University of Kerbala

A Study of Bacteremia in Patients with Acute Leukemia

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيم

يُطَافُ عَلَيْهِمْ بِكَأْسٍ مِنْ مَعِينٍ (٤٥) بَيْضَاءَ لَذَّةٍ لِلشَّارِبِينَ (٤٦) لَا فِيهَا غَوْلٌ وَلَا هُمْ عَنْهَا يُنْزَفُونَ (٤٧)

صدق الله العلي العظيم

سورة الصافات الآيات (٤٥–٤٧)

Dedication

I would like to dedicate this thesis to

My supervisor, Dr. Alaa, who was my support and a candle that lit my way in this life and taught me the meaning of being cultured, virtuous and generous and how to obtain God's approval and love by helping people

My family who has supported me a lot at this point. Especially my grandfather and my father, may God have mercy on them, they were and will continue to motivate me to reach the highest ranks of knowledge, as for my mother, any achievement I do is only in order to see the sparkle of pride and play in her eyes after years of fatigue and effort in leaving my father

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Nabaa

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I would like to thank all of my friends, family and relatives who helped me.

Nabaa

Supervisor certification

We certify that this entitle thesis (**A Study of Bacteremia in Patients with Acute Leukemia**) was prepared under my supervision at the department of Clinical Laboratories, at the College of Applied Medical Sciences, University of Kerbala, as a partial requirements for the degree of Master in Clinical Laboratories.

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We are members of the discussion committee certify that we read this thesis entitled **'' A study of Bacteremia in Patients with Acute Leukemia** " and we discussed Mr. student **Nabaa Azhar Abdulmuttaleb Abdulhussein** in its contents. It is adequate for the award of the certification of Master of Clinical Laboratories with **excellent** grade.

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11 / 8 / 2022

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List of Abbreviations

Abbreviations	Items
4AAP	4- Amino antipyrine
ABEI	N-(4-aminobuty)-N-ethylisoluminol
Ags	Antigens
AIDS	Acquired Immunodeficiency syndrome
AKI	Acute kidney injury
AL	Acute leukemia
ALAT	Alanine aminotransferase
ALD	Acute liver damage
ALL	Acute lymphoblastic leukemia
ALL-L1:	small uniform cells

ALL-L2:	large varied cells.
ALL-L3:	large varied cells with vacuoles (bubble-like features)
Allo	Allogeneic
ALP	Alkaline Phosphatase
ALT	Aspartate aminotransferase
ALT/ULN	Alanine aminotransferase / Upper Limits of normal
AML	Acute myeloid leukemia
Ampc	Ampicillin β- Lactamase
AMR	Antimicrobial resistance
APACHE	Acute physiology and chronic health evaluation
APL	Acute promyelocytic leukemia
aPTT	Activated partial thromboplastin
ARDS	Acute respiratory distress syndrome
ART	Interrupting Antiretroviral therapy
AST	Alanine aminotransferase
AST	Antibiotics susceptibility test
ATL	Adult T-cell leukemia/ lymphoma
ATRA	Alletrans retinoic acid
AUC	Area under the curve
AYAs	Adolescents and young adults
B-ALL	B- cell Acute lymphoblasticLeukemia
BBFs	Bacterial biofilms
BCG	Bromocresol green
BMI	Body mass index
BNP	Brain natriuretic peptide
BSI	Blood stream infections
CAR	C-reactive protein to albumin ratio
CCL3	C-C Motif chemokine ligand 3
CE	Cholesterol esterase
CHE	Cholesterol esterase
CHO	Cholesterol oxidase
CO	Cholesterol oxidase
CPE	Carbapenems-producing Enterobacteriaceae
CR	Complete remission
CR	Carbapenem resistant
Cr	Creatinine
CRE	Carbapenem-resistant Enterobacteriaceae
CRP	c- reactive protein
CR-PA-BSI	Carbapenem resistant- pseudomonas aeruginosa blood stream infection

CTC	Common toxicity criteria
CVC	Central venous catheter
CXCL12	C-X-C Motif chemokine 12
Cysc	Serum cystatin C
D-D	D-Dimer
DIC	Disseminated intravascular coagulation
DOMSO	Dimethyl sulfoxide
DsBMT	N,N-bis(4- sulphodutyl) m- toluidine disodium
EDTA	Ethylene diamine tetra acetic acid
EMFs	Electromagnetic field
ESBL	Extensive -spectrum beta- lactamase
ESR	Erythrocyte sedimentation rate
ETP	T-cell precursor
EUH208	Contain (name of sensitivity substance)
EUH210	Safety a sheet a available request
FAB	French, American ,and British
FDP	Fibrin degradation product
FISH	Fluorescence in situ hybridization
GGT	Gamma-glutamyl transferase
ɣ-GT	Gamma-glutamyl transferase
GGT/ULN	Gamma-glutamyl transferase/ Upper Limits of normal
GK	Glucokinase
GLU	Glucose
GM-CSF	Granulocyte – macrophage colony- stimulating
GN	Gram negative
GNRs	Gram negative rods
GO	Gemtuzumab ozogamcin
GOD	Glucose oxidase
GP	Gram positive
GPCs	Gram positive cocci
GPO	Glycerol-3- phosphate oxidase
H2O2	Hydrogen peroxidase
HB	Hemoglobin
HBV	Hepatitis B virus
HDL	High density lipoprotein
HEDTA	Hydroxy ethylene di aminetriacetic
HIV	Humman Immunodeficiency virus
HM	Hematological malignancies
hs-CRP	High sensitivity C-reactive protein
HSCT	Hematopoietic stem cell transplant

ICH	Intracranial hemorrhage
ICU	Intensive care units
IDSA	Infectious disease society America
IFCC	International federation of clinical chemistry
IFN-α	Interferon – α
IL-1	Interleukin – 1
IL-6	Interleukin 6
KPC	Klebsiella pneumonia carbapenemase
LAC	Lupus anticoagulant
LDH	Lactate Dehydrogenase
LDL	Low density lipoprotein
LPa	Lipoprotein A
LPL	Lipoprotein lipase
M/F	Male/Female
M0:	Myeloblastic without differentiation
M1:	Myeloblastic with little or no maturation
M2:	Myeloblastic with maturation
M3:	Promyelocytic
M4:	Myelomonocytic
M4e**o:**	Myelomonocytic with eosinophils
M5a	Monocytic without differentiation (monoblastic)
M5b:	Monocytic with differentiation
M6:	Erythroleukemic
M7:	Megakaryocytic
MCV	Mean-corpuscular volum
MD	Moldova
MDH	Malate dehydrogenase
MDR	Multi drugs resistant
MDR-PA-BSI	Multidrug resistance -pseudomonas aeruginosa blood stream infection
MDS	Myelodysplastic syndrome
MIC	Minimum inhibitory concentration
MIF	Migration inhibitory factor
MOD	Multiple organ dysfunction
MPL	Mixed phenotype acute leukemia
MRSA	Methicithin- resistant staphylococcus aureus
MTT	Tetrasodium salt
NAD	Nicotinamide adenine dinucleotide
NADH	nicotinamide adenine dinucleotide (NAD) + hydrogen (H)
NCI	National cancer Institute

