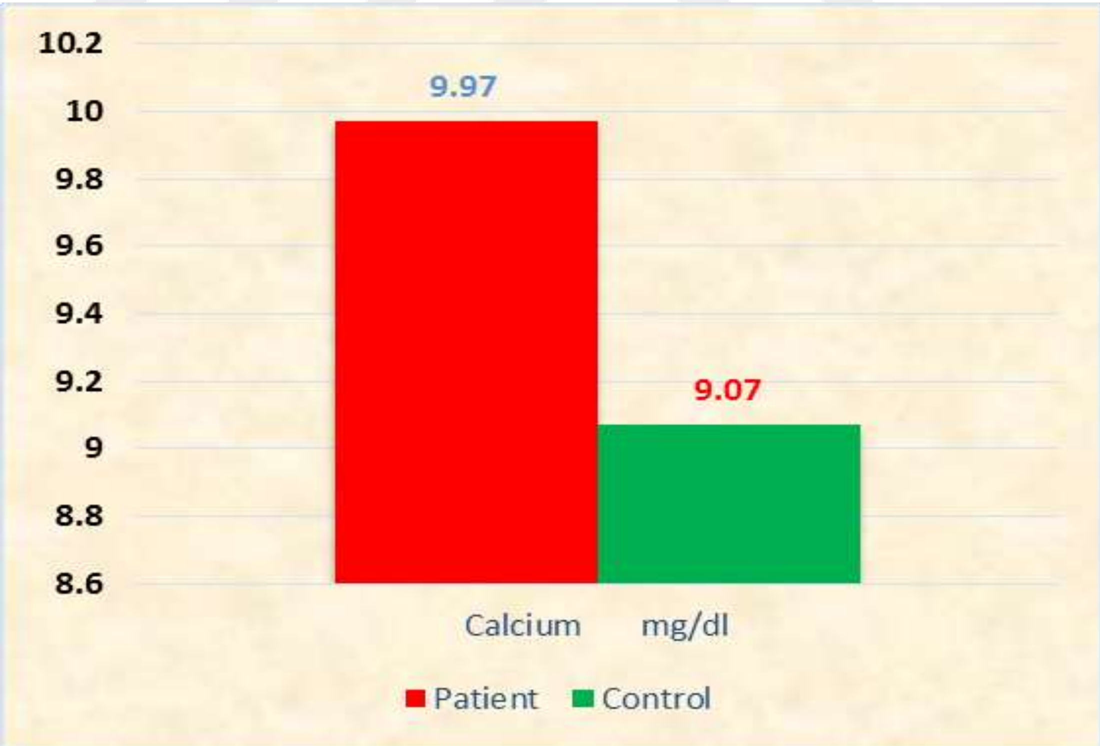

Figure 4.9 Comparison of calcium in patients and control groups

5. CONCLUSSION AND RECOMMENDATION

Leukemia, more often referred to as leukemia, is a category of blood malignancies that originate in the bone marrow and proceed to the generation of an abnormally large number of blood cells. These blood cells are known as blasts or leukemia cells because they are not fully grown (Sharma *et al.* 2018) cancer of the blood and bone marrow. It may be initially asymptomatic, but leukemia can cause fatigue, weakness, and easy bruising and bleeding, among others. Leukemia is a cancer of the blood cells, usually the white blood cells though it can start in other types of blood cells (Vardiman *et al.* 2009).

The aim of study is to assess Study some of the Liver and renal function in Iraqi patients with leukemia suffering from leukemia. Know the relationship between leukemia and some of the renal and liver function may give to the doctor a visualization to modify the treatment of the patient and focus on the status of renal and liver function.

5.2 Results of Demographic and Clinical Characteristics of the Study Groups

5.2.1 ALT, AST

Several studies have shown associations between liver enzymes ALT, AST and leukemia patients (Saito *et al.* 2009), where the current study in Table 4.1 showed a decrease in the moral difference between leukemia patients (15.73 ± 7.75) compared to control (26.38 ± 17.08) in ALT concentration ($P \leq 0.05$), while the same study showed no significant difference between leukemia patients (22.68 ± 9.05) compared to control (25.43 ± 9.11) in AST concentration ($P \geq 0.05$). These results are consistent with the results of the study (Prati *et al.* 2002) when it examined the relationship between liver enzymes and their effects with leukemia patients in India. The ratio between ALT and AST is usually used to diagnose leukemia, as the level of ALT enzyme in the blood rises dramatically when the liver is injured or damaged, but in chronic liver diseases that worsen gradually, the level of AST enzyme begins to rise in the blood after damage to other organs, Therefore, based on the results of the AST/ALT ratio, it is possible to predict the pathological status of liver diseases and their associations with leukemia patients (Omagari *et al.* 2009).

