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The relationship between ABO / Rhesus factor, and Acute Lymphoblastic Leukemia in Children Suffering from Leukemia Attending Tripoli Medical Center

Thesis Submitted to the University of Zawia for the fulfill of

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ABSTRACT

Introduction: Leukemia is the most common childhood cancer, accounting for 30% of all diagnoses. Acute lymphatic leukemia and chronic spicy leukemia are the most common types, accounting for 60% of all cases. **Materials and Methods:** The study analyzed blood changes in 160 patients from newborns to 15 years old at Tripoli Medical Center's Department of Oncology and Hematology. Data were analyzed using GraphPad Prism, with a significance level of $P < 0.05$, and percentages and graphs were calculated using Microsoft Excel. **Results:** The study found that male cases (61.25%) were prevalent, while female cases were 38.75%. Acute lymphocytic leukemia (ALL) was the most common, accounting for 92.50% of the total, while acute myeloid leukemia (AML) was rare. ALL was prevalent in the age group 9-11 years (27.50%), followed by 6-8 years (24.37%). AML was high in the age group 6-8 years (4.37%). Blood type (A) had the highest percentage among fathers and mothers, followed by O. Rh+ blood group had a higher frequency than Rh- blood group in all blood groups, suggesting a higher potential for developing blood cancers. The study also found a significant increase in white blood cells (WBC) during injury cases and a significant decrease in hemoglobin (Hb) and platelet leukocytes (PLT) compared to the control group. The study confirmed that the results of the questionnaire on risk factors for 30 children with leukemia, with most cases being male and the blood group for the injured being A+. Cancer treatments, including radiotherapy and chemotherapy, can cause skin problems such as redness, rash, dryness, peeling, and itching. 73.33% of the children answered that their skin color is normal, possibly due to the child's initial treatment and the ongoing chemotherapy and radiotherapy. The study also investigated the family history, with 46.66% of the children having relatives with dysfunctional types of cancer. **Conclusion:** Research on blood leukemia in Libya is limited, necessitating further studies from other geographical and environmental areas. The relationship between blood and leukemia is unclear; environmental factors like factories and refineries could contribute to the disease's appearance.

Acknowledgements

DEDICATION

For me

Declaration

I hereby declare that the work in this thesis is my own except for quotations and summaries which have been duly acknowledged

Hiba Abdulmenem Arosi

Date: /   /

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ABBREVIATIONS

Ab	Antibody
ALC	Absolute lymphocyte count
All	Acute Lymphatic Leukemia
AML	Acute Myeloid Leukemia
ANLL	Acute Nonlymphocytic Leukemia
CBC	Complete Blood Count
CGH	Comparative Genomic Hybridization
CLL	Chronic Lymphocytic Leukemia
CML	Chronic Myelogenous Leukemia
FAB	French-American-British
FISH	Fluorescence In Situhybridization
Hb	Hemoglobin
HCL	Hairy cell leukemia
JCML	Juvenile Chronic Myelogenous Leukemia
LL	lymphocytic leukemia
LGLL	Large Granular Lymphocytic Leukemia
MAb	Monoclonal Antibody
MRD	Minimal Residual Disease
PAb	Polyclonal Antibodies
Ph	Philadelphia
PLT	Platelets
Ppb	Part per billion
RBC	Red Blood Corpuscles
Rh Factor	Rhesus Factor
SKY	Spectral Karyotyping
TMC	Tripoli Medical Center
WBC	White Blood Cell Count
WHO	World Health Organization

Chapter I

Introduction

1. Introduction

While overall occurrence is infrequent, leukemia stands as the predominant form of childhood cancer, comprising 30% of all cancer diagnoses in children under 15 years old. Within this demographic, Acute Lymphatic Leukemia (ALL) surpasses acute pelvic Acute Myeloid Leukemia (AML) by over five times, constituting 78% of childhood cancer diagnoses (Linet 1999). Chronic spicy leukemia constitutes the majority of other childhood leukemia instances, accounting for around 12% of all leukemia cases and over 60% of ALL cases (Sandler and Ross 1997).

In the United States, childhood leukemia experienced a non-statistically significant increase between 1975 and 2002. This rise could potentially be attributed to alterations in diagnostic procedures, enhanced accuracy, and improved reporting. The incidence of childhood leukemia maintains stability at three to four new cases per 100,000 children under 15 years annually, with a peak occurring between 2 and 5 years of age (Greenlee *et al*. 2000; Gurney *et al*. 1995; Margolin *et al*. 2001).

Regarding childhood AML, the peak incidence occurs during the first year of life, followed by a gradual decline over the subsequent four years, remaining relatively constant throughout childhood (Gurney et al. 1995). The incidence of ALL, particularly T-cell ALL, is slightly higher in boys than girls (Kersey *et al*. 1973; Margolin *et al*. 2001). Nevertheless, girls exhibit a higher percentage of ALL leukemia cases during the first year of life (Gurney *et al*.

1995; Ries *et al*. 1998). No gender-based differences in AML incidence are observed.

Across childhood, the rate of leukemia incidence among American children of African descent is nearly half that of Caucasian children on average. In the initial years of life, the ALL incidence among American children of African origin is approximately one-third of the average among Caucasian children; however, African American children aged three and above have higher rates than Caucasians (Gurney *et al*. 1995; Zahm and Devesa 1995, Pollock *et al*. 2000).

1.1 Blood and its Components

Blood serves as a fluidic life-saving organ, characterized by a combination of cellular components, furrows, and crystals. Given the distinct relative densities of various blood constituents, the application of centrifugal force allows for the separation of sediments based on their rate and size (Hardwick 2008). Blood is a solution of numerous chemicals with various types of suspended cells (Watson 2005). It comprises two primary components: blood cells, encompassing red blood cells, white blood cells, and platelets, constituting about 45% of the total blood volume; and plasma, making up the remaining 55% (Watson 2005).

1.1.1 Plasma

Plasma, a transparent liquid with a straw hue, predominantly comprises water, constituting 91.5% of its overall composition. The remaining content consists

of proteins (7%) and non-protein dissolved substances (1.5%). The multifaceted roles of water in plasma encompass acting as a solvent, facilitating the retention of cellular components from the blood, and functioning as a heat distributor (Tortora and Derrickson 2009). Among the plasma proteins are albumin, globulin, fibrinogen, optrumbin, and hyninoplain, which play a pivotal role in maintaining vascular pressure in blood vessels, regulating fluid movement between blood vessels and the interstitial space. Additionally, these proteins contribute to blood viscosity (Tortora and Derrickson 2009).

Blood viscosity, a factor influencing blood pressure, increases with viscosity, resulting in elevated peripheral resistance. Plasma devoid of fibrinogen, designated as serum, is a yellow fluid obtained after thrombus formation (Thibodeau and Patton 2012). Mineral salts in plasma, including chloride, phosphates, sodium carbonate, potassium, and calcium, must maintain a delicate balance for optimal bodily tissue function. Salt serves various purposes, such as cytoplasm and nucleoplasm formation, acting as an insulator to neutralize acids or alkalis, and preserving blood pH (Ashton 2007). Electrolyte balance is upheld by organizing positively charged ions, predominantly sodium, and negatively charged ions, particularly chloride and bicarbonate (Watson 2005).

Plasma also harbors final products from carbohydrates, proteins, and fats, such as glucose, amino acids, fatty acids, glycerin, and vitamins absorbed from the digestive system. Additionally, gases like oxygen, carbon dioxide,

and nitrogen, along with byproducts from protein metabolism like urea and uric acid, are present. Other constituents encompass antibodies and antitoxins defending against bacterial infection, hormones from glands, and enzymes without specific channels (Watson 2005).

Up until the early eighties, leukemia stood as the primary cause of cancer-related childhood deaths in the United States (Zipf *et al*. 2000). The overall childhood leukemia death rate decreased by 20% from 1975 to 1995 (Linet *et al*. 1999), with a notable decline compared to childhood brain tumor mortality (Bleyer *et al*. 1998). The current treatment success rate for childhood leukemia is approximately 75-80%, while for AML, it ranges between 40 and 45% (Pui *et al*. 2003). Ethnic or cultural differences in treatment commitment have not been systematically examined in various U.S. populations, hindering definitive conclusions on the impact of such disparities on children's outcomes with ALL (Bhatia 2004).

1.1.2 Blood cells

There are three main types of blood cells:

- **Erythrocytes (Red Blood Cells).**

- **Leucocytes (White Blood Cells).**

- **Thrombocytes (platelets).**

(Thibodeau and Patton 2012). At least two million red blood cells are manufactured every second (Tortora and Derrickson 2009), a balance between the rate of red blood cell destruction. Blood is the formation of new

blood cells and occurs mainly in the bone marrow. Other organs, including the liver, spleen, lymph nodes, and thymus gland in the blood while developing the fetus. The liver and spleen also respond to the lack of blood cells in the presence of the disease.

All blood cells are formed from stem cells in the bone marrow. These stem cells are not distinct cells that have the ability to reproduce themselves and ripen in many different types of blood cells ((Ashton 2007). When the stem cell is divided and ripe, it becomes either lymph or splash. The lymphatic predecessor ultimately ripens in the B Lymphocytes B and T and the natural killer cells (Munro 2009). The Speed Stem Step Cell develops into any of the (Munro 2009):

1. Megakaryocyte-erythrocyte precursors that lead to the development of platelets and red blood cells.

2. Granulocyte-monocyte precursors that lead to the development of white blood cells. Once the blood cells reach maturity, they are released into the bloodstream (Figure 1).

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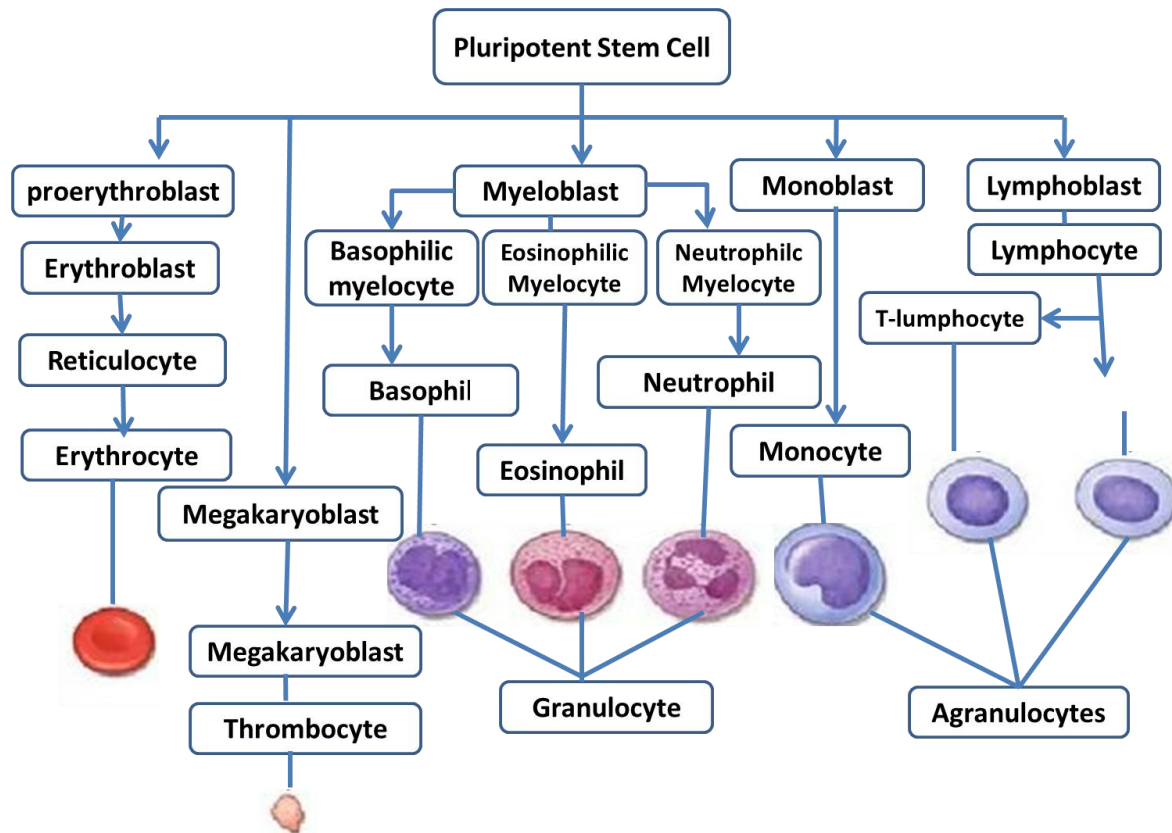
(Figure 1.1): Origin and development of blood cells. (Farley *et al* 2012)

Erythrocytes, or red blood cells, originate in the red bone marrow located in the spongy bones situated at the ends of long bones and irregular bones, such as shear and storytelling. The process of red blood cell formation is known as erythropoiesis, and the hormone erythropoietin, primarily synthesized in the kidneys, regulates the average sorting of bone marrow cells towards red blood cells (Munro 2009).