NE	Neutrophil
ODCAL	Optical density of calibration
ODH2O	Optical density of water
OPG	Osteoprotegerin
OS	Overall survival
PCT	Procalcitonin
PEG-ASP	Pegasparaginas
PH	Philadelphia
PLT	Platelets
PMS	Phosphate solution
POD	Peroxidase
PT	Prothrombin time
RhD	Rhesus D
RLUs	Relative light units
SA	Serum Albumin
SALI	Sepsis associated liver damage
SEER	The surveillance , epidemiology , and end results
SIRS	Systemic inflammatory response syndrome
SOFA	Sepsis relative organ failure
T-ALL	T- cell Acute Lymphoblastic Leukemia
TBIL	Total bilirubin
TC	Total cholesterol
TCP	Thrombocytopenia
TG	Triglyceride
TNAP	Tissue – non specific ALP
TNF	Tumor necrosis factor
TSB	Total serum bilirubin
UK	United kingdom
ULN	Upper Limits of normal
US	United state
USA	United state America
VLDL	Very low density lipoprotein
VOD	Veno-occulasive disease
VRE	Vancomycin-resistant enterococcus
VTE	Symptomatic venous thromboembolism
WBC	White blood cells
WHO	World health organization

Summary

The term leukemia is derived from the Greek words “leukos” and “heima,” which refer to excess white blood cells (WBC) in the body. Leukemia, once considered a single disease, was first recognized around the 4th century. By the end of the 19th century, leukemia was classified into four subtypes: acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), chronic myeloid leukemia, and chronic lymphocytic leukemia. Currently, the diagnosis of leukemia is known to be comprised of a variety of hematopoietic neoplasms that are both complex and unique. Each subtype can be further distinguished by morphologic differences, cytogenetic abnormalities, immunophenotype, and clinical features. These distinguishing characteristics affect both prognosis and selection of optimal treatment.

Patients with acute leukemia are highly susceptible to infectious diseases due to factors related to the disease itself, factors attributed to treatment, and specific individual risk factors in each patient. Patients with chemotherapy-induced neutropenia are at particularly high risk, and microbiological agents include viral, bacterial, and fungal agents. The etiology is often unknown in infectious complications, although adequate patient evaluation and sampling have diagnostic, prognostic and treatment-related consequences. Bacterial infections include a wide range of potential microbes, both Gram-negative and Gram-positive species.

The aims of the study are to identify the most common bacterial species in blood stream bacteremia patients with acute leukemia , study antibiotic susceptibility pattern of their bacteria .

The research was carried out between October 2021 and May 2022. In the Imam Hussein center for oncology and hematology / Karbala health directorate. A case control study was performed on 104 acute leukemia patients ,48 ALL , 56

AML, 16 with bacterial infection ,88 without bacterial infection and 50 healthy. A ten-milliliter sample of venous blood was obtained from patients and AHC group . There are subjected to laboratory tests : blood culturing procedures that we must follow, and several analysis have been performed as a result, including Liver function tests (AST, ALT, ALP, GGT, Albumin, TSB, DB, TP and LDH), General parameters (Age, Gender), Physiological Parameters (ABO), Immunological and Serological parameters (WBC,CRP and IL-6), Hematological parameters (D-Dimer ,PLT and), Microbiological examinations (Bacterial Identification and Antibiotics Susceptibility Tests).

The results were AST(35.530) U/l , ALT(40.656) U/l, ALP(92.738) U/l, GGT(71.109) U/l, Albumin(42.069) g/l, TSB(0.503) mg/dl, DB(0.177) mg/dl, TP(67.914) g/l, LDH(712.098) U/l, WBC(12.350) 10^3/ µl, CRP (45.031) mg/l,IL-6(36.498) pg/Ml, D-Dimer(1586.492) ng/ml, PLT(132.826) µl .

In acute leukemia with bacterial infection, the most common blood group was O. *Staphylococcus hemolyticus* was the most prevalent bacterial cause of infection in acute leukemia patients, and most of the Gram-positive bacterial isolates were resistant to cephalexin, kanamycin, amikacin, cefdinir, clarithromycin, cefepime, ceflaxin, azithromycin and amikacin , while Gram-negative bacteria were resistant to all types of antibiotics.

In acute leukemia without bacterial infection there were some correlation between some parameters CRP and IL-6 Also, between GGT and LDH, as well as a positive correlation (0.612 and 0.669), respectively. Also there were correlation in ALT and AST , IL-6 and Direct bilirubin, It was also a positive correlation (0.766 and 0.670), respectively. Albumin and total protein had a positive correlation (0.698) with a significance correlation at (0.01). There was a significant link between albumin and direct bilirubin (0.05) at the same time, as it was

negatively correlated (-0.514). There was also a negative correlation between Albumin and Age, CRP, and IL-6 (-0.545, -0.566, and -0.575), respectively.

There were some differences in correlation values in acute leukemia with bacterial infection, such as between age and WBC, as it was positive correlation (0.639). And between IL6 and Age, Also, between Age and WBC as it were positive correlation (0.529, 0.767), respectively. Also there were correlation in CRP and D-Dimer, as it was positive (0.634). There was correlation between AST , WBC , IL6 and D-Dimer, As a result, there was a positive correlation (0.910, 0.718, 0.566), respectively . There was a positive correlation between GGT and ALT (0.540). Correlation also had been seen Albumin and PLT, as there was positive correlation (0.644). Also there were correlation between Direct bilirubin and D-Dimer , PLT and ALT, as there were positive, inverse, and positive connection (0.630, -0.689, and 0.537), respectively . While there was a negative association between Total Protein and IL6, and positive correlation between Total protein and PLT , Albumin , as there was inverse and positive correlation (-0.697, 0.789, and 0.864) , respectively. There was correlation between LDH and WBC, IL6, D-Dimer, and AST, as there were positive correlation (0.834, 0.618, 0.726, and 0.957), respectively.

The study conclusions that *Staphylococcus hemolyticus* was the most common bacterial species that causes bacteremia in patients with acute leukemia, most gram positive and all gram negative resistance of all antibiotics.

Chapter One
Introduction

Chapter One : Introduction

1.1. Introduction

Leukemia is a complex collection of hematological cancers that is divided into various subgroups, each with its own biological characteristics. It is a hematological clonal neoplasm caused by a variety of causes that cause somatic mutations in pluripotent stem cells and progenitor cells. In that it can self-replicate, differentiate, and feed progenitor cells into the multiple hematopoietic lineages, mutated neoplastic cells function like hematopoietic stem cells. These leukemic unipotent stem cells can mature to phenocopies of mature blood cells to variable degrees. The cause of leukemia is yet unknown. However, various variables have been linked to the development of leukemia, including hereditary inheritance, genetic mutations, epigenetic lesions, ionizing radiation, chemical and other occupational exposures, therapeutic medications, smoking, and some viral agents (Kassahun *et al*., 2020) .