5.2.2 ALP

One of the enzymes in the blood plasma that works in an alkaline medium (pH = 9 - 10.5) where the activity of alkaline phosphate increases in the plasma as a result of various conditions, some of which are normal physiological and some of them are pathological that indicate certain lesions (Babu *et al.* 2020). Some studies have shown correlations with the concentration of alkaline phosphatase in the serum of leukemia patients (Brichacek and Brown 2019). Table 4.1 shows that there was no significant difference between leukemia patients (250.73 ± 100.1) compared to control (291.48 ± 170.4) in ALP concentrations ($P \geq 0.05$). These results are consistent with those obtained by (Matsushita *et al.* 2013).

5.2.3 BR

Bilirubin levels that are above the normal level may indicate the presence of different types of liver or gallbladder duct problems. Sometimes, high levels of bilirubin may be caused by an increased rate of red blood cell damage (hemolysis). There are several studies of researchers that revealed correlations between leukemia patients and the concentration of bilirubin through the increase or decrease in the patients' serum (Scharschmidt *et al.* 1982).

Table 4.1 shows that there was no significant difference between leukemia patients (0.55 ± 0.37) compared to control (0.58 ± 0.31) in the concentration of bilirubin ($P \geq 0.05$). These results are identical to those obtained by the researcher (Watson 1977) when he noticed that there were no significant differences for some patients in China.

5.2.4 Albumin

One of the proteins that are made by the liver, as it accounts for about 60% of the total proteins in the blood, and there are a number of studies that have found close correlations between albumin concentration and leukemia serum (He and Carter 1992). Table 4.1 shows that there is no significant difference between leukemia patients (36.64 ± 9.19) compared to control (34.36 ± 5.73) in the concentration of albumin ($P \geq 0.05$). These results were identical to the study of some researchers when they found correlations in the serum of leukemia patients and their direct correlations with albumin concentration (Lichenstein *et al.* 1994).

5.2.5 LDH

HDL assay is used to detect serum lipoprotein levels in patients with leukemia (Holmes and Goldberg 2009). Table 4.2 shows a decrease in the significant difference between leukemia patients (425.83 ± 99.38) compared to the control (333.33 ± 197.4) in LDH concentration. These results did not match what the researcher discussed (Madern 2002) when he did not find any change in the percentage of lipoprotein in the serum of leukemia patients.

5.2.6 Blood urea

The concentration of urea or the concentration of nitrogen present in urea in the blood of leukemia patients (Sjöden *et al.* 1985). Is examined, as the current study in Table 4.3 showed a significant decrease in the significant difference between leukemia patients (19.12 ± 8.50) compared to the control (28.58 ± 7.30) in urea concentration ($P \leq 0.05$). Where these results were identical to what was stated by the researcher (Markou 2014) when he discovered variations in the urea content in the blood serum of leukemia patients from a Nigerian group of infected individuals.

5.2.7 S. Creatinine

This test aims to detect the levels of creatinine in the blood of patients with leukemia, which gives a picture of the efficiency of kidney work. A British study found associations between creatinine concentration and the cause of its changes in the serum of leukemia patients (Stevens and Levin 2013). Table 4.3 shows a decrease in the significant difference between leukemia patients (0.67 ± 0.29) compared to control (0.89 ± 0.37) in the concentration of creatinine ($P \leq 0.05$). These results are in agreement with the results of (Brosnan and Brosnan 2007) in Mexico when they found a decrease in creatinine concentration in the serum of leukemia patients.

5.2.8 Uric acid

Several studies showed correlations between the concentration of uric acid, which consists of (oxygen, carbon, hydrogen, nitrogen) and leukemia patients. Where the current study in Table 4.3 showed a decrease in the significant difference between leukemia patients (3.73 ± 1.73) compared to the control (5.49 ± 1.69) of uric acid concentrations ($P \leq 0.05$). These results are inconsistent with those obtained by (Ray *et al.* 2000).

5.2.9 Calcium

Calcium concentration analysis in the serum of leukemia patients is performed to determine the amount of ionized calcium and total calcium in the body, which helps to detect many health problems, including kidney problems (Brini *et al.* 2013). Where the current study showed in Table 4.3 that there was no significant difference between leukemia patients (9.97 ± 2.31) compared to the control (9.07 ± 0.80) in the concentration of calcium ($P \geq 0.05$). These results do not agree with the results of our study, as there is a significant increase in the level of calcium concentration compared to the results (Peacock 2010).

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APPENDICES

APPENDIX 1. Reagent got

APPENDIX 2. Alkaline phosphatase

APPENDIX 3. Reagent albumin

APPENDIX 4. Reagent Total and direct bilirubin

APPENDIX 5. Reagent Uric Acid

APPENDIX 6. Reagent Calcium

APPENDIX 7. Reagent urea U.V

APPENDIX 8. Clinical chemistry system sat 450

APPENDIX 9. Centrifuge

APPENDIX 10. Laboratory incubator

APPENDIX 11. Bilirubin meter

APPENDIX 12. Spectrophotometer

APPENDIX 13. Pipette

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