The development of red blood cells involves several stages before they enter the bloodstream. Erythroblasts, initially large cells containing nuclei and a minimal amount of hemoglobin, progress into normoblasts. Normoblasts are

smaller cells with increased hemoglobin content and reduced nuclei size. Subsequently, the nucleus disintegrates and disappears, leading to the stage of reticulocytes, characterized by interconnected indicators within the cytoplasm. Finally, as the threads vanish, fully mature red blood cells are released into the bloodstream (Watson 2005). These mature erythrocytes are distinguished by their biconcave disc shape, as illustrated in Figure 2.
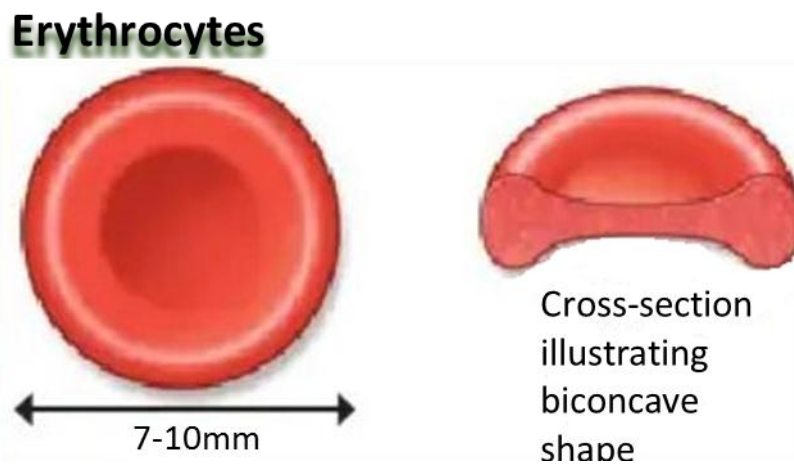
(Figure 1.2): The red blood cells. (Farley *et al* 2012)

Erythrocytes, or red blood cells, are manufactured in the red bone marrow situated within spongy bones found at the ends of long bones and irregular bones, such as shear and storytelling. Erythropoiesis, the production of red blood cells, is regulated by the hormone erythropoietin, predominantly synthesized in the kidneys (Munro 2009).

Red blood cells undergo distinct developmental stages before entering circulation. Erythroblasts, initially large cells with nuclei and minimal hemoglobin, transform into normoblasts—smaller cells with increased hemoglobin and reduced nuclei size. Subsequent stages involve the disintegration of the nucleus, leading to the formation of reticulocytes. Ultimately, fully mature red blood cells devoid of nuclei are released into the bloodstream (Watson 2005). Characterized by a biconcave disc shape (Figure 2), their abundance and unique form play a crucial role in enhancing the total surface area for gas exchange (Thibodeau and Patton 2012). With a diameter of 7-10 mm, these cells lack a nucleus, facilitating easy shape changes for smooth passage through small capillaries (Gordon-Smith 2009). Red blood cells house hemoglobin, a protein that attracts and carries oxygen (Watson 2005).

Upon traversing the lungs, red blood cells form oxyhemoglobin as oxygen combines with hemoglobin. The oxygenated blood, appearing light red, is transported to tissues, where oxygen release occurs. Consequently, hemoglobin assumes a dull color, resulting in the purple-red hue of unoxygenated blood (Watson 2005). Additionally, red blood cells transport some carbon dioxide from tissues (Munro 2009), and the amount they carry is contingent on their hemoglobin content.

The lifespan of red blood cells is approximately 120 days (Munro 2009). Once aged, phagocytes in the spleen, liver, and red bone marrow consume these cells. Hemoglobin undergoes division into heme and globin, with globin

returning to protein stores as amino acids for reuse or secretion in urine. Iron, part of heme, is stored, recycled, and transferred from the liver to the red bone marrow through the transport protein transferrin. The liver converts the pigment into bile pigments, excreted in feces through a complex process (Tortora and Grabowski 2004).

Leucocytes, or white blood cells, play a pivotal role in recognizing and safeguarding the body against foreign invaders like microorganisms and cancer cells. These cells, categorized into phagocytes and lymphocytes, can exit the bloodstream and migrate to tissues based on chemical mediators' signals (Ashton 2007). Phagocytic cells, including granulocytes and monocytes, respond to chemical mediators, migrating to impact locations where they eliminate microorganisms through phagocytosis. Granulocytes, constituting up to 75% of white blood cells, have a lifespan of approximately 21 days and include neutrophils, eosinophils, and basophils (Watson 2005). Neutrophils combat bacteria, eosinophils mobilize against disorders involving parasites, neoplasms, and allergens, while basophils are crucial in immediate hypersensitivity reactions.

Lymphocytes and monocytes, constituting 25% of white blood cells, are non-granulated cells referred to as agranular cells (Tortura, 2005). Within 24-36 hours of circulating in the blood, monocytes migrate to tissues, maturing into macrophages. Both monocytes and lymphocytes play vital roles in recognizing foreign invaders, presenting foreign antigens to lymphocytes, and stimulating the immune response (Munro 2009). Lymphocytes, produced in

lymph nodes and lymphatic tissue, are involved in antibody production (Watson 2005).

White blood cells, with a limited lifespan, necessitate continuous replacement (Tortora and Derrickson, 2009). Their numbers increase in response to bleeding, infection, or inflammation, influenced by cytokines that regulate their growth, differentiation, and immune function (Tortora 2005).

The term leucopenia describes an abnormally low level of white blood cells, potentially caused by exposure to radiation, shock, or specific chemotherapeutic agents (Tortora and Grabowski 2004).

(Figure 1.3): The Granulocytes. (Farley, *et al.,* 2012)

Thrombocytes, also known as platelets, are smaller than red blood cells and are produced in the bone marrow. Thrombopoietin, a regulatory hormone, stimulates platelet production by influencing the bone marrow (Munro 2009). Platelets play a crucial role in blood clotting, or hemostasis, with a lifespan of

8 to 11 days. Those not utilized in hemostasis undergo destruction by macrophages in the spleen (Waugh and Grant, 2006).

The essential process in preventing excessive blood loss involves three broad stages of clotting. The initial stage entails blood vessel spasm or stenosis, where the vessel cavity narrows in response to serotonin production by platelets upon contact and adherence to damaged blood vessel walls. The second stage involves the formation of a platelet dam, where sticky platelets aggregate, releasing substances like adenosine to attract more platelets to the injury site, forming a temporary seal. The final stage is coagulation, accomplished by the composition of fibrin threads, leading to hemostasis or blood clotting (Waugh and Grant 2006).

1.1.3 Blood Group

The ABO system categorizes blood into four fundamental groups based on the presence or absence of antigens (agglutinogens) on red blood cell surfaces, with A and B being the two antigens. Blood group A has antigen A, blood group B has antigen B, blood group AB has both A and B, and blood group O has neither A nor B. Plasma contains agglutinins, or antibodies, which induce agglutination when incompatible red blood cells are mixed. The ABO system antibodies are named anti-A and anti-B, suspended in the plasma (Watson 2005). Individuals with blood group A generate anti-B and lack anti-A, leading to the presence of anti-B in their plasma. Similarly, individuals with blood group B produce anti-A and lack anti-B, resulting in anti-A in their plasma. Blood group AB lacks antibodies, while blood group

O has both anti-A and anti-B. Blood group AB is considered the universal recipient as transfusing type A or B blood is deemed safe due to the absence of antibodies causing cell agglutination. Blood group O is termed the universal donor since it lacks A and B antigens, making it safe for transfusion into individuals with blood groups A, B, AB, or O (Watson 2005). In blood transfusion practice, compatibility is meticulously checked, as ABO systems may match, but other antigen systems on donor or recipient cells might not. Transfusing ABO-incompatible blood components can lead to agglutination and hemolysis, where the immune system attacks and destroys transfused cells (Waugh and Grant 2006).

1.1.4 Rhesus System

The Rhesus factor or Rhesus antigen is present in about 85% of the population (Waugh and Grant 2006). Those who possess this factor are Rhesus positive, and those who do not are Rhesus negative. If a negative person receives positive donor blood, the antigen stimulates the production of antibodies to the so-called anti-Rh antibodies. If a second positive transfusion is given at a later time, the cells that are transported and destroyed (hemolysed) will be modified, with serious or fatal consequences for the recipient (Tortora and Derrickson 2009).

1.2 The Cancer

Approximately 1500 individuals succumb to cancer each day in the United States, contributing to over 8 million new global diagnoses annually. In

developed nations like the United States, where infectious diseases and malnutrition have declined, approximately one in three people may develop cancer in their lifetime, becoming a significant cause of death. Cancer, rather than a contemporary ailment, has a historical presence dating back thousands of years, evidenced by ancient skeletons and Egyptian records documenting cases over 4000 years ago. The discovery of cancer in a jaw tumor in 1932 by Louis Leeki in Australia marked a pivotal moment, suggesting cancer's existence in human populations for at least a million years (Bozzone and Donna 2009).

The mid-twentieth century witnessed a surge in global cancer prevalence, leading to the National Cancer Act of 1971, which bolstered research efforts and funding to combat the disease. Progress in understanding cancer emerged from studying natural cell functions and contrasting them with cancer cells. While cancer encompasses over 100 types affecting various body cells and systems, the common denominator is abnormal cell division. Defects in DNA disrupt cellular communication and growth control, allowing cancer cells to invade and spread, disrupting normal organ functions and potentially proving fatal (Bozzone and Donna 2009).

Despite the gravity of cancer, recent research offers hope for treatment and prevention. Understanding specific genes involved in cancer has become a focal point, with efforts directed at unraveling the disease's workings, causes, and genetic roots. Early detection methods are under exploration, with an emphasis on studying proteins secreted by cancer cells. Notably, advances in

childhood leukemia treatment and the development of drugs like Herceptin for certain breast tumors showcase progress. Prevention remains a powerful strategy, as more than 50 % of cancers could be averted through lifestyle choices such as avoiding smoking, excessive sun exposure, and adopting a healthy diet. While treatments improve, prioritizing prevention helps mitigate diagnostic anxieties and potential treatment-related pain (Bozzone and Donna 2009).

1.2.1 Leukemia

Leukemia denotes a condition affecting white blood cells in the bone marrow, characterized by their excessive proliferation, which hampers the production of red blood cells and platelets in the red bone marrow. The diminished production of red blood cells leads to reduced oxygen levels and abnormal blood clotting (Tortora and Derrickson 2009). This type of leukemia manifests aggressively, reaching its zenith within a short period of weeks or months (Waugh and Grant 2006). Alternatively, leukemia can present as chronic, displaying less aggressiveness and a more discernible population of white blood cells. Common indicators of leukemia encompass fatigue, cold and pallid skin, weight loss, fever, night sweats, excessive bleeding, and frequent infections (Tortora and Derrickson 2009).

Leucocytosis, characterized by an elevated white blood cell count due to the presence of many immature and abnormal white cells in the bone marrow, is observed in both acute and chronic leukemia. Diagnostic investigations involve microscopic examination of blood cells, revealing elevated white

blood cell counts, diminished red blood cells, low hemoglobin levels, and reduced platelet counts. A definitive diagnosis is typically established through a bone marrow biopsy. Subsequent to diagnosis, appropriate leukemia treatment commences (Alexander et al. 2006).

Leukemia encompasses various types, including the acute form, which rapidly peaks within weeks or months (Waugh and Grant 2006). Conversely, chronic leukemia exhibits a less aggressive progression with more distinct white blood cells. Recognizable signs and symptoms include fatigue, cold and pallid skin, fever, night sweats, bleeding tendencies, and recurrent infections (Tortora and Derrickson 2009). Both acute and chronic leukemia entail an upsurge in immature and abnormal white blood cells, accompanied by a decline in red blood cells, hemoglobin, and platelets. Microscopic examination of a bone marrow biopsy or sample serves as the diagnostic modality for leukemia (Alexander *et al*. 2006).

1.2.2 Childhood Leukemia

Childhood cancer is rare, with a reported incidence in the United States of approximately 1 case per 7,000 children age 15 years and younger. In contrast to the adult population, in whom solid tumor malignancies predominate, almost 40% of childhood cancers are hematologic malignancies (leukemia and lymphoma). Leukemia is the most frequent malignancy that occurs during childhood and comprises approximately 30% of all childhood cancers. Leukemia is a malignant tumor that affects children in childhood and constitutes about 30% of all types of cancers that affect children. In the past,

it was a rare tumor, so its incidence in the United States of America for example, was very small, one case for every 7,000 children aged. 15 years or less. Nearly 40% of childhood cancers are hematological malignancies, divided between leukemia and lymphoma.

Historically, leukemia was classified initially into four groups based on clinical presentation and morphologic appearance of the malignant cells:

1.   Acute Lymphocytic Leukemia (ALL)

2.   Acute Nonlymphocytic Leukemia (ANLL)

3.   Chronic Myelogenous Leukemia (CML)

4.   Chronic Lymphocytic Leukemia (CLL).

Research studies during the last two decades, which evaluated morphological regulation, immunity, regulation of growth, molecular cells, and molecular deformities in leukemia cells, have proven that leukemia represents a more heterogeneous group of malignant tumors, which initially suggested the classification of the four groups (Hutter 2010). However, the initial classification designations are still used clinically, and they remain useful in considering how to classify childhood cancer in childreen(Table 1).

Table 1.1 Frequency of types of childhood leukemia in historic classification*(Hutter, 2010)

Leukemia Classification	% of Childhood Leukemia
Acute lymphocytic (ALL)	80
Acute nonlymphocytic (ANLL)	13
Chronic myelogenous (CML)	7
Chronic lymphocytic (CLL)	Virtually none
*Based on cellular morphology and clinical features.	

It has been documented that the incidence of childhood leukemia, specifically acute lymphatic leukemia (ALL), is elevated in children between the ages of 2 and 5 years. Gender disparities have been noted, indicating a higher incidence in boys. Disparities were also observed in the prevalence based on ethnicity, with lower rates reported in African American children compared to their white counterparts, particularly within the age group of 2 to 5 years. While leukemia appears to occur slightly more frequently among children of Hispanic origin compared to non-Hispanic children, the extent of this difference is not as distinct as the contrast observed between non-Hispanic and African American children (Hutter 2010).