The most common types of acute leukemia (AL) are acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) , (ALL) is most common in children, while (AML) can occur in children and youngsters but mainly affects adults(Mahaja *et al*., 2014). Mixed phenotype acute leukemia (MPAL) is a small heterogeneous group of ALs with blasts displaying markers from several developmental lineages. MPAL represents for 2-5 % of all AL cases, depending on the diagnostic criteria utilized and the age distribution of the patients (Cernan *et al*., 2017) .The most frequent cancer in children is acute lymphoblastic leukemia (ALL), clinically and morphologically, it is diverse. It is morphologically divided into L-1, L-2, and L-3 sub-types using FAB (French, American, and British) criteria. Acute Myeloid Leukemia (AML) is a category of hematological cancers that develop in myeloid, monocyte, erythroid, and megakaryotic cell lineages in

the bone marrow. Acute Myeloid Leukemia is classified as M-0 to M-7 subtypes using the FAB classification system (Gupta *et al*., 2019) .

In 2018, it is estimated there were a total of 437 thousand new cases and 309 thousand cancer deaths from leukemia worldwide(Dong *et al.*, 2020). Risk factors with conclusive evidence for ALL include congenital genetic disorders such as Down syndrome, neurofibromatosis, Fanconi anemia and Bloom syndrome. Ionizing radiation (from sources such as diagnostic imaging or atomic bomb) is the only confirmed and generally accepted environmental risk factor (Van Maele-Fabry *et al*., 2019) .

The risk for developing AML in the majority of cases is biological rather than environmental, with the only established pediatric AML cause being in utero exposure to ionizing radiation . Other exposures, e.g. maternal chemical exposure and parental age, have only limited evidence supporting their association with AML (An *et al*., 2017).

Certain studies revealed that , the most common clinical manifestations of leukemia were weakness and lethargy, fever, cervical lymphadenopathy, bleeding, abdominal pain, and cold, with anemia, reduced white blood cell and platelet counts in circulation, abdominal cramps, and lymph nodes being the main causes of these symptoms. Leukemia usually strikes suddenly and without warning. Clinical signs are typically nonspecific and develop into a disease over time. Parents will specifically state that their child has been in good health (Madmoli, 2018).

Blood stream infections (BSI) are common in individuals with haematological malignancies, with rates ranging from 11% to 38%. Crude mortality rates range from 12 to 42 percent, with some studies reporting attributable death rates as high as 30 percent. Acute leukemia patients who have been diagnosed with AL go through a process of continual chemotherapy rounds

and significant extended neutropenia. Furthermore, the gastrointestinal mucosa's integrity is altered, and indwelling intravascular catheters are commonly used, making these individuals a high-risk group for blood stream infection (Garcia-Vidal *et al*., 2018) .

Bacteria are responsible for the great majority of blood stream infections. In the past, *Staphylococcus aureus* was the most common cause of leukemia-related infections that resulted in death. In 1960s and 1970s, *Escherichia coli* , *Klebsiella spp*., and *pseudomonas aeruginosa* dominated gram-negative bacteremia following the widespread use of β-lactam antibiotics (Kjellander, 2016). In a neutropenic patient, fever may be the only evidence of a blood stream infection , with the normal focused symptoms and indications being decreased by the lack of efficient innate immunity. When gram-negative organisms are implicated, the fatality rate from septic shock and multi-organ failure can be as high as 40%. Feverish neutropenia due to delays in chemotherapy delivery and dose changes, it has a major influence on morbidity and an indirect effect on death. Overall, broad-spectrum antibiotics are suggested for new febrile neutropenic presentations, and the importance of knowing the patient's risk of infection with resistant organisms when designing initial therapy and escalation techniques is confirmed (Conn *et al*., 2017).

There has been a worldwide surge in multidrug resistant (MDR) strains, and several initiatives have attempted to raise public awareness about the fact that there are bacteria for which there are few or no active medications. The acronym ESKAPE (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter* spp.) summarizes the most threatening pathogens circulating today (Gustinetti and Mikulska, 2016) .

Aim of The Study:

1. Identify the most common bacterial species in blood stream bacteremia patients with acute leukemia .
2. Study antibiotic susceptibility pattern of their bacteria .
3. Conducted the clinical and laboratory tests that include: Immunological and Serological parameters (white blood cells (WBC), , C- reactive protein (CRP), proinflammatory cytokine Interleukin – 6 (IL-6)), Hematological parameters (Platelets (PLT), D-Dimer (D-D), ,Biochemical parameters (alanine transaminase (ALT) ,aspartate aminotransferase (AST),alkaline phosphatase (ALP) , gamma- glutamyl transferase (GGT) , Albumin, Total bilirubin, Direct bilirubin, lactate dehydrogenase (LDH) .

Chapter Two
Literatures Review

2.1. Literatures Review

2.1.1. Acute leukemia

2.1.1.1. An overview of acute leukemia disease

Acute leukemia is a kind of blood cancer in which immature progenitor cells in the bone marrow clonally grow. If left untreated, this infiltration leads to severe thrombocytopenia, anemia, and leukopenia, which can lead to death in a matter of weeks (Hansen *et al.*, 2020) . Acute leukemia encompasses a vast number of different types of leukemia, making practical classification difficult. However, morphologic features, genetic anomalies, hypothesized etiology, cell of origin, immunophenotypic traits, and clinical characteristics can all be used to classify it. Depending on the origin of the blast cell, acute leukemia can be divided into two types:

1. Acute myeloid leukemia (AML)
2. Acute lymphoblastic leukemia (ALL) (Mohapatra et al., 2014).

Almost all patients with ALL and AML failing to achieve initial remission die of leukemia or its treatment, usually within 6 months. Recently, bone marrow transplants from HLA-identical siblings have been used to treat patients *(Biggs et al.,* 1992) . Therapy for leukemia improves overall survival in older acute myeloid leukemia patients. Based on their comorbidities, most patients up to 80 years of age should be considered for treatment. New therapies including hypomethylating agents and allogeneic hematopoietic cell transplantation are promising and must be compared with other chemotherapy regimens (Oran and *Weisdorf*, 2012) .

2.1.1.1.1. Acute myeloid leukemia (AML)

Acute myeloid leukemia (AML) is a type of leukemia that affects clonal proliferation and differentiation of myeloid progenitor cells, which lose their ability to differentiate and respond to regular proliferation regulators. In the absence of treatment, this loss results in deadly infection, hemorrhage, or organ

invasion within a year of diagnosis. Patients less than 60 years old are treated with cytotoxic "chemotherapy," which can cure 20–75 % of patients depending on leukemia-cell cytogenetics. Chemotherapy, on the other hand, only achieves this result in around 10% of senior patients due to their incapacity to withstand treatment and, more importantly, the correlation of old age with cytogenetic anomalies involving chromosomes 5 and 7 (Estey and Döhner, 2006) .

The age-adjusted incidence of AML in the United States is 4.3 per 100,000 per year (US). The incidence increases with age in the United States, with a median age of 68 years at the time of diagnosis AML has a number of causes. Some patients have had prior exposure to DNA-damaging chemicals, whether pharmacological, occupational, or environmental, which has been linked to AML, although the majority of cases are still unsolved. The most frequent kind of acute leukemia is adult , which has the lowest 5-year survival rate (24 %) (Shallis *et al.*, 2019) .

The prevalence of AML increases with age, rising from 1.3 cases per 100,000 in people under 65 to 12.2 cases per 100,000 in those over 65. Although advances in AML treatment have improved outcomes for younger patients, the elderly, who account for the majority of new cases, have a poor prognosis, is still bad. Even with current treatments, up to 70% of individuals aged 65 and up will succumb to their condition within a year after diagnosis (De Kouchkovsky and Abdul-Hay, 2016) .

In the leukemic blasts of about 55 % of people with AML, non-random clonal chromosome abnormalities (balanced translocations, inversions, deletions, monosomies, and trisomies) can be found. These chromosomal alterations have helped to classify the disease, and they have previously been identified as the most important prognostic predictor for complete remission, relapse risk, and overall survival (Döhner and Döhner, 2008) .

The most common reason for an allogeneic hematopoietic cell transplant is acute myeloid leukemia. The number of transplant candidates has increased as a result of reduced-intensity conditioning, making transplantation a viable option for those in their later years who are more commonly affected. For persons with intermediate or high-risk acute myeloid leukemia, reduced-intensity conditioning allogeneic transplantation is now the standard of therapy, and it's becoming more popular among the elderly and those with medical problems. Despite the fact that it cures a substantial number of patients, post-transplant recurrence is still an issue in the low-intensity conditioning setting (Sengsayadeth *et al*., 2015) .

2.1.1.1.2. Acute lymphoblastic leukemia (ALL)

Acute lymphoblastic leukemia (ALL) is a type of cancer that affects the T and B cells . According to the French-American-British (FAB) Cooperative Group classification system, ALL is an aggressive neoplasm defined by the presence of more than 30% lymphoblasts in the bone marrow or peripheral blood. Despite the fact that most ALLs have a hypercellular marrow that is predominantly made up of lymphoblasts, a blast count of more than 20% is enough to diagnose acute leukemia in the World Health Organization's (WHO) Classification of Neoplastic Diseases of Hematopoietic and Lymphoid Tissues or Lymphomas, which was recently proposed. (Lai et al., 2000)

The first sign of this sickness could be a test of the peripheral blood. Although elevated peripheral blood blast numbers may make the diagnosis of ALL obvious in certain patients While others may have fewer specific symptoms Neutropenia, thrombocytopenia, and normochromic or normocytic anemia with reticulocytopenia are examples of these conditions (Lai *et al*., 2000).

Acute lymphoblastic leukemia (ALL) can afflict both children and adults, however it is most frequent in children aged 2 to 5. A variety of factors, including external and endogenous exposures, genetic predisposition, and chance, are

thought to be responsible for ALL. With risk assessment biologically based aspects of leukemic cells and therapeutic response, therapeutic adjustment based on the pharmacodynamics of the patient and pharmacogenomics, In recent trials, the survival rate of pediatric ALL has climbed to over 90% (Inaba *et al*., 2013).

85% of cases being of B-cell lineage, and 15% T-cell lineage . Recent T-cell acute lymphoblastic leukemia (T-ALL) has a subtype, according to research termed ‘‘early T-cell precursor’’ (ETP) ALL that comprises up to 15% of T-ALL, and is associated with a high risk of treatment failure (Zhang *et al*., 2012) .

ALL has been heralded as a pediatric cancer success story, with recent studies indicating cure rates of over 80%. This was accomplished by optimizing the doses and schedules of long-used chemotherapy medicines. In adult ALL, similar approaches have not had the same level of success; the cure rate is estimated to be between 20% and 40%. Adults have higher-risk characteristics upon diagnosis, which make them more susceptible to chemo-resistance and sickness recurrence after a period of complete remission (CR). Adult ALL treatment with targeted medications has improved survival in a number of subgroups (Jabbour *et al*., 2015).

2.2.2. Causes of Acute leukemia

1. Genetic disorders: Down syndrome ,klinefelter syndrome ,patau syndrome ataxia telangiectasia, shwachman syndrome, kostman syndrome neurofibromatosis , fanconi anemia , li-Fraumeni syndrome.
2. Physical and chemical exposures: Benzene ,Drugs such as pipobroman Pesticides ,cigarette smoking , embalming fluids , herbicides.
3. Radiation exposure: Nontherapeutic, therapeutic radiation.
4. Chemotherapy: Alkylating agents ,Topoisomerase-II inhibitors Anthracyclines ,Taxanes (Deschler and Lübbert, 2006).

2.2.3.Epidemiology

ALL is a more prevalent type of childhood cancer, In which the AML – M3 and ALL – L2 were the most common leukemia subtypes (NASIM et al., 2013).

In the USA, ALL incidence was estimated at 1·57 per 100000 people in 2014, with approximately 5960 new cases diagnosed and 1470 deaths in 2018.1,2 The male to female ratio is about 1·2:1,2 and this disease is more frequently reported in children. Agespecific incidence is highest in children aged 1–4 years, then drops sharply through childhood (5–14 years), adolescence, and young adulthood (15–39 years), reaching the lowest point between 25 years and 45 years.1 Only a small increase in the incidence of this disease is seen after this age range, with around 60% of acute lymphoblastic leukemia diagnosed before the age of 20 years old.1 Outcome has improved considerably over the past four decades, with an increase of 5-year overall survival from 31% in 1975 to nearly 70% in 2009. However, these results hide important disparities; although 5-year overall survival reached 90% in children with acute lymphoblastic leukemia, only 25% of patients older than 50 years old were alive 5 years after diagnosis, highlighting the need for further improvements in treatment for older adult patients (≥40 years) (Malard and Mohty, 2020) .

In 2010, the annual incidence of AML was 3.43 per 100,000 , but it has steadily risen since then, with annual incidence rates regularly exceeding 4.2 per 100,000 per year since 2010. In the Surveillance, Epidemiology, and End Results (SEER) program, AML (including acute promyelocytic leukemia [APL] had an age-adjusted incidence of 4.3 per 100,000 person-years in 2016. The incidence

rates of AML in the United Kingdom (UK), Canada, and Australia are similar to those in the United States when adjusted for age (Shallis *et al*., 2019).

In Iraq, leukemia account >6% of cancer patients, and acute leukemia represents more than 60% of leukemia patients (Mjali et al., 2021).

2.2.4 Risk factors of acute leukemia

A number of probable risk variables (e.g., environmental, genetic, or infectious) have been investigated in epidemiologic studies of acute leukemias in an attempt to determine the disease's origin. Only one environmental risk factor (ionizing radiation) has been found to be significantly linked to either ALL or AML; the rest [e.g., electromagnetic fields (EMFs), cigarette smoking] have been found to be weakly or inconsistently linked to either type of juvenile leukemia (Belson *et al*., 2007).