1.2.3 Types of Leukemia

The types of leukemia can be grouped based on how quickly the disease develops and gets worse:

1. Chronic leukemia

Early in the disease, the characteristics of leukemia cells may have a special nature as the blood cells continue to be able to do some of the work of normal white blood cells. People may not have any symptoms at first, where often find chronic leukemia during a routine checkup before there are any symptoms.

Slowly, chronic leukemia gets worse. As the number of leukemia cells in the blood increases, people get symptoms, such as swollen lymph nodes or infections. When symptoms do appear, they are usually mild at first and get worse gradually.

2. Acute leukemia

The leukemia cells are incapable of performing the functions of normal white blood cells. This form of cancer is distinct from the chronic variety, as it is characterized by a rapid increase in the number of leukemia cells, leading to a swift deterioration. Acute leukemia typically progresses rapidly. Leukemia types can also be categorized based on the specific type of white blood cell affected. The disease may originate in either lymphoid cells or myeloid cells. Refer to the illustration of these cells. Leukemia impacting lymphoid cells is referred to as lymphoid, lymphocytic, or lymphoblastic leukemia. On the other hand, leukemia affecting myeloid cells is known as myeloid, myelogenous, or myeloblastic leukemia.

Other types of leukemia:

1. **Chronic lymphocytic leukemia (CLL):**

The most common form of leukemia in adults, in which lymphocytes look fairly normal but are not fully mature and do not function correctly against infection. The malignant cells are found in blood ,bone marrow, collect in enlarge the lymph nodes. CLL affects lymphoid cells and usually grows slowly. It accounts for more than 15,000 new cases of leukemia each year. Most often, people diagnosed with the disease are over age 55. It almost never affects children.

2. **Chronic myeloid leukemia(CML):**

CML affects myeloid cells and usually grows slowly at first. It accounts for nearly 5000 new cases of leukemia each year. It mainly affects adults.

A malignant disease involving the white blood cells belonging to the myeloid line that is due to a chromosome rearrangement called the Philadelphia (or Ph) chromosome translocation. Abbreviated CML. CML has several phases that succeed one another

3. **Acute lymphocytic leukemia (ALL):**

ALL effects lymphoid cells and grows rapidly. It affects approximately 5,000 new cases of leukemia. ALL is the most common type of leukemia in children, and also infected adults.

4. Acute myeloid leukemia(AML):

AML affects bone cells through myeloid cells, also has nature of grows rapidly. There are 13,000 new cases of AML per year. It occurs in all ages young kids and adults.

5. Hairy cell leukemia (HCL):

HCL is sometimes considered a subset of CLL but does not fit neatly into this pattern. It is a rare type of chronic leukemia. HCL is incurable but may easily treatable in some cases. It was reported that 80% of affected people are adult males. There are no reported cases in young children. Survival is 86% to 100% at ten years. (Dameshek and Gunz 1958).

1.2.4 Acute Leukemia

Acute leukemia represents a malignancy affecting the blood-forming organs, impacting one or more cell lines within the blood-forming system. It originates from immature cells responsible for producing red blood cells, white blood cells, or platelets. The condition is marked by the predominant replacement of the bone marrow with abnormal and unconventional blood cells, resulting in reduced numbers of red blood cells and platelets in the peripheral blood. These disorders are categorized based on the origin of the abnormal blood cells, such as lymphocytes, myeloid cells, a combination of both, or unconventional cells.

In contrast, chronic leukemia encompasses a spectrum of diseases characterized by uncontrolled proliferation of mature cells within the blood-forming system. The classification of chronic leukemia is contingent upon the specific type of cells constituting the blood (Tebbi, 2021).

Despite significant advancements in treatment acute leukemia, its causes remain largely unknown. Various genetic and environmental factors have been proposed, including both pre-existing and acquired genetic mutations, exposure to radiation, and certain chemicals, especially during pregnancy and the `throughout one's life. The influences of inherited genetic variations, pre-existing medical conditions, exposure to infectious agents, lifestyle factors, prior medical treatments, and numerous other elements have been suggested, yet none universally applies to all cases.

Disparities in incidence rates and prognoses related to age, gender, race, disease type, geographical location, and other factors are intriguing but lack a comprehensive explanation. Developments in genomic profiling, encompassing genome-wide gene expression, DNA copy number analysis, and single nucleotide polymorphism (SNP) genetic technology, may contribute to unraveling the role of heredity in these variations.

Hypotheses regarding the development of acute lymphocytic and lymphoblastic leukemia have been delineated, involving a combination of genetic and infectious factors leading to leukemia formation. Various environmental conditions before and after birth, along with exposure to

infections, including the flavivirus, have been suggested. The precise nature, timing, sequence of events, and mechanisms underlying leukemia development necessitate further investigation (Tebbi, 2021).

Classification, Diagnosis, and Prognosis

Over the past two decades, the morphological diagnosis of Acute Myeloid Leukemia (AML) and Acute Lymphoblastic Leukemia (ALL) relied on the French-American-British (FAB) classification. However, more recently, the World Health Organization (WHO) classification has been introduced, taking into account criteria such as cytogenetics, molecular genetics, and previously undescribed morphological and immunological findings (Harris *et al*., 1999).

The diagnosis of acute leukemias necessitates a comprehensive approach involving the morphological assessment of peripheral blood smears, bone marrow aspirate, and core biopsy, along with cytogenetics, molecular genetics, and immunophenotyping. Immunophenotyping is especially crucial in sub-classifying patients with ALL. A key indicator of AML is when at least 20% of identified cells in the blood or bone marrow are blasts of myeloid origin. In AML cases, cytogenetics plays a significant role as a prognostic factor, predicting treatment response (Grimwade *et al*., 1998; Mrozek *et al*., 2009).

Chromosomal abnormalities are prevalent in acute myelogenous leukemia, including (t'8;21'), among others. Patients with specific translocations like

t(8;21), t(15;17), t(16;16), or inv(16) exhibit a favorable outcome with induction chemotherapy and intensive post-remission consolidation chemotherapy. Conversely, abnormalities involving chromosomes 5 or 7, 11q23, or complex karyotypes correlate with a very poor outcome using current induction and post-remission chemotherapy. Patients with a normal karyotype or trisomy 8 fall within the intermediate prognosis category. In adults with ALL, the presence of t (9;22) or t (4;11) indicates a very poor prognosis. Patients with t (9;22) ALL are rarely if ever, cured with chemotherapy alone. Immunophenotypic assessment of surface antigens expressed on leukemic blast cells aids in diagnosis and holds crucial implications for the treatment and prognosis of myeloid, T, and B lineage leukemias.

Innovative techniques such as fluorescence in situ hybridization (FISH), spectral karyotyping (SKY), comparative genomic hybridization (CGH), minimal residual disease (MRD) monitoring, and DNA microarrays are transforming the landscape of leukemia diagnosis, prognosis, and classification. FISH, for instance, enables rapid testing for specific chromosomal translocations in both metaphase and interphase cells.
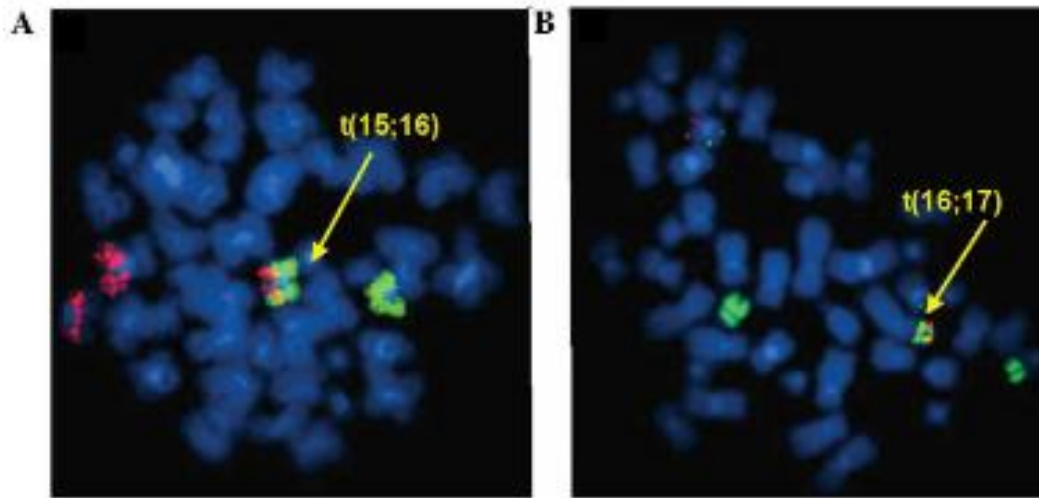
(Figure1.4) Coexistence of; (A) Karyotype analysis revealed 46, XX,t (15;16;17)(q24;q24;q21) and the arrows indicate the t(15;16;17)(q24;q24;q21). Fluorescence in situ hybridization analyses using LSI PML (15q22; Spectrum Orange)/RARA (17q21; Spectrum Green) dual colour/dual fusion probe revealed a (B) typical PML/RARA dual colour dual fusion signa (Burak UZ, 2013).

One of the crucial methods for genotype detection is Spectral Karyotyping (SKY), employing a fluorescently labeled chromosome painting probe to automatically display all chromosomes in color. This enhances the precision and sensitivity of cytogenetic analysis, particularly when dealing with complex karyotypes. Comparative Genomic Hybridization (CGH) is a sensitive technique identifying regions with genomic deletion or amplification, potentially revealing new disease genes. Monitoring Minimal Residual Disease (MRD) using RT-PCR-based amplification and quantification of fusion genes proves valuable in predicting relapse (Golub *et al.*, 1999). Additionally, DNA microarray analysis of genetic expression definition files can advance traditional diagnostic tests. Expression arrays, for example, can distinguish AML from ALL samples based solely on gene expression patterns (Golub *et al.*, 1999). Furthermore, expression array

analysis has revealed that ALL associated with MLL translocations constitutes a distinct subtype of acute leukemia, easily discernible from both AML and other types of ALL (Armstrong *et al*., 2002). Expression profiling serves as a valuable tool for categorization, subtyping discovery, and predicting outcomes in B and T lymphocytes (Ferrando *et al*., 2002; Yeoh *et al*., 2002).

In Figure 1.5, highlighted by the yellow star, aggressive cytotoxic chemotherapy remains the main approach for treating all cases of acute leukemias. Leukemias exhibiting favorable outcomes are identified in blue, those with unfavorable prognoses in red, and those with an uncertain or intermediate prognosis in white. Acute leukemia involves two categories of cooperating mutations: those promoting enhanced proliferation and/or survival and those hindering hematopoietic differentiation.
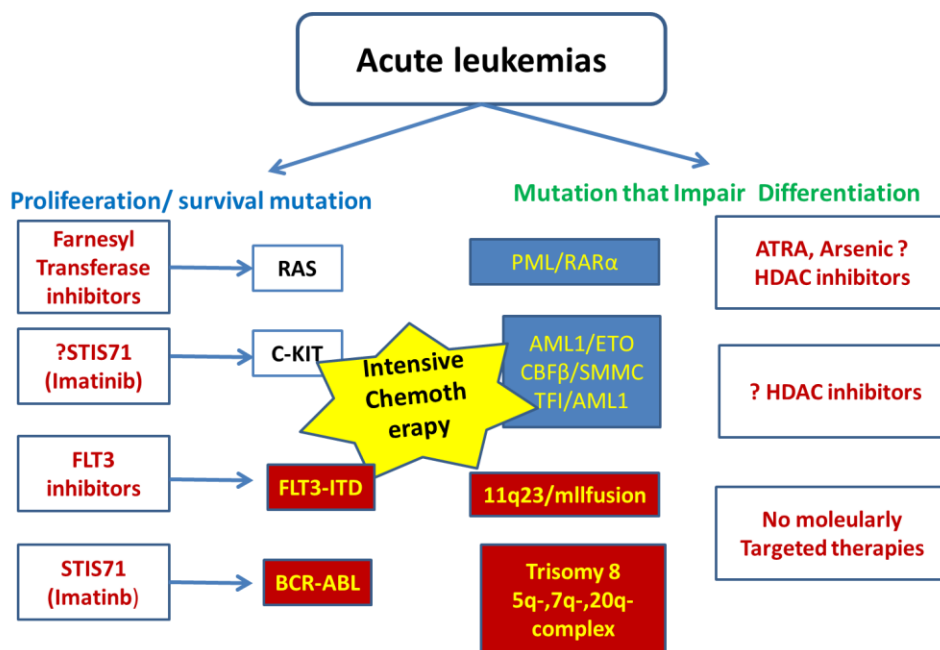
(**Figure1.5**) Pathogenesis and treatment of acute leukemia

1.2.5 Chronic leukemia

Chronic leukemia encompasses a wide range of disorders, some of which were not identified until the end of the last two decades (Morrison, 1994). Significant progress has recently been made in the biology and treatment of these disorders. The role of newer therapeutic approaches is determined, using biological response rates, nucleoside theories, monoclonal antibodies, and bone marrow transplantation. The types of chronic lymphocytic leukemia (CLL), Pro lymphocytic leukemia (PLL), large granular lymphocytic leukemia (LGLL), hairy cell leukemia (HCL), and chronic myelogenous leukemia (CML) have been identified (Morrison, 1994).

1.2.6 Chronic Lymphocytic Leukemia (CLL)

Chronic lymphocytic leukemia, characterized by the abnormal proliferation of lymphocytes, was initially described by Galton and Damchek in the mid-1960s. Over 95 percent of diagnosed cases fall under the category of chronic lymphocytic leukemia, with approximately 10,000 new cases reported annually in the United States alone. The incidence of CLL appears consistent across different racial groups, with males experiencing twice the occurrence observed in females. CLL tends to be more prevalent in older age, yet its cause remains unknown. Unlike other malignancies, there is no observed increase in infections following exposure to radiation or alkylator treatment, and no viral association has been identified (Morrison, 1994).

In the early 1970s, healthcare professionals noted a significant rise in patients being diagnosed at asymptomatic stages, increasing from 30 to 40%, and more recently reaching 60% through routine blood count screenings (Rozman and Emilio, 1995).

Common symptoms experienced by patients include swollen lymph nodes, fatigue, and weight loss. A distinctive characteristic of CLL's natural progression is the gradual accumulation of B lymphocytes over time. Consequently, symptoms do not manifest early until lymphocytes proliferate, leading to the enlargement of the spleen and liver. Additionally, the white cell count may elevate, and anemia and thrombocytopenia may occur due to bone marrow infiltration (Figure 1.6: Rozman and Emilio, 1995).

A   B
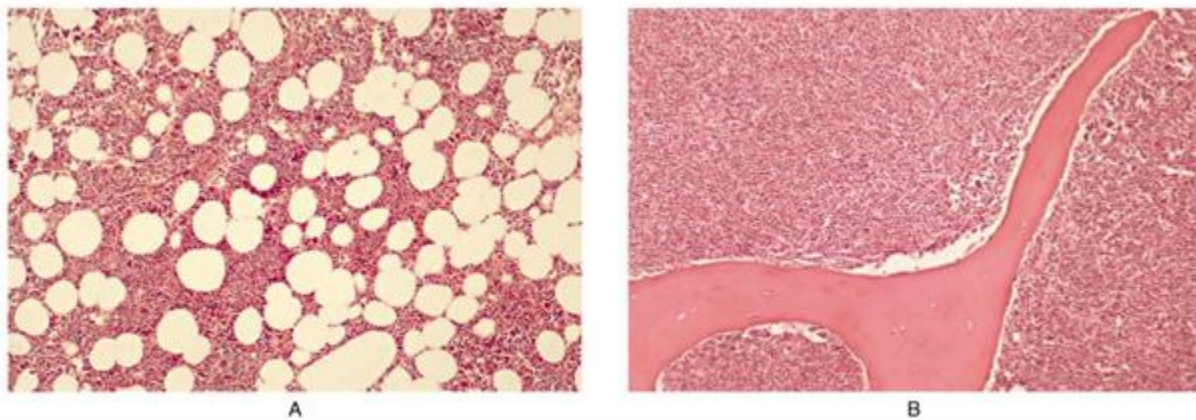
(Figure 1.6). Bone Marrow–Biopsy Specimens of CLL in an Early (Panel A) and Late (Panel B) Stage (Hematoxylin and Eosin, ×75). In Panel A, there is interstitial infiltration by lymphocytes, sparing other hematopoietic precursors and fat cells. In Panel B, there is diffuse replacement of all marrow components by the neoplastic lymphocytes (Rozman and Emilio 1995).

In recent times, numerous studies have focused on the biological significance of the inactivated P53 function, where chromosomal abnormalities have

enabled the identification of patients at risk of disease development and lower survival rates. Encouragingly, clinical trial treatments have shown increased rates of full and overall response when administered as an initial treatment for CLL symptoms (Byrd *et al*., 2004).

Certain patients may undergo a swift decline in blood and organ function, experiencing symptoms at diagnosis or shortly afterward that necessitate treatment. However, initiating treatment for patients in the early stages may not necessarily be linked to prolonged survival. Recently, effective treatment modalities, including antibody chemotherapy and autologous or allogeneic stem cell transplantation, have been developed. Treatment options exhibit variations in effectiveness, toxicity, and cost, emphasizing the growing need for new algorithms that incorporate novel treatment risks (Byrd *et al*., 2004).

Mechanism of Chromosomal Mutation in CLL:

As mentioned in the introduction, lymphocytes initially accumulate in the bone marrow and then spread to lymph nodes and other lymphoid tissues, eventually inducing splenomegaly, hepatomegaly, and systemic symptoms such as fever, night sweats, fatigue, early satiety, and unintentional weight loss. Chromosomal mutations occur due to changes in chromosome structures, chromosomal rearrangements, or other chromosomal abnormalities, such as changes in missing chromosomes or chromosome numbers. As stated earlier, these changes usually take place during crossing over or cell division (Boes, 2017).

Clinical properties are often diagnosed when there is a significant increase in absolute lymphocytes Countc (ALC). Patients may not have any systematic complaints at the time of diagnosis, so it is defined by an increase in absolute lymphocyte count (ALC). ALC is calculated as the total white blood cell count (WBC) multiplied by the percentage of lymphocytes in the peripheral blood. If more than 4000 µl lymphocyte is found in adult patients, it is a common hematologic abnormality. It is typical for the lymphocyte count to rise briefly after an infection, and a count much higher than 3,000 lymphocytes in a microliter of blood defines lymphocytosis in adults. In children, the number of lymphocytes for lymphocytosis varies with age, reaching as high as 8,000 lymphocytes per microliter. Even if it is absent in the diagnosis, lymphocytes, and spleen enlargements will be present in most patients during the disease. In patients with more advanced disease, symptoms and signs may include anemia, lymphadenopathy, and infections. Other affected sites may include the mucous membranes, lungs, skin, and bones (Morrison, 1994), (Coates *et al.*, 2020).
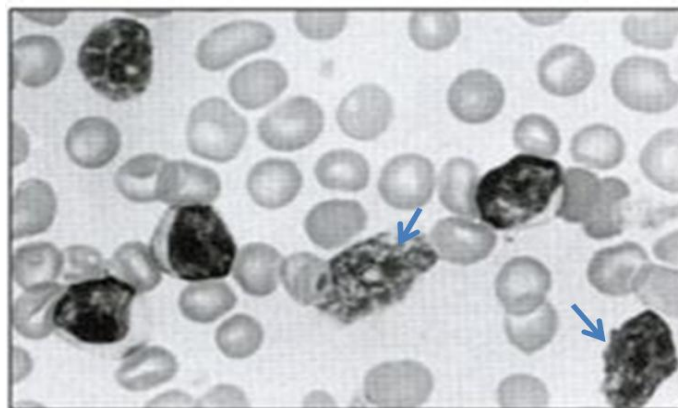
(**Figure 1.7**). Small, uniform, mature-appearing lymphocytes and damaged lymphocytes or"smudge cells" on a blood smear from a patient with chronic lymphocytic leukemia(Wright's Giemsa, original magnification x400) (Morrison 1994).

(Table 1.2): Minimum Requirements for the Diagnosis of CLL (Morrison 1994).

Minimum Requirements for the Diagnosis of CLL
• Absolute peripheral blood lymphocytosis with mature lymphocytes, which is sustained for ≥4 weeks, with no other identifiable cause: Absolute lymphocyte count >10 x 109/L with either marrow involvement or a Bcell phenotype OR Absolute lymphocyte count >5.0 x 109/L with both marrow involvement and a B cell phenotype • Hypercellular or normocellular bone marrow with ≥30% mature lymphocytes • Peripheral blood lymphocyte phenotype B-cell lineage with expression of low-density surface immunoglobulin with either kappa or lambda light chain* CD5+, CD2–, CD3– † Rosette formation with mouse red blood cells‡ • Mature lymphocytes with <55% atypical mature or immature lymphoid cells
*Normal peripheral blood lymphocytes express high-density surface immunoglobulin. †A small number of CD5+ B cells are normally present in lymph nodes and are increased following allogeneic bone marrow transplant, in patients with rheumatoid arthritis, and in fetal and early postnatal life. ‡A marker of mature B cells. CLL = chronic lymphocytic leukemia.

1.2.7 Chronic Myelogenous Leukemia (CML)

Chronic Myelogenous Leukemia is a clonal disorder that involves a stem cell consisting of blood. It represents around 15 percent of all leukemia. Although

its causes are unknown, the disease has an increased occurrence in people with radiation exposure (Zhou *et al.*, 2015).

CML is a malignant cloning disorder of the blood-forming stem cells that leads to an increase in red blood cells and platelets in the peripheral blood and the infiltration of the bone marrow in the bone marrow (Figure 1.7) (Sawyers 1999).
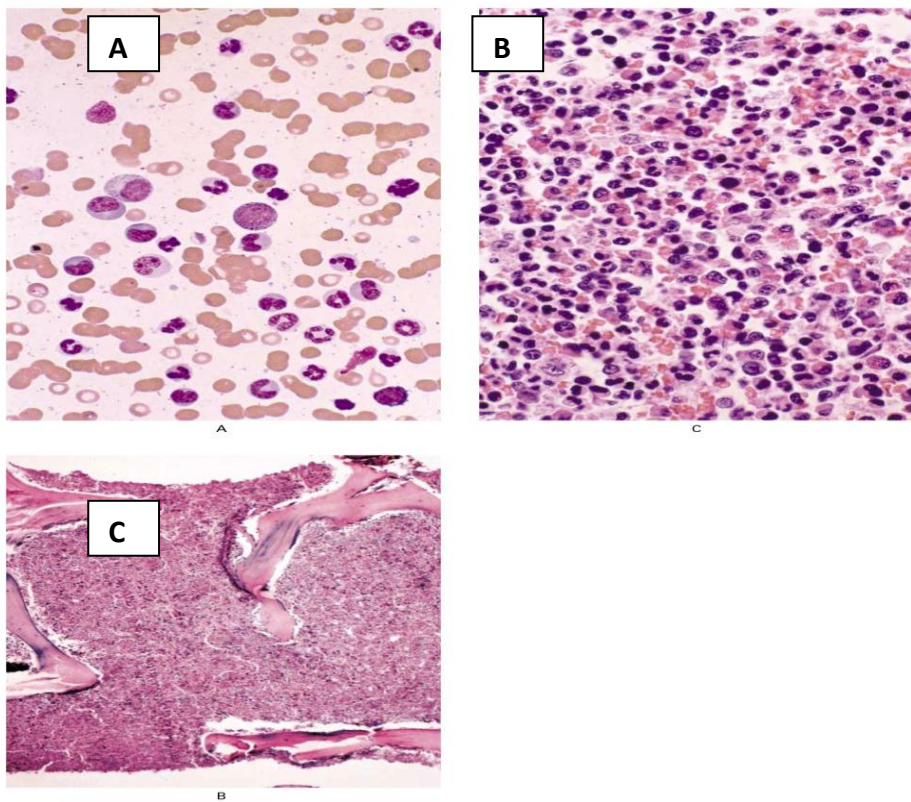
(Figure 1.8). Photomicrographs of a Peripheral-Blood Sample and Bone Marrow Samples. A; shows a peripheral-blood smear with numerous myeloid cells, including myelocytes and a basophil (center) (Wright's stain, ×40). B; a bone marrow specimen obtained with a trephine shows marked hyper-cellularity and almost no fat (hematoxylin and eosin, ×40). C; marked myeloid hyperplasia is evident in the bone marrow specimen at a higher magnification (hematoxylin and eosin, ×160). from a Patient with Chronic Myeloid Leukemia (Rozman and Montserrat 1995)

The Philadelphia (Ph) chromosome was first described in 1960 by Nowell and Hungerford. In 1973, Rowley determined that the Ph chromosome arose from a reciprocal translocation resulting in a shortening of the long arm of chromosome 22, defined cytogenetically. Ph chromosomes are present in over 90% of chronic myelogenous leukemia (CML) patients and in around 25% of adult acute lymphocytic leukemia (ALL) patients (de Lavallade, 2013).

(Table 1.3): Characteristics of Patients with Chronic Myeloid Leukemia at Presentation (Sawyers 1999).

Characteristics of Patients with Chronic Myeloid Leukemia at Presentation.
Clinical findings*
Fatigue, anorexia, weight loss Splenomegaly Hepatomegaly
Peripheral-blood findings
Elevated white-cell count (usually greater than 25,000/mm3) Elevated platelet counts in 30 to 50 percent of cases Basophilia Reduced leukocyte alkaline phosphatase activity All stages of granulocyte differentiation visible on peripheral Smear
Bone marrow findings
Hypercellularity, reduced fat content Increased ratio of myeloid cells to erythroid cells Increased numbers of megakaryocytes Blasts and promyelocytes constitute less than 10 percent of all cells
*Approximately 40 percent of patients are asymptomatic.