Smoking, being overweight, and eating a high-fat diet are all risk factors for leukemia. Cigarettes include substances that cause leukemia, such as benzene, and epidemiological studies have found that smokers have a slightly increased risk of leukemia, particularly myeloid leukemia. Exposure to benzene, high-dose ionizing radiation, chemotherapeutic drugs, and electromagnetic fields are all examples of these causes. Benzen is a solvent that has been utilized in the leather, printing, and petrochemical sectors, as well as in the manufacturing of a wide range of agents. Benzene is a carcinogen that can be found in the workplace and in the environment, such as tobacco smoke. For several decades, there has been a link between an excess of leukemia incidence and mortality, particularly in AML. By avoiding these causes, leukemia prevention may be achieved, because only 15% to 20% of leukemia cases can be explained by currently available risk factors (Garcia-Vidal *et al*., 2018). Bleeding and thrombosis are major risk factors for early death in patients with acute leukemia (Rickles *et al*., 2007).

2.2.5 Clinical features of Acute Leukemia

The clinical signs and symptoms of AML are diverse and nonspecific, but they are usually directly attributable to the leukemic infiltration of the bone marrow, with resultant cytopenia. Typically, patients present with signs and symptoms of fatigue, hemorrhage, or infections and fever due to decreases in red cells, platelets, or white cells, respectively. Pallor, fatigue, and dyspnea on exertion are common. Leukemic infiltration of various tissues, including the liver (hepatomegaly), spleen (splenomegaly), skin (leukemia cutis), lymph nodes (lymphadenopathy), bone (bone pain), gingiva, and central nervous system, can produce a variety of other symptoms. An isolated mass of leukemic blasts is usually referred to as a granulocytic sarcoma. Hyperleukocytosis (more than 100,000 white cells per cubic millimeter) can lead to symptoms of leukostasis, such as ocular and cerebrovascular dysfunction or bleeding. There may also be metabolic abnormalities (e.g., hyperuricemia and hypocalcemia), although these are rarely found at presentation (Lowenberg *et al*., 1999) .

2.2.6. The Coagulopathy of Acute Leukemia

Disseminated intravascular coagulolation (DIC) is distinguished by systemic intravascular activation of the coagulation system from various causes that can result in multiorgan failure, thrombosis, and/or excessive bleeding(Wang *et al*., 2020).

In acute leukemias, particularly acute myeloblastic leukemia (AML), bleeding symptoms are common and apparent in the early stages of the disease. Hemostatic diseases involving the consumption of coagulation factors and platelets, as well as thrombocytopenia caused by blast cell invasion of the bone marrow, are common causes of these symptoms. Thrombosis of the major arteries

is uncommon in AML, although it is becoming more common in both children and adults with acute lymphoblastic leukemia (ALL). The risk of serious hemorrhages varies depending on the kind of acute leukemia and the type of treatment used, an according to the FAB classification, APL, the promyelocytic M3 subtype of AML, usually presents with a life-threatening hemorrhagic crisis. Fatal hemorrhages caused by APL-associated coagulopathy were a common cause of induction remission failure before the introduction of alletrans retinoic acid (ATRA) in the care of APL patients (Barbui and Falanga, 2001).

Acute promyelocytic leukemia (APL) is associated with (DIC) , as seen by abnormal coagulation parameters and low platelet counts, and is potentially lethal if not treated promptly. ALL, like non-APL AML subtypes, can cause (DIC). While the morphology of red blood cells in a peripheral blood smear is frequently assessed for schistocytes, a useful morphologic feature that may be present in DIC of induction remission failure, the formal determination of DIC involves evaluation of coagulation parameters such as D-dimer levels, prothrombin time, thrombin time, fibrinogen concentration, and platelet counts (Shahmarvand *et al*., 2017). Coagulation disturbances especially due to DIC are common at presentation in acute leukemias and more often seen with AML than with ALL. It is recommended that routine screening for DIC be done for all leukemia patients at presentation, particularly those diagnosed with AML (Dixit *et al*., 2007).

Major determinants of the pathogenesis of clotting activation in hematologic malignancies include: (1) tumor cell-derived procoagulant, fibrinolytic and proteolytic factors and inflammatory cytokines; (2) cytotoxic therapies; and, (3) infectious complications (Rickles *et al*., 2007).

2.2.7. Pathogenesis

2.2.7.1. Acute myeloid leukemia pathogenesis

The emergence of oncogenic fusion proteins as a result of particular chromosomal translocations is linked to the pathophysiology of acute myeloid leukemia. The transcription factor is usually one of two partners in each fusion protein, whereas the other has a wider range of functions but is often involved in cell survival and apoptosis control. As a result, AML-associated fusion proteins act as abnormal transcriptional regulators, altering myeloid differentiation, determining a stage-specific halt in maturation, and increasing cell survival in a cell-type-specific manner. The recruitment of aberrant co-repressor complexes, changes in chromatin remodeling, and disruption of specific subnuclear compartments are all common causes of erroneous transcriptional network control (Alcalay *et al*., 2001), oxygen free radical levels were noticeably higher in malignant cells than in normal leukocytes(Zhou *et al*., 2013).

2.2.7.2. pathogenesis of acute lymphoblastic leukemia (ALL)

The exact pathogenetic mechanisms in the development of acute lymphoblastic leukemia are unknown. Only some cases are genetic syndromes, such as Down syndrome, Bloom's syndrome, ataxia-telangiectasia, and Nijmegen breakage syndrome(Hajializadeh *et al*.,2018). The *BCR\ABL* gene rearrangement is caused by a chromosomal disorder known as the Philadelphia chromosome (Ph). A constitutively active protein tyrosine kinase is produced by this fusion gene, and it plays an important role in leukemogenesis. This genetic anomaly is found in up to 30% of adult acute lymphoblastic leukemia (ALL), and it is believed to be the most detrimental prognostic factor for ALL patients (Yanada *et al*., 2006*)*.

2.2.8 Diagnosis of acute leukemia

The laboratory examination of individuals suspected of having acute leukemia (AL) is complicated, and it has changed dramatically as advanced laboratory techniques have been implemented. Erroneous transcriptional network

control is frequently caused by the recruitment of aberrant co-repressor complexes, changes in chromatin remodeling, and disruption of specific subnuclear compartments. For a thorough understanding of acute myeloid leukemiamogenesis and the development of disease-specific therapies, it will be necessary to identify and characterize AML fusion proteins regulate both common and particular target genes. Except for the identification of the megakaryocytic lineage in acute megakaryoblastic leukemia, immunophenotyping to identify precursor B-cell from precursor T-cell ALL (T-ALL) was not included, nor were other immunophenotypic markers used. Despite the fact that a few FAB categories were linked to reoccurring chromosomal abnormalities, genetic investigations were not included in the categorization (particularly acute promyelocytic leukemia and acute myelomonocytic leukemia with aberrant eosinophils) (Arber *et al*., 2017).

For particular leukemia detection, techniques such as fluorescence in situ hybridization (FISH), immunophenotyping, cytogenetic analysis, and cytochemistry are used (Mohapatra *et al*., 2010). When blasts account for 30% or more of the nucleated cells in a patient's peripheral blood (PB) sample (Weinkauff *et al.*, 1999). Standard light microscopy morphology and cytochemistry, as well as a comprehensive panel of immunological markers that identify antigens in the membrane or cytoplasm of myeloid and lymphoid cells, can classify most instances of acute leukemia as myeloid or lymphoid. (Matutes *et al*., 1997). Finally, gene expression profiling using DNA microarrays may improve conventional diagnostic and prognostic testing (Gilliland and Tallman, 2002).