The most common abnormality on physical examination is splenomegaly, which is found in up to half of patients. Some benign chronic stages turn fatal within three to five years. Increasing doses of hydroxyurea or busulfan should reduce the number of neutrophils. In contrast to the maturation of CML cells during the chronic phase, cancer cells fail to mature and thus resemble the behavior of some other cancer cells like the lymphocytes found in patients with acute leukemia (Kavalerchik, 2008). Patients in the chronic phase have 20 % or fewer immature myeloid cells in the peripheral blood and 30 % or less in the BM (Figure 1.9).
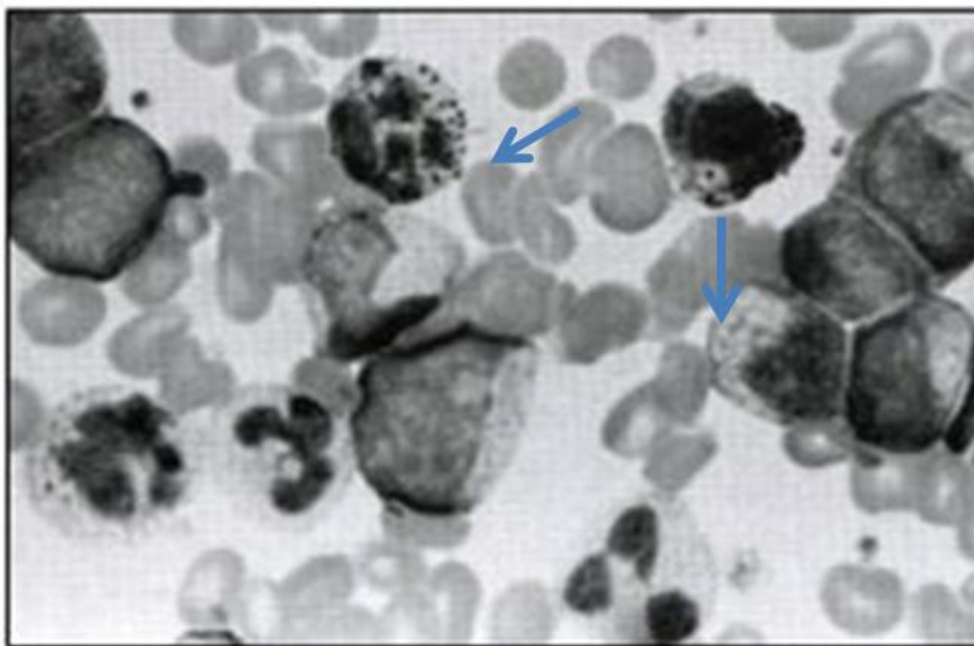
(**Figure 1.9**). Blood smear from a patient with chronic-phase chronic myelogenous leukemia showing left shift to rare myeloblasts in the granulocyte series and an increase in basophils (Wright's Giemsa, original magnification X400) (Shi *et al*., 2015)

1.3 Antibodies and Antigen

An antibody (Ab) is a protein that serves the immune system against foreign bodies such as bacteria and viruses. It is known as a monoclonal antibody (mAb) that is specialized in producing each immunoglobulin by one copy of the cell so that it acts on another molecule in the preparation. Polyclonal antibodies (pAb) are produced by B lymphocytes that respond to several epitopes of the antigen. Monoclonal antibodies represent new reagents that may become an additional treatment method shortly for patients with malignant disease (Ritz and Schlossman 1982).

- **Obstacles to Using Serotherapy:**

The effort in making antisera with the desired specificity.

The relatively low standard of some reagents.

The incapability to produce and administer the large quantities of specific antisera that would be necessary for clinical use.

Recently, some of these limitations have been addressed by generating antibodies to hybrid tumors to human tumor cells (de Carvalho and Rand 1963).

1.4 The aims

To our knowledge, very few studies have evaluated the frequency and distribution of ABO blood groups among children suffering from acute lymphoblastic leukemia in the west of Libya (Tripoli region) and their association with our environment. So, the present study aimed to investigate

the relationship between ABO blood and Rhesus factor with acute lymphoblastic leukemia in children attending Tripoli Medical Hospital. The current study attempted to determine the frequent gender and age group most affected by this disease and compare the results obtained with the results of other studies.

The objectives of the study can be defined in the following points:

1. To determine whether ALL or AML is more common between both genders.

2. Investigate The Relationship of ALL To The Blood Group Type of The Patient.

3. Detect the blood groups of the parents to find out whether they are related to the children's risk of the disease.

4. Analyze the reality of acute leukemia infection and link the results to skin tone between study cases.

5. Determine the most likely age groups developing acute leukemia as well as the most likely ages at which the disease will begin to appear.

Chapter II
Materials and Method

2. Materials and Method

2.1 Study design and population

The present study was conducted on 160 cases of patients who attended the hospital regularly at the Tripoli Medical Center (TMC) Department of Oncology and Hematology. Ages included new-borns up to the age of 15 years. The study also included 48 cases of healthy people, 12 cases from each age group, to compare blood changes in each type.

2.2 Experimental Design

Patients were divided into four age groups of both sexes. Each age group consisted of a certain number of samples along with 48 pediatric health conditions (control group) taken from both sexes. The control group was also divided into 4 groups. The comparison was made according to age groups through tests of their biochemical parameters.

2.3 Method of Work

Patient files (160 case studies) were examined to ensure the ABO group and their parents as well. After obtaining written approval from the parents of the patients, an organized random sample of 12 patients (6 males and 6 females) was taken from each age group by drawing 5 ml of venous blood to test blood parameters.

2.4 Blood Sampling

The blood parameters of all the study samples were evaluated through their records, and to confirm the integrity of the results, a 5 ml blood sample was drawn from the study sample cases. This was represented in 12 randomly selected samples to examine changes in the blood and its components. This procedure was performed from the beginning of November 2021 to January 2022. All blood changes were compared with those of healthy children, according to their age group, with a focus on blood group type (ABO). The reproductive health factor of their parents was also studied, including the Rh factor for both the affected and their parents.

2.5 Determination of Blood Groups

Blood groups were determined using the open slide method, where a drop of donor or recipient blood is mixed with anti-A, anti-B, and anti-D separately. Three drops of blood sample from a sterile finger prick were placed into three different locations on a clean glass slide followed by a drop of blood grouping reagents: anti-A, anti-B, and anti-D. This method was adopted to determine blood groups and the Rh factor.

2.6 Detecting Variables

Hematological parameters were examined, including complete blood cell count (CBC), before and after starting chemotherapy. Additionally, platelets and the average RBC volume were examined before and after chemotherapy. Hematocrit value, mean corpuscular volume, mean corpuscular hemoglobin,

mean corpuscular hemoglobin concentration, white blood cell count, differential count of leukocytes, and blood platelet count were determined using an automated hematology analyzer Sysmex (KX 21) machine in the laboratory of Tripoli Medical Centre.

2.7 Statistical Analysis

Data were subjected to One-Way ANOVA (Analysis of variance) using GraphPad Prism. The difference between means ± SD was tested at $P < 0.05$ using Duncan's multiple range test. In all statistical tests, the probability level of $P < 0.05$ was considered significant. Some data were described statistically using Microsoft Excel.

Chapter III
Results

3.Results

The present study was conducted in order to investigate the relationship between ABO blood grouping and Rhesus factor with acute lymphoblastic leukemia in children for samples were collected from attending patients in Tripoli Medical Hospital. The current study attempted to determine the frequent gender and age group most affected by this disease and compare the results obtained with the results of other studies, also identifying the risk factors most closely related to this type of cancer, that were identified in the aims of the study.

3.1 leukemia cases depending on age, gender, and type of leukemia

3.1.1 Determine the percentage of males and females with leukemia, regardless of the age and type of disease

The current study showed that the incidence in males was more than in females, the following table (3.1) shows the ratios between them.

Table (3.1) It shows the percentage of males and females in the nurse cases of leukemia for two types

Gender	Number	Percent
Male	98	61.25%
Female	62	38.75%
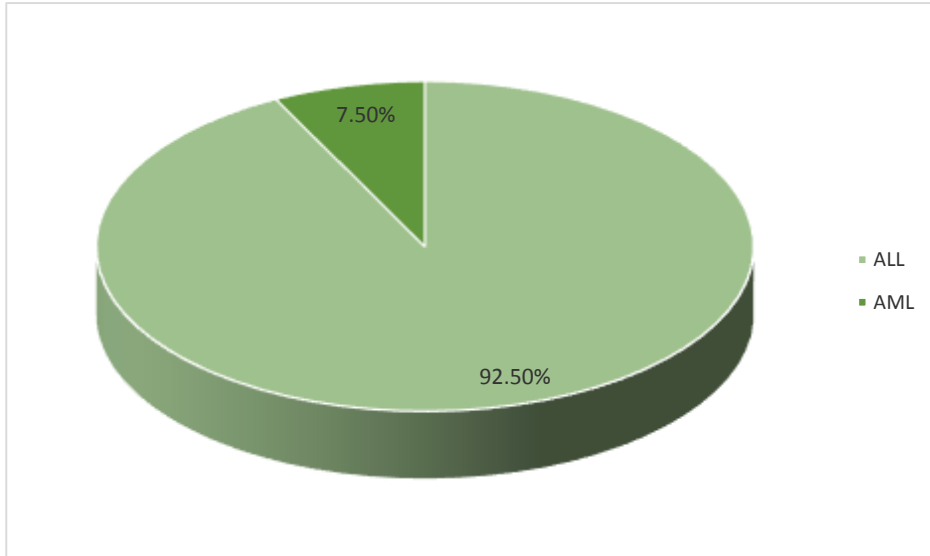
(Figure 3.1). percentage of males and females in the nurse cases of leukemia for two types

3.1.2 Identify the highest cases of leukemia types, regardless of age and gender

Examine the relationship between the number of cases of ALL and AML. The results showed that ALL had a higher incidence rate (92.50%). This finding aligns with previous studies, as shown in Table 3.2. Acute lymphatic leukemia (ALL) is most common in children, and various environmental factors may contribute to the occurrence of these malignant tumors during childhood (Rafieemehr *et al*., 2019).

Table (3.2) It shows the percentage of leukemia types infection (ALL, AML) For children

Type	Number	Percent
ALL	148	92.50%
AML	12	7.50%
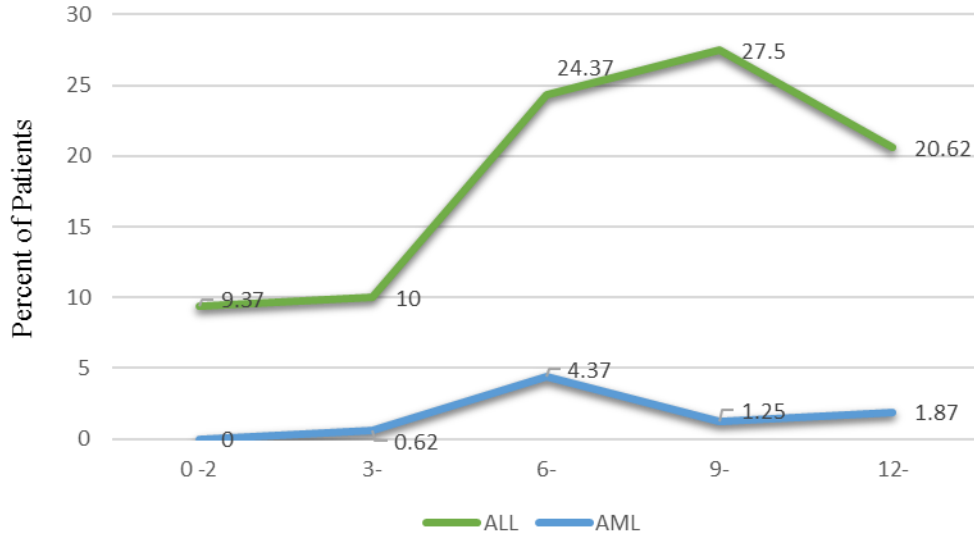
(Figure 3.2). Percentage of leukemia depending on leukemia type (ALL/AML) and age groups

3.1.3 Determine the percentage of people with leukemia for the two types according to age

This study reveals a significant contrast in the occurrence of leukemia types across different age groups. The largest percentage of type ALL occurred in the 4th age group (9-11) years, with the lowest percentage in the 1st age group (0-2) years. Regarding AML, the highest percentage was in the age group (6-8) and the lowest in the 1st age group (0-2), with a rate of 0%. Refer to Table 3.3 for details.

Table (3.3) it shows the percentage of leukemia with its two types, depending on age

AGE	ALL	Percent	AML	Percent	Total
0-2	15	9.37%	0	0%	15
3-5	16	10%	1	0.63	17
6-8	39	24.37%	7	4.37%	46
9-11	44	27.50%	2	1.26%	46
12-<15	33	20.62%	3	1.87%	36
Total	148	91.86	12	8.13%	160

3.2 The results of the leukemia cases in children, according to the data of the blood group

One of the most important objectives of the study is to determine the relationship of the disease to the type of blood type, as well as the Rh factor, considering that current studies indicate the relationship of some diseases to the type of type.

3.2.1 The results of leukemia cases in children, according to blood, group regardless of Rh

It can be noted through the Table (3.4) that type of blood group of children with leukemia, was more focus between (A) by 55% of the total of the injured, followed by the blood group (O) by (30%) of the total of the injured,

and the blood group (B) ranked third with 12.5% as well as the lowest blood group (AB) by 2.5 % for most age groups. This indicates that the relationship between ABO blood groups and blood malignant tumors.

Table (3.4) Determine the ABO of the patients according to age groups

AGE	A	%	B	%	AB	%	O	%
0-2	6	40	2	13.33	2	13.33	5	33.33
3-5	7	41.17	4	23.52	0	0	6	35.29
6-8	27	58.69	4	8,69	0	0	15	32.6
9-11	30	65.21	4	8.69	0	0	12	26.08
12-<15	18	50	6	16.66	2	5.5	10	27.77
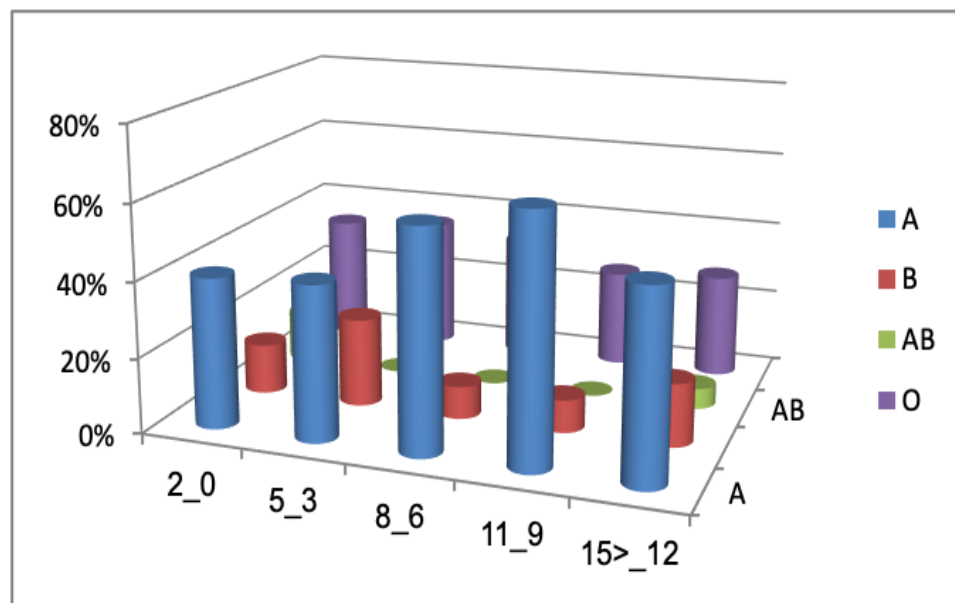
(Figure 3.3). Determine the ABO of the patients according to age groups. It is noted that the highest cases rates are among blood type A, especially for the age group 9-11, then group 6-8.