2.3. Immunological and Serological parameters of the study

2.3.1. White blood cells (WBC)

The role of white blood cells (leucocytes) is to defend the body against invading pathogens. Leucocytes are far less common than erythrocytes, although their

numbers increase dramatically during an infection. Divided into granulocytes (neutrophils, eosinophils and basophils) and agranulocytes (monocytes and lymphocytes), leucocytes can recognize foreign material and either engulf cells or secrete membrane-disrupting chemicals that can destroy the organism. Lymphocytes play an important role in the immune response to disease, monitoring the internal environment and producing antibodies against pathogens (Ashton, 2007).

2.3.2. C- reactive protein (CRP)

C-reactive protein (CRP) is an acute inflammatory protein that increases up to 1,000-fold at sites of infection or inflammation. CRP is produced as a homopentameric protein, termed native CRP (nCRP), which can irreversibly dissociate at sites of inflammation and infection into five separate monomers, termed monomeric CRP (mCRP). CRP is synthesized primarily in liver hepatocytes but also by smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes (Sproston and Ashworth, 2018).

2.3.3. Interleukin – 6

IL-6 is a 26 kDa secreted protein that consists of 184 amino acids with two N-glycosylation sites and four cysteine residues. It is a pleiotropic cytokine that functions in various biological systems and organs. In the innate immune response, IL-6 is promptly synthesized by myeloid cells, such as macrophages and dendritic cells, upon recognition of sterile or non-sterile pathogens through toll-like receptors (TLRs) at the site of infection or tissue injury. In the adaptive immune response, IL-6 plays a critical role in B cells, inducing plasma-cell differentiation and the ability to produce antibodies, and is also required for proliferation of myeloma cells and the survival of plasmablast cells. IL-6 transgenic mice display plasmacytosis in various immune organs such as the lymph nodes, spleen, and thymus, each of which contain a high percentage of plasma cells, and

these mice also exhibit an increased number of megakaryocytes in bone marrow (Kang *et al*., 2019).

2.4. Hematological parameters of the study

2.4.1. D-Dimer

D-dimer is an indirect marker of fibrinolysis and fibrin turnover; this molecule exhibits unique properties as a biological marker of hemostatic abnormalities as well as an indicator of intravascular thrombosis. D-dimer is a soluble fibrin degradation product that results from the systematic degradation of vascular thrombi through the fibrinolytic mechanism. Because of this, the D-dimer serves as a valuable marker of activation of coagulation and fibrinolysis in a number of clinical scenarios. Most commonly, D-dimer has been extensively investigated for excluding the diagnosis of venous thromboembolism (VTE) and is used routinely for this indication. In addition, D-dimer has been evaluated for determining the optimal duration of anticoagulation in VTE patients, for diagnosing and monitoring disseminated intravascular coagulation, and for monitoring other conditions in which the patient is at high risk of bleeding or thrombosis. Limitations of the assay include D-dimer elevation in a constellation of clinical scenarios (age, pregnancy, and cancer) and lack of clinical standardization (Johnson *et al.*, 2019).

2.4.2. Platelets

Platelets are anucleate cell fragments derived from MK in the bone marrow (BM) and are key players in hemostasis (Brass *et al*., 2016).They are the second most abundant cell in the circulation (150–400 × 10^9/L, (Koenen, 2016).and thus, well situated to rapidly respond to vascular damage and attract leukocytes to sites of injury (Trzeciak-Ryczek *et al*., 2013). It has also become clear that platelets elicit several non-hemostatic immune functions (Eriksson *et al*., 2019).For example, platelets are capable of direct pathogen binding by expressing pathogen-associated molecular pattern (PAMP) receptors and thus mediate anti-infective immunity (Dib

et al., 2020); they can kill pathogens by both encapsulation and anti-microbial peptides .Platelets also contribute to innate immunity to affect adaptive immune responses and they do so by expressing a wide range of functional immune receptors . These receptors enable interactions with immune cells at the vascular endothelium and in the red pulp of the spleen . For example, platelets contain the largest pool of circulating Fc gamma receptor IIA (FcγRIIA) and this allows them to interact with immune complexes and ultimately form platelet-leukocyte aggregates that can immobilize pathogens (Maouia *et al*., 2020).

2.5. Biochemical parameters of the study

2.5.1. Alanine Transaminase (ALT)

Serum alanine aminotransferase (ALT) is a readily available, inexpensive, and routine biochemical assay used in clinical practice (Kim *et al*., 2008). Initially, many concerns were voiced regarding the clinical significance of ALT activity on viral and toxic hepatitis, muscular dystrophy, and other muscular diseases , which might cause a substantial increase in the ALT level (Giannini *et al*., 2005), in a relatively low percentage of the overall population. However, more and more metabolic disorders, such as obesity, hyperlipidemia, and diabetes mellitus (DM) have been observed independently associated with mild-to-moderate ALT elevation . The series of metabolic disorders were referred to metabolic syndrome (MetS) , and featured insulin resistance and obesity. The clinical implication of ALT elevation in representing MetS has caused worldwide concern (Yun *et al*., 2011) , in Western and Eastern countries with the rapidly increasing prevalence of obesity . Currently, ALT measurement is not only widely used in detecting the incidence, development, and prognosis of liver disease with obvious clinical symptoms, but also provides reference on screening the overall health status during health check-ups (Pratt and Kaplan, 2000).

2.5.2. Aspartate Aminotransferase (AST)

Aminotransferases (also called transaminases) are ubiquitous pyridoxal-5'-phosphate-dependent enzymes that catalyze reversible transfer of amino group from amino acids to α-keto acids. These enzymes play a key role in the metabolism of amino acids in all species. Transamination reaction was discovered in muscle tissue in 1937 by Braunstein and Kritzmann . In early 1950s various methods for aminotransferase measurements were developed and indications for diagnostic testing (mostly for liver disease)(McGill, 2016). AST structure is similar across various species. In humans, AST exists as two genetically and immunologically distinct isoenzymes: cytoplasmic AST (cAST or GOT1) and mitochondrial AST (mAST or GOT2) (Panteghini, 1990). Both isoenzymes catalyze the same reaction albeit with different kinetics, share a sequence homology of ~45% and are thought to have evolved from a common ancestral gene (via gene duplication) (Hayashi *et a*l., 1990) . The enzyme consists of two identical dimers where each dimer consists of a large and a small domain (McPhalen *et al.,* 1992). Each monomer of cytoplasmic AST represents a polypeptide chain of 413 amino acid residues with a secondary structure consisting of α-helices and β-strands and a molecular weight of approximately 45 kD (18,19). Each dimer has an identical binding site for pyridoxal5'-phospha (Ndrepepa, 2021).

2.5.3. Alkaline Phosphatase (ALP)

Alkaline phosphatase (ALP; E.C.3.I.3.1.) is an ubiquitous membrane-bound glycoprotein that catalyzes the hydrolysis of phosphate monoesters at basic pH values. Alkaline phosphatase is divided into four isozymes depending upon the site of tissue expression that are Intestinal ALP, Placental ALP, Germ cell ALP and tissue nonspecific alkaline phosphatase or liver/bone/kidney (L/B/K) ALP. The intestinal and placental ALP loci are located near the end of long arm of

chromosome 2 and L/B/K ALP is located near the end of the short arm of chromosome 1. Although ALPs are present in many mammalian tissues and have been studied for the last several years still little is known about them. The bone isoenzyme may be involved in mammalian bone calcification and the intestinal isoenzyme is thought to play a role in the transport of phosphate into epithelial cells of the intestine (Sharma *et al*., 2014).

2.5.4. Gamma – glutamyl Transferases (GGT)

GGT is present in the cell membranes of many tissues, including kidneys, bile duct, pancreas, gallbladder, spleen, heart, brain and seminal vesicles. It consists of two polypeptide chains, a heavy and a light subunit, with the active site in the light subunit. GGT is involved in the transfer of amino acids across the cellular membrane and leukotriene metabolism. It is also involved in glutathione metabolism by transferring the glutamyl moiety, leaving the cysteine product to preserve intracellular homeostasis of oxidative stress (Dominici *et al.*, 2005). GGT can be used in different diagnostic and prognostic algorithms or scores for liver disease . It is one of the most powerful predictors of development of presence of liver disease in patients discovered to have first-time abnormal LFTs (McLernon *et al*., 2014).

2.5.5. Serum Albumin (SA)

Serum albumin is synthesized in the liver. Concentration of serum albumin (SA), a multifunctional circulatory protein, is influenced by several factors, including its synthesis rate, catabolism rate, extravascular distribution, and exogenous loss. Moreover, both nutritional status and systemic inflammation affect the synthesis of SA. Determining SA concentration aids in risk prediction in various clinical

settings. It is of interest to understand the prognostic value of SA in the full spectrum of cardiovascular disease (CVD) in the era of newly developed pharmacological and interventional treatments. Proper interpretation of SA in addition to established risk factors potentially provides a better risk discrimination and thereby presents an option to modify therapeutic strategies accordingly(Chien *et al*., 2017).

3.5.6. Total serum Bilirubin (TSB) and Direct Bilirubin (DB)

Bilirubin is an orange-yellow pigment of bile that results from the degradation of various heme-containing proteins, especially from hemoglobin catabolism. Heme is broken down into biliverdin, which is converted into unconjugated or indirect bilirubin (UCB). UCB is water-insoluble and enters circulation bound to albumin. In the liver, glucuronic acid is added to UCB (conjugation) to render it water-soluble (direct bilirubin); finally, it is either excreted into bile or recirculated back to the bloodstream, where it is filtrated by the kidneys and excreted through urine (Cappellini *et al*., 2017). Elevation of plasma bilirubin levels is a frequent finding both in primary and hospital care. All liver lesions induce a decrease in the hepatocyte cell count, which may cause hyperbilirubinemia . Hyperbilirubinemia can originate from an alteration in any stage of bilirubin metabolism: excess production, impaired liver uptake, conjugation defects, or biliary excretion defects (Fevery, 2008).

2.5.7. Total Protein

The protein concentration of serum is an indicator of the hydration state of the body. Elevated concentrations are found in dehydration and lowered concentrations

are found when edema is present. Prolonged bed rest results in decreased total protein concentration. As a consequence of pathological states, decreased levels of

serum albumin will result in lowered total protein concentrations (Zheng *et al*., 2017).

2.5.8. Lactate Dehydrogenase (LDH)

Lactate dehydrogenase (LDH) is an important enzyme of the anaerobic metabolic pathway. It belongs to the class of oxidoreductases, with an enzyme commission number EC 1.1.1.27. The function of the enzyme is to catalyze the reversible conversion of lactate to pyruvate with the reduction of NAD+ to NADH and vice versa (Siekmann *et al*., 2002). Lactate dehydrogenase is an enzyme that is present in almost all body tissues. Conditions that can cause increased LDH in the blood may include liver disease, anemia, heart attack, bone fractures, muscle trauma, cancers, and infections such as encephalitis, meningitis, encephalitis, and HIV. LDH is also a non-specific marker of tissue turnover, which is a normal metabolic process. Many cancers cause a general increase in LDH levels or an increase in one of its isozymes. Thus it can be a non-specific tumor marker not useful in identifying the type of cancer. Because LDH is non-specific and routine isozyme measurement is usually unavailable in clinical laboratories, LDH measurements provide incomplete information, and alternate assays such as CK for muscle, ALT for liver, troponin for heart diseases, etc. are needed (Farhana and Lappin, 2022)

Additionally, LDH activity is affected by hemolysis of the blood sample. Since red blood cells (RBCs) contain their own LDH protein, hemolysis causes an artifactual increase leading to false-positive high results. Besides, any cellular necrosis can result in increased serum concentration, and its ubiquitous distribution throughout tissues confers a severe handicap to its wider clinical utility as a biomarker (Farhana and Lappin, 2022).

2.6. Blood groups (ABO) and acute leukemia

loss of A, B, and H antigens from the surface of red blood cells has been a recurrent observation in patients with hematologic malignancy, particularly those malignancies in which the myeloid lineage is involved (Bianco *et al*., 2001). This antigen loss might be either a factor predisposing to acute leukemia, an effect secondary to acute leukemia or only an association. Loss of the precursor H antigen with loss of A or B antigens as an indirect consequence, loss of A or B antigens as the primary change, alterations involving both the H and the A or B antigens, acquired abnormalities in red cell membrane morphology, alteration of the blood group gene products, and steric modifications of the enzyme required to convert H substance are among possible mechanisms of malignancy-induced ABO alteration (Salmon *et al*., 1984).

2.7.Bacterial Infections

2.7.1. Bacterial infection associated with acute leukemia

A positive isolate in a blood culture that was coupled with clinical symptoms was characterized as a blood stream infection ,which is a life-threatening consequence of a malignant hematologic condition that can be fatal. To develop a direct basis for blood infections, blood cultures and medication sensitivity tests were performed (Panawala, 2017).

Bacterial infections can be caused by a large variety of microorganisms, both Gram-negative and Gram-positive. *Pseudomonas aeruginosa, methicillin-resistant Staphylococcus aureus (MRSA),* vancomycin-resistant *Enterococcus* (VRE), and even carbapenemase-producing *Enterobacteriaceae* (CPE) are all susceptible to Extensive-spectrum beta-lactamase resistance (ESBL), are all examples of reoccurring problems with antibiotic resistance (Hansen *et al*., 2020).

Sepsis is a life-threatening organ failure caused by a dysregulated host response to infection . The detrimental host response is caused by microbial infiltration of the circulation or the release of microbial products. Sepsis is one of the top 10 causes of death in the United States. The mortality rate of individuals with sepsis is reduced by several fold when infections are delayed in starting or being covered (Kjellander, 2016).