3.2.2 The distribution of leukemia cases for children, according to ABO and (Rh)

A+ represented the highest percentage among (all age groups), followed by type O+ (also in all age groups), then B+, and the lowest types among the study sample were O- and AB- The following table (3.5) for the distribution of blood types of the study sample in all groups. The age group studied also revealed the blood relationship of those infected to all age groups and the Rhesus factor (Rh).

Table (3.5) Analysis of the proportions of blood types of the study sample and its Rh factor according to age groups

AGE	A⁺	A⁻	B⁺	B⁻	AB⁺	AB⁻	O⁺	O⁻
0-2	40%	0%	13.30%	0%	13.30%	0%	33.30%	0%
3-5	29.41%	11.76%	23.52%	0%	0%	0%	35.29%	0%
6-8	56.52%	2.17%	4.34%	4.34%	0%	0%	30.43%	2.17%
9-11	56.52%	8.69%	6.52%	2.17%	0%	0%	26.08%	0%
12-<15	38.88%	11.11%	16.66%	0%	2.77%	2.77%	27.77%	0%
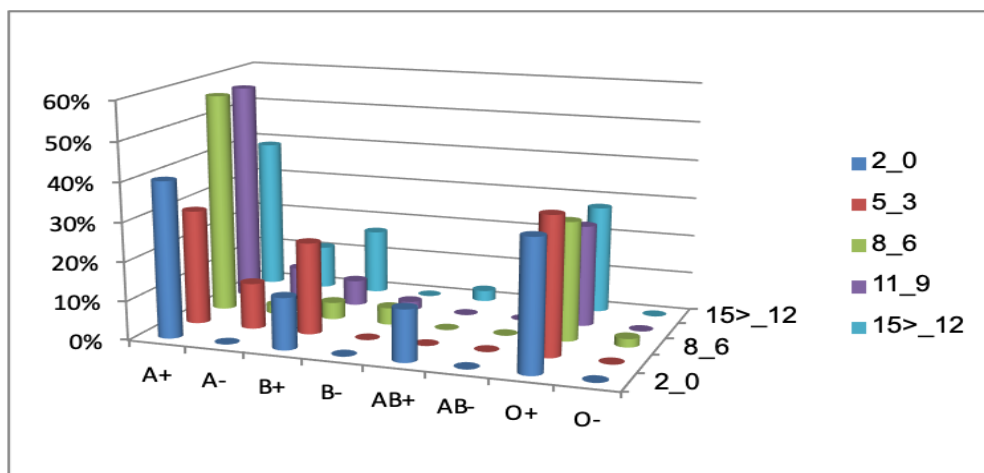
(Figure 3.4). relationship of children with leukemia and age groups blood group with (Rh)

3.2.3 The Studying the relationship of the parents' ABO to the ABO of the children with cancer

Unfortunately, the current study has found some parent's ABO recorders, not all patients. It has been observed through the data that the blood type (A) was the highest percentage among other factions of the father and the mother, followed by the type (O). The following table and Figure show this relationship according to age groups.

Table (**3.6**) The relationship of the ABO of children with cancer to the ABO of the parents for the first age group (0-2) years

BG	A	B	AB	O
BG SUN	40%	13.33%	13.33%	33.33%
BG MUM	53.33%	6.66%	20%	20%
BG DAD	33.33%	13.33%	6.66%	46.66%

47

It is clear from Table (3.6) that the highest incidence of infection among infants within this age group is among ABO (A), followed by (O), and the highest correlation with the mothers' blood group is A, reaching approximately 53%, while the father's blood group is the highest, reaching 46. % almost.
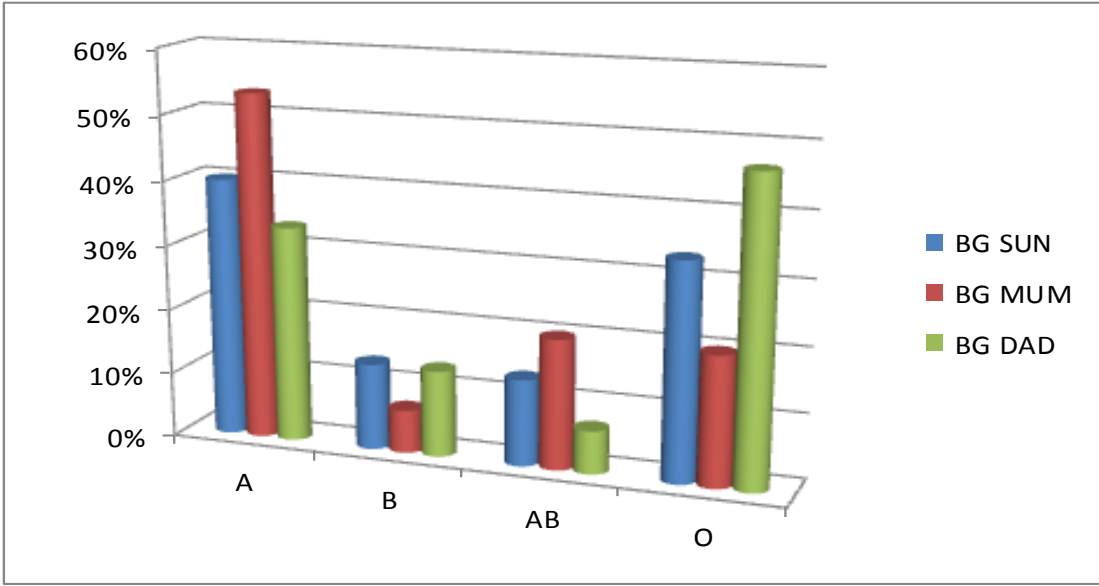
(Figure 3.5). The relationship of ABO of the affected children comparing to ABO of parents for the 1st age group (0-2) years

Table (3.7) The relationship of the ABO of children with cancer to the ABO of the parents for the second age group (3-5) years.

ABO	A	B	AB	O
BG SUN	41.17%	23.52%	0%	35.29%
BG MUM	41.17%	29.41%	0%	29.41%
BG DAD	41.17%	17.64%	11.76%	29.41%

Regarding the second age group (3-5), it became evident that leukemia is concentrated in blood group A for affected children in this group. Similarly, both parents, whether father or mother, carry the same blood group.

(Figure 3.6). The relationship of ABO of the affected children comparing to ABO of parents for the 2nd age group (3-5) years.

Table (3.8) The relationship of the ABO of children with cancer to the ABO of the parents for the third age group (6-8) years

ABO	A	B	AB	O
BG SUN	58.69%	8.69%	0%	32.60%
BG MUM	56.52%	15.21%	10.86%	17.39%
BG DAD	45.65%	8.69%	10.86%	34.78%

In the third age group of patients, a relationship appeared to be found between the blood type of the parents and the affected child, as blood type A was the predominant among them.

(Figure 3.7). The relationship of ABO of the affected children comparing to ABO of parents for the 3rd age group (6-8) years.

Table (3.9) The relationship of the ABO of children with cancer to the ABO of the parents for the age group (9-11) years

ABO	A	B	AB	O
BG SUN	65.20%	8.69%	0%	26.08%
BG MUM	58.69%	6.52%	0%	17.39%
BG DAD	43.47%	10.86%	21.73%	23.91%

50

Likewise, in the 4th age group, there is a strong correlation between the ABO of the parents and the ABO of the affected children, which is type A, followed by blood type O as is the percentage in the table (3.9).
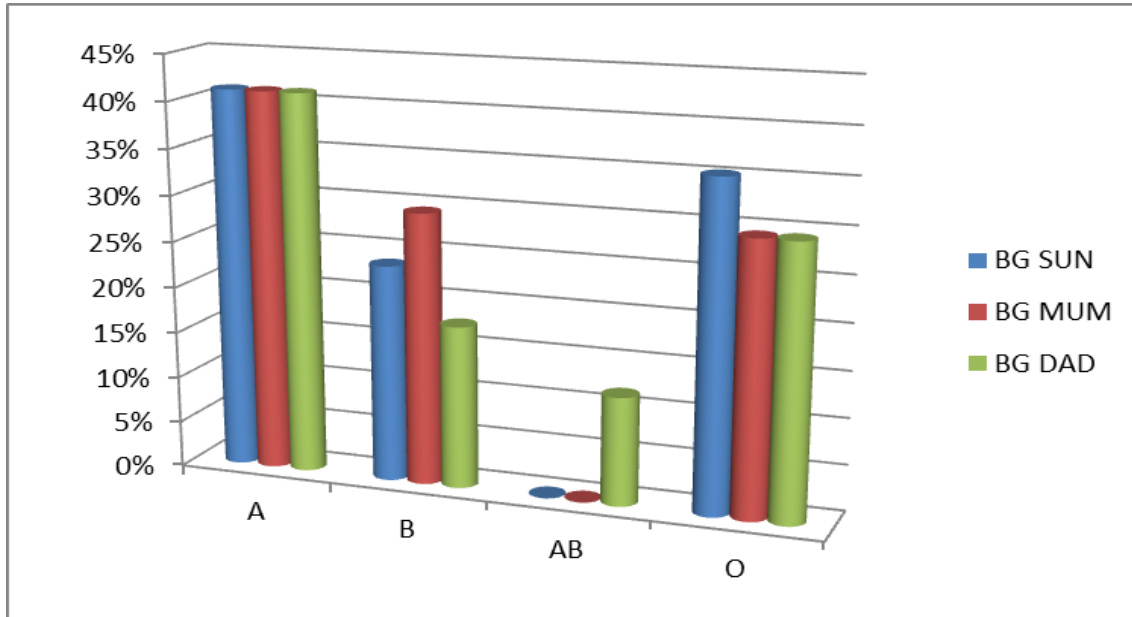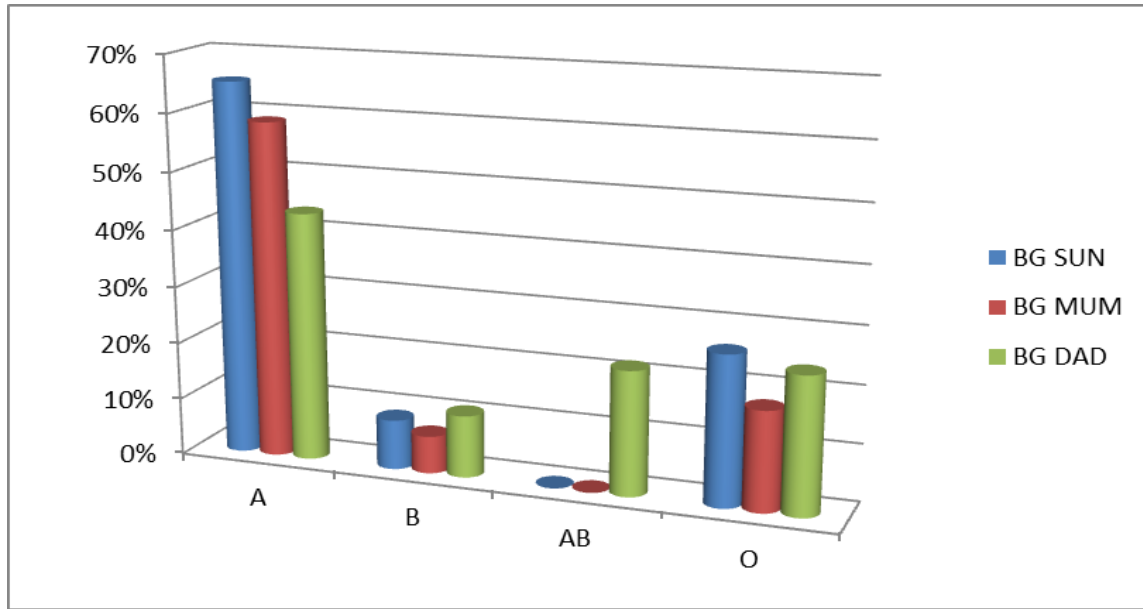

(Figure 3.8). The relationship of ABO of the affected children comparing to ABO of parents for the 4th age group (9-11) years.