Patients with hematological malignancies who receive chemotherapy or hematopoietic stem cell transplants face a high risk of infection. In hematological malignancy patients, distinguishing infectious from noninfectious episodes is more difficult due to the common symptom of fever. Fever can be induced by a multitude of factors, including pathogen infection, graft-versus-host disease, engraftment syndrome, and thrombotic microangiopathy; as a result, pinpointing the source of the fever is crucial for prompt antibiotic therapy (Ma *et al*., 2020). Gram-negative bacteria were the most common pathogens in acute leukemia patients (Yao *et al.*, 2017).

2.7.2. Clinical features of Bacterial Infections

Fever, chills, hypotension, hypothermia (particularly in the elderly), diaphoresis, nervousness, change in mental status, tachypnea, tachycardia, hyperventilation are all symptoms that occur when the human immune system is challenged with pathogenic organisms in the circulation . Symptoms of a broad immunological response include lower vascular tone and the likelihood of organ damage . Neutrophil leukocytosis, thrombocytopenia, toxic neutrophil granulations, and disseminated intravascular coagulation are all hematologic abnormalities. Other metabolic signs include respiratory alkalosis, renal signs like

acute tubular necrosis, oliguria, or anuria, gastrointestinal signs like upper gastrointestinal bleeding, cholestatic jaundice, increased transaminase levels, or hypoglycemia, and cholestatic jaundice, increased transaminase levels, or hypoglycemia .

A systemic inflammatory response syndrome (SIRS) to a body harm (such as infection, burns, or trauma) that requires the presence of one or more of the following conditions:

1. The onset of a fever or hypothermia
2. Tachycardia
3. Tachypnea
4. Leukopenia or leukocytosis
5. C-reactive protein (CRP) levels are high.
6. Procalcitonin levels in the blood are abnormally high.
7. Changes in mental state
8. Severe edema or a favorable fluid balance
9. Hyperglycemia
10. Arterial hypotension .
11. Organ dysfunction .
12. Hyperlactatemia
13. Mottling or decreased capillary filling (Martinez and Wolk, 2016).

2.7.2.1 Neutropenia

The term "neutropenia" refers to a decrease in the quantity of neutrophils in the blood stream. Acute neutropenia is prevalent, although neutrophil production problems are uncommon. Acute neutropenia is usually well tolerated and returns to normal within a few weeks. Neutropenia that develops it substantially more

harmful as a result of underlying hematologic abnormalities. When neutrophil production is low and consumption is high, acute neutropenia develops over a few days. Reduced neutrophil formation, increased destruction, or severe splenic sequestration create chronic neutropenia, which can persist three months or longer (Boxer, 2012).

Neutropenia is characterized as either an acquired myeloid progenitor cell abnormality, which is less prevalent, or an inherent deficiency produced by insufficient proliferation and maturation of myeloid progenitor cells in the bone marrow, which is rare . Absolute neutrophil levels of fewer than 500/L are considered severe neutropenia, raises the risk of bacterial or fungal infections. The identification of genetic abnormalities influencing neutrophil precursor development, adhesion, and apoptosis has led to the discovery of other severe congenital neutropenia syndromes. There has been progress in understanding cell biology, including membrane structures, secretory vesicles, mitochondrial metabolism, ribosome biogenesis, transcriptional regulation, and cytoskeletal dynamics, as well as the risk of myelodysplasia and acute myeloid leukemia (Boxer, 2012).

According to the Infectious Diseases Society America (IDSA) guidelines, infections in neutropenic patients are classified as high risk (prolonged neutropenia >7 days; neutrophils count ≤ 100/mm3; significant concurrent comorbidity; clinically unstable) or low risk (neutropenia expected to resolve within 7 days; no active medical comorbidity, clinical stability at onset of the febrile episode); most of them are patients with solid tumors receiving conventional therapy). Prophylaxis with levofloxacin during neutropenia has been found to be successful in preventing all infections in high-risk patients (De Rosa *et al*., 2013).

Infection is more common in neutropenic acute leukemia patients and is associated with increased virulence and resistance of gram positive bacteria than in

non-neutropenic acute leukemia patients. In bacterial species associated with neutropenic acute leukemia patients, antibiotic resistance is higher than in non-neutropenic acute leukemia patients. In cases where bacterial growth was found, neutropenic acute leukemia patients had a poorer remission rate than non-neutropenic acute leukemia patients. As a result, the earlier an infection is discovered, the better the prognosis of the disease (Abedelnasser *et al*., 2020).

2.7.3.Causes of bacterial infections

People suffering from hematological cancers blood stream infections were three times more common in Hematological malignancies patients than in those with other malignancies. Granulocytes from patients with acute myeloid leukemia (AML) have quantitative and qualitative abnormalities, making them susceptible to bacterial infection. Acute lymphoblastic leukemia causes qualitative changes in lymphocytes, resulting in hypogammaglobulinemia and a reduction in cell-mediated immunity, making the patients more susceptible to bacterial infections. Chemotherapeutic treatments frequently exacerbate these deficiencies, resulting in long-term neutropenia and disruption of mucosal barriers, increasing the risk of infection .Acute leukemia patients who have disease- or treatment-related immunosuppression are still at risk for life-threatening infections, including infections caused by resistant organisms, antimicrobial-related adverse events, and higher treatment costs, despite advances in antimicrobial therapies and prophylaxis (Logan *et al*., 2020).

2.7.4. Risk Factors of Bacterial Infections

1. **Genetic predisposition**: Variations in important innate or adaptive immune response genes may influence virus susceptibility or outcome.
2. **Hospitalization**: Aplasia is common following severe chemotherapy for AML, and it generally necessitates a lengthy stay in the hospital. It is generally known that bacteria can cause nosocomial illnesses.
3. **Neutropenia:** Neutropenia is still the most important risk factor for both acute leukemia and Myelodysplastic Syndromes (MDS) patients. The involvement of neutrophils in the onset and execution of the acute inflammatory response, as well as the eventual resolution of infection, is well established.
4. **Neutrophil impairment** : Infections may be associated to neutropenia, but more importantly, to qualitative granulocytic abnormalities, especially in MDS patients. Neutrophil dysfunction in MDS patients could be caused by a combination of factors, including differentiation abnormalities in the multipotent stem cell compartment.
5. **Comorbidities and age:** Infectious complications in acute leukemia continue to be a major risk factor as people get older**.**
6. **Application of devices :** In leukemic patients, long-term central venous catheters, short-term central lines, and peripherally inserted central lines are increasingly used for chemotherapy and sample collection. The catheters break down the skin barrier and become colonized with skin and nosocomial flora, allowing pathogens to bypass local defenses and transmit diseases more easily. Gram-positive bacteria are becoming more common as quinolone prophylaxis and chemotherapy regimens improve (e.g. Staphylococcus coagulase positive) (Pagano and Caira, 2012).

2.7.5. Types of bacterial infections

In the United Kingdom, 62 % of BSIs in patients with hematological malignancies (HM) were caused by gram negative strains of *Staphylococcus*, and similar gram negative predominance has been recorded in Northern Europe and the United States. In Italy, Turkey, Egypt, and China, GN isolates were responsible for more than half of the BSIs in HM patients (Lalaoui *et al*., 2020).

In patients with hematological malignancies, *aureus* bacteremia is not uncommon