Table (3.10) The relationship of the ABO of children with cancer to the ABO of the parents for the fifth age group (12->15) years

ABO	A	B	AB	O
BG SUN	50.00%	16.60%	5.50%	27.77%
BG MUM	41.66%	25%	16.60%	16.60%
BG DAD	33.33%	16.60%	13.88%	36.11%

Also, in the 5th age group, there is a strong correlation between the ABO of the parents and the ABO of the affected children, which is type A, followed by blood type O as is the percentage in the table (3.10).
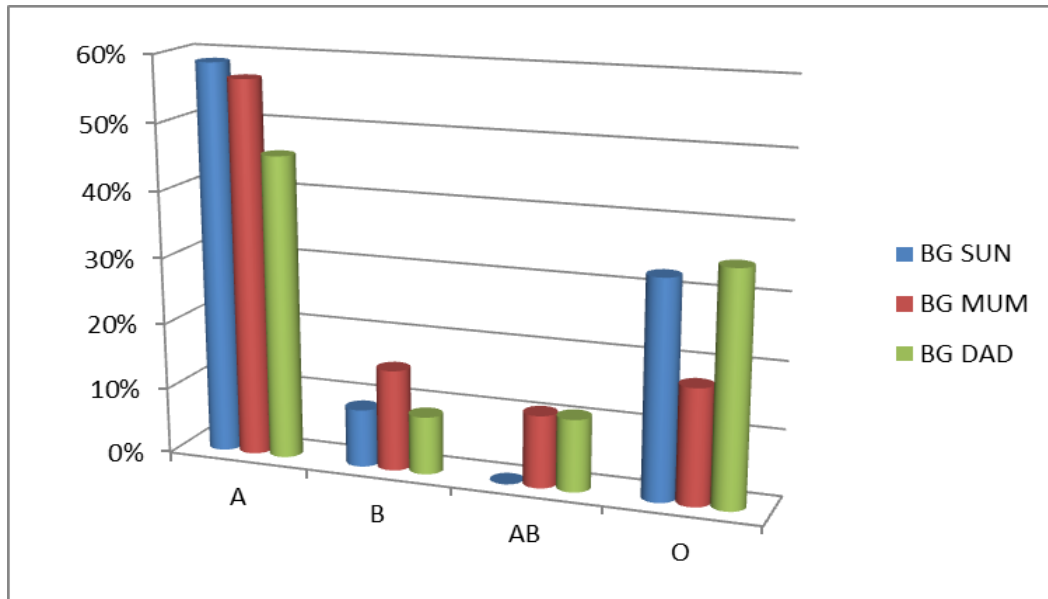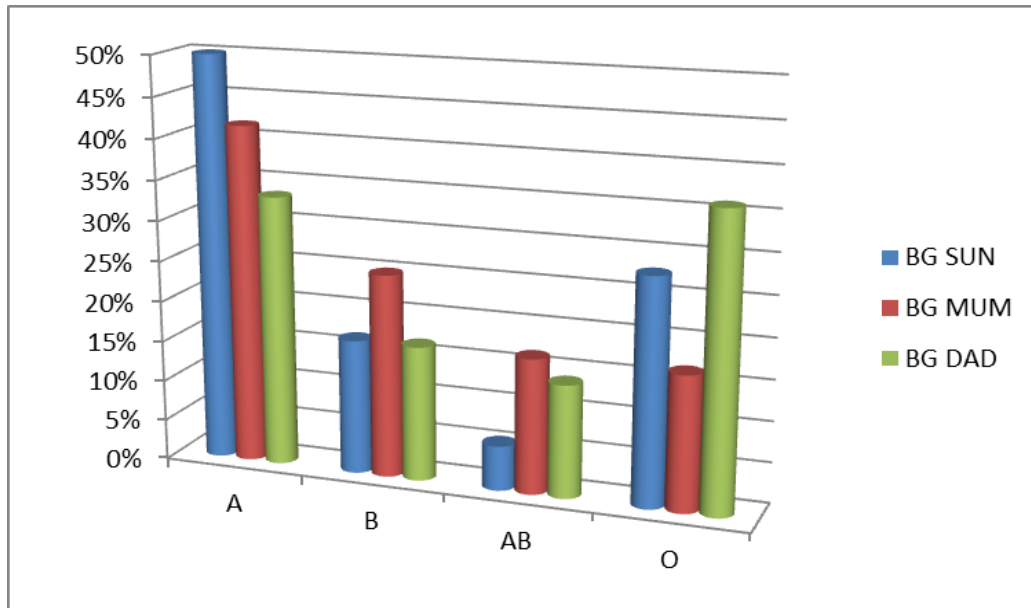

(Figure 3.9). The relationship of ABO of the affected children comparing to ABO of parents for the 5th age group (12->15) years.

3.4 Haematological and Biochemical Parameters of Blood Serum

The values were counted as mean ± SD for haematological properties for all samples, then comparison control group with the experimental group. Although there are differences in WBC, HB, and PLT the differences were not statistically significant compared to regular values. On the other hand, the results showed a statistically significant increase ($P < 0.05$) in WBC when age

periods (0-2) and (6-8) from Cases of injury, An increase in WBC levels towards regular control values, Table (3.11). (Figure 1.10).

Table (3.11) Haematological alteration in WBC to all age groups.

AGE	WBC/mm3	
	Control Group MEAN ±SD	Experimental Group MEAN ±SD
0-2	10.80 ±2.84	46.42 ± 46.96**
3-5	9.22 ±2.86	30.71± 37.89
6-8	7.27 ±2.91	40.79± 57.42*
9-11	7.66 ±2.67	33.66± 60.97
12>15	10.6 ±3.92	31.53± 61.64
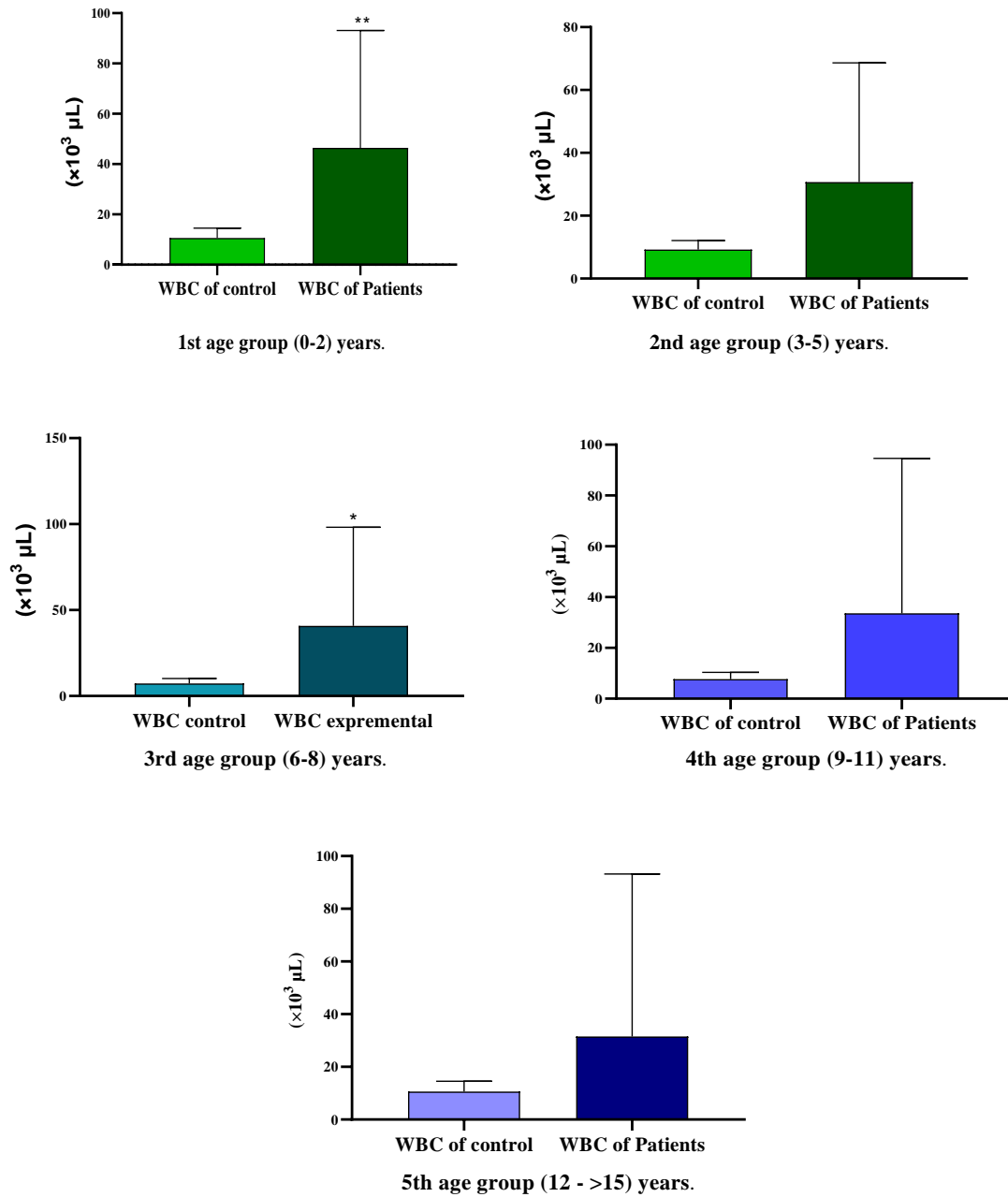
(Figure 3.10). The mean±SD values for haematological properties (WBC) from different samples of and Comparison control group with experimental group

The results also show high a significant decrease in HB in the experimental group compared with the control group in age periods (3-5),(6-8),(12-15) from Cases of injury. Table (1.12). (Figure 1.11).

Table (3.12) Haematological alterations in HB to all age groups.

	HB	
	Control group	**Experimental group**
AGE	MEAN ±SD	MEAN ±SD
0-2	12.15± 2.19	17.48±26.51
3-5	11.60 ±1.28	9.34± 2.39[**]
6-8	11.98± 0.91	6.86 ±2.46[****]
9-11	12.05± 0.86	9.90 ±11.41
12>15	12.63 ±1.21	8.15± 2.73[****]

HB level of the 1st age (0-2) years.

P= 0.54

HB level of the 2nd age group (3-5) years.

P= 0.0062

HB level of the 3ed age group (6-8) years

P= 0.001

HBlevel of the 4th age group (9-11) years

P=0.51

HBlevel of the 5th age group (12->15) years

P= 0.0001

(Figure 3.11). The mean±SD values for haematological properties (Hb) from different samples of and Comparison control group with experimental group

The results also show high a significant decrease in PLT in the experimental group compared with the control group in all age periods from Cases of injury. Table (1.13). (Figure 1.12).

Table (3.13) Haematological alterations for PLT for all age groups

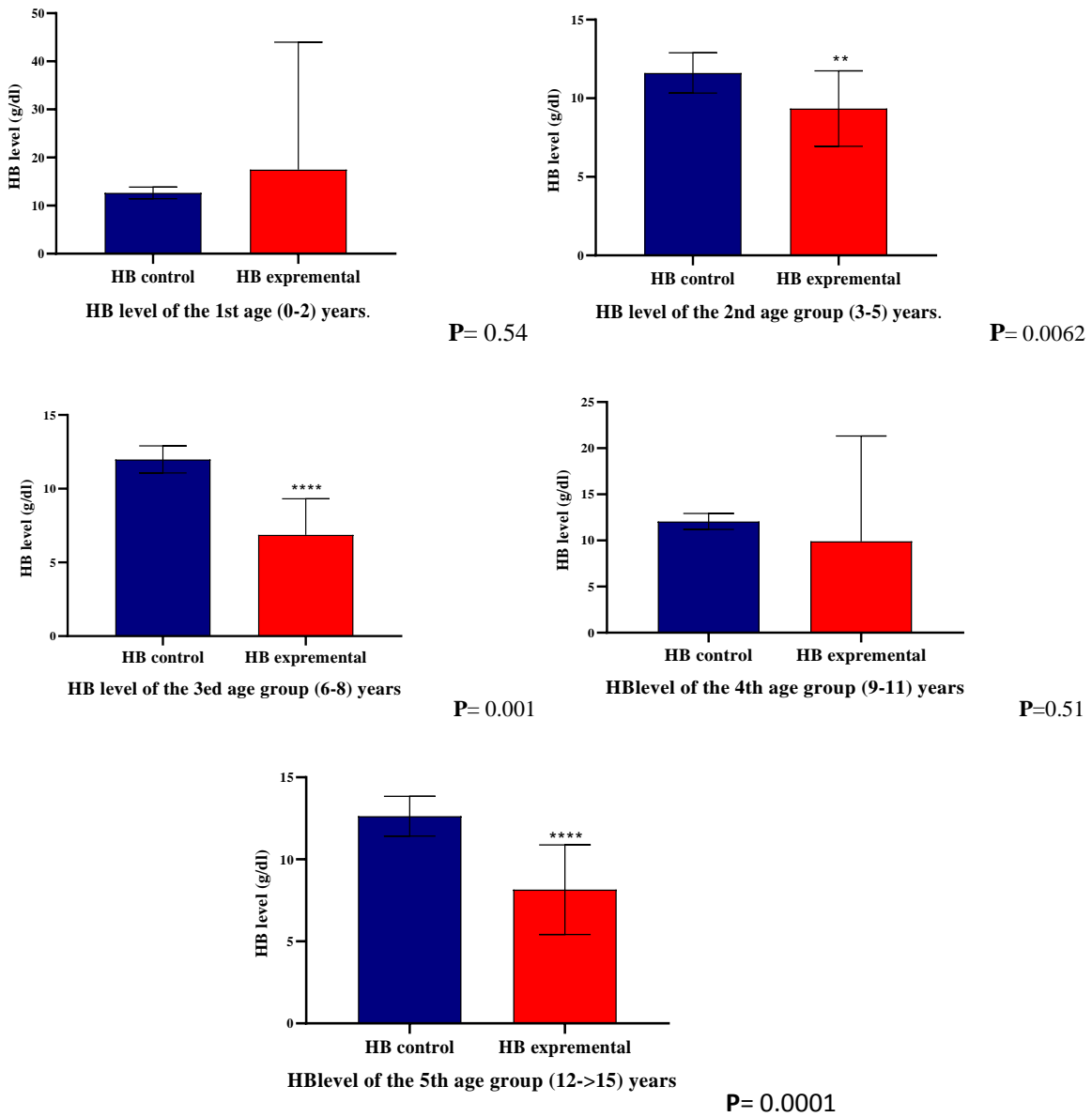|	PLT	
	Control Group	**Experimental Group**
AGE	MEAN ±SD	MEAN ±SD
0-2	317.58±160.28	112.6±147.4 ***
3-5	309.83±141.80	78.51±73.97 ****
6-8	296.41±131.71	77.39±85.93 ****
9-11	282.66±71.83	57.38±62.8 ****
12<15	302.08 ± 71.83	106.05 ± 117.03 ****
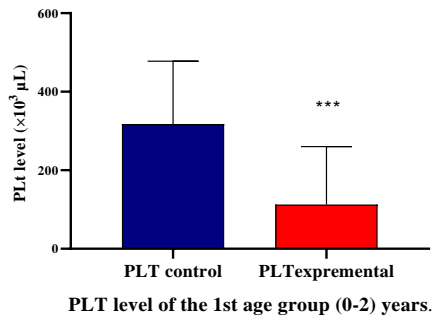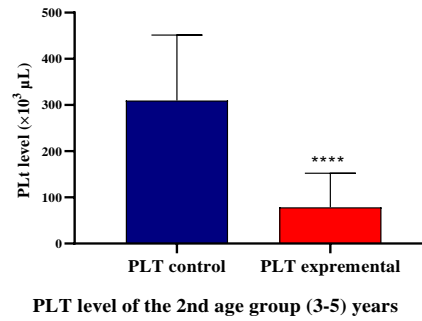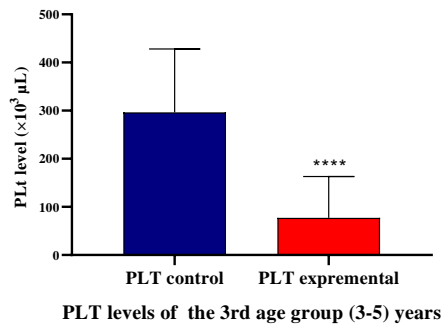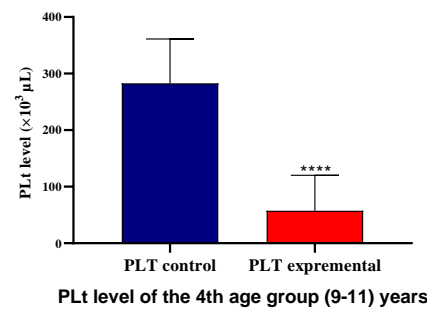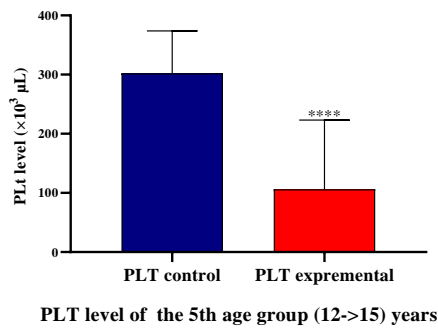
(Figure 3.12). The mean±SD values for haematological properties (PLT) from different samples of and Comparison control group with experimental group

3.5 The analysis of questionnaire data

Through the second chapter of materials and methods, the questionnaire included 30 children with leukemia of both genders who attended the Tripoli Medical Center Oncology Department. The questionnaire focused on risk factors, and the results were as follows:

1. Distribution of patients according to age groups

The results showed that the most age group (4-6) by 33.33% and the lowest rate (13-15) by 6.66%, Table (4.14) shows this.

Table (4.14) Distribution of cases according to age groups

AGE	1-3	4-6	7-9	10-12	13-15
N	5	10	7	6	2
%	16.66%	33.33%	23.33%	20%	6.66%

2. Distribution of patient according to gender

The results showed that the percentage of males in the current study is 70% more than females which was 30%, Table (4.15).

Table (4.15). Distribution of cases according to gender

gender	N	%
Male	21	70%
Female	9	30%

3. Distribution of patients according to ABO/Rh

The results of the questionnaire showed that the most patients were among (A$^+$) by 66.6%, then followed (O$^+$) by 20%, then (B$^+$) and (O$^-$) by an equal rate of 6.66%, Table (4.16).

Table (4.16). Distribution of patient according to blood group

Blood group	N	%
A$^+$	20	66.60%
B$^+$	2	6.66%
O$^-$	2	6.66%
O$^+$	6	20.0%

4. Distribution of cases according to skin color

The results of the different skin color were that by 73.33% regular, 20% white and 6.66% brown, Table (4.17).

Table (4.17). Distribution of patients according to skin color

Skin color	N	%
Brawn	2	6.66%
Normal	22	73.33%
White	6	20.0%

5. Distribution of patients according to type of injury

The cases were also distributed according to the type of infection, and most of them were infected with the type of acute leukemia(ALL) by 80% Table (4. 18)

Table (4.18). Distribution of patients according to type of injury

Type of injury	N	%
ALL	24	80%
Histiocytosis	1	3.30%
JCML	1	3.30%
Sarcoma	2	6.66%
Allergy	1	3.30%
Acute anemia	1	3.30%

6. Distribution of patients according to another question

The questionnaire questions were various about the disease and the family history of the disease, treatment, etc., and all this is shown in the table (4.19).

Table (4.19) Distribution of patients according to another question

Did he perform operations in the past	N	%
YES	4	13.33%
NO	26	86.66
Was a marrow cultivated before?		
YES	0	0%
NO	30	100%
The patient's condition is currently		
Healing	5	16.66%
Under treatment	25	83.33%
Do you have any of the family with the same disease		
YES	14	46.66%
NO	16	53.33%
Is it previously presented to radiation		
YES	2	6.66%
NO	28	93.33%
Have you been treated with chemotherapy in the past?		
YES	2	6.67%
NO	28	93.33%
Have you been treated now with chemotherapy?		
YES	23	76.66%
NO	7	23.33%
Have you been treated with radiotherapy?		
YES	1	3.33%
NO	29	96.66%
Have the vaccinations were taken at the time from birth		
YES	28	93.33%
NO	2	6.66%
family members		
1	6	20%
2	8	26.66%

3	4	13.33%
4	9	30%
5	3	10%

His arrangement in the family

1th	13	43.33%
2th	4	13.33%
3th	9	30%
4th	4	13.33%

Chapter IV

Discussion

4.Discussion

4.1 Presenting the results of cases of blood leukemia in children, depending on age, gender and type of disease

One of the most common types of cancer in children is leukemia, which represents 25-30 % of all types of cancer in children and adolescents (National Cancer Institute 2018).

In the current study, most male cases (61.25%) were, while the female rate was 38.75%, This conclusion is similar to those mentioned in other environments in the world where leukemia in children is more common in boys than girls (Atlanta 2018, National Cancer Institute 2018, Al-Shamahy *et al*. 2021).

acute lymphocytic leukemia(ALL) was the most common, accounting for (92.50%) of the total, and acute myeloid leukemia (AML) was few accounting for (7.50%) of the total. and this is consistent with findings from Atlanta: American Cancer Society (2016) and Shamahy *et al* (2021).

In the current study, ALL was prevalent in the age group 9 - 11 years (27.50%) then age group 6- 8 years (24.37%), This does not comply with Shamahy *et al* (2021). Everything was prevalent in the 1-5 years of age (53.5 %). acute myeloid leukemia (AML) was high in the age group 6-8 years (4.37%) and this differs from that reported elsewhere in the world where AML is most commonly diagnosed in children who are under one year (Belson *et al* 2007).

4.2 The results of the leukemia cases in children, according to the data of the blood group

The children with leukemia, most of them have a blood group (A) (55%) of the total of the injured, followed by the blood group (O) (30%) of the total of the injured, and the blood group (B) ranked third with a percent (12.5%) as well as the lowest blood group (AB) by (2.5 %) for most age groups. This is compatible with a study by Tavasolian *et al* That the blood group (A) had the highest percentage of cases. They were there in some other studies, which were the result of blood group (O) the highest percentage followed blood group (A) (Hama *et al*. 2022; Sakić2012; Alavi *et al*.2006). It has been observed through the data that the blood type (A) was the highest percentage among other factions of the father and the mother, followed by the type (O). This may correspond to the percentage of children with leukemia from (A) and (O).

The Rh+ blood group had more frequency than the Rh- blood group in all blood groups. Therefore, children with blood groups A+ and O+ show a higher potential for developing different types of blood cancers. This is compatible with) Zand *et al* 2010)".

4.3 Hematological and Serum Biochemical Parameters

The rates of AML patients presenting with hyper leukocytosis, commonly defined as a white blood cell (WBC) count greater than 100,000/_L and independently associated with adverse outcomes, vary among available studies and range from 8–12% in randomized clinical trials to 9–18% in a

previous study (Feng *et al*. 2019). The development of leukostasis in AML has been attributed to a disruption in microcirculation due to increased blood viscosity and reduced deformability of myeloid blasts compared to both lymphoid blasts and mature myeloid cells. However, clinical manifestations of leukostasis can already occur with lower WBC counts (Röllig and Ehninger, 2015). The current study aligns with the above findings, as our results indicated a significant increase in white blood cells, especially in the first and second age groups.

Hemoglobin deficiency, indicating low hemoglobin compared to the normal rate, leads to anemia. Since hemoglobin is the main ingredient in the blood, its lack means suffering from anemia. Low hfr m,emoglobin levels can be caused by various cancers, including leukemia, Hodgkin's lymphoma, and multiple myeloma. These types of cancers can cause anemia by destroying or preventing the production of healthy red blood cells.

The results of this study show a significant decrease in Hb in the experimental group compared with the control group in age periods (3-5), (6-8), and (12-15) from cases of injury. This is compatible with a study (Kakaje *et al*., 2020).

Leukemia can decrease a person's platelet count to less than 150,000 per micL. Experts consider this a low platelet count, regardless of age or gender. Blood tests, such as a CBC. The results of this study show a significant decrease in PLT in the experimental group compared with the control group in all age periods from cases of injury. This is compatible with a study by (Dai *et al*, 2021).

4.4 Analysis of Data from the Study's Patient Records

In confirmation of the study results, specifically the risk factors, the results of the questionnaire that we carried out on 30 children with leukemia supported this study. Analysis of patient data indicated that this type (ALL) is the most infected, and most cases in males were more than females, as well as the blood group for the injured (A+), was the most subsequent percentage, then (O+). This corresponds to our studies and previous research.

Cancer treatments, including radiotherapy and chemotherapy, can cause several skin problems. Common changes in the skin include redness, rash, dryness, peeling, and itching. The color of the skin may change and become lighter or darker in certain places. It is also common for cancer patients to have ulcers or cracks in the skin. The results of the study were 73.33% of the answers that the skin color is normal. The absence of skin alterations in the study sample is an indication of the good quality of types of treatments for leukemia. It may also be the reason that most of the study cases are recent from chemotherapy and radiation therapy, and it is possible that if the duration of treatment is extended, the expected skin changes may appear. Our results with Sani reported that from 15 to 22% of leukemia patients suffer from skin problems as a result of radiotherapy and chemotherapy (Saini, 2020).

The current study supports family history as an important risk factor for the disease, where 46.66% had relatives with dysfunctional types of cancer, as explained by (Rudant *et al*,.2007). A family history of cancer was associated with an increased risk of HL. The ORs were higher when at least 2 relatives

had a history of cancer or when 1 case occurred before age 46 years. Only HL was significantly associated with a family history of hematopoietic malignancies, mainly because of a significant association with a history of HL.

Conclusion

- The study findings support the hypothesis of familial susceptibility to childhood leukemia but do not suggest familial susceptibility to childhood.

- Leukemia-related anemia is evident, with a significant hemoglobin decrease in specific age periods, and platelet count reduction across all age groups.

- Skin alterations due to treatments are uncommon, indicating the efficacy of good quality leukemia treatments. Extended treatment may lead to skin changes.

Contribution

he study provides important insights into pediatric leukemia in Libya, covering prevalence, demographic s, blood group associations, and hematological parameters. Emphasizing the significance of family history as a risk factor, these findings contribute to refining treatment strategies and preventive measures.

Future work

1.   There is limited research on childhood leukemia in Libya. Additional studies are imperative to enhance our understanding of the disease.

2.   Conducting future investigations in other geographical and environmental settings will provide a comprehensive understanding of the disease's prevalence and characteristics.

3.   The connection between blood composition and leukemia remains ambiguous. Further research is needed to elucidate this relationship.

4.   Environmental factors and pollutants, including factories, stature, and oil refineries, might contribute to the onset of the disease. Therefore, in-depth research on these aspects is warranted.

5.   Explore other areas of research, including mortality rates, treatment modalities, and recovery rates, to obtain a holistic view of the disease."

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جامعة الزاوية

كلية العلوم

قسم الأحياء ـ علم الحيوان

العلاقة بين عامل **ABO / Rhesus** ، وسرطان الدم الليمفاوي الحاد لدى الأطفال الذين يعانون من سرطان الدم المترددين على مستشفى طرابلس الطبي

رسالة مقدمة لجامعة الزاوية لنيل درجة الماجستير من قبل:

هبة عبد المنعم العروسي

اشراف الدكتور :

فكري أبو شوفة

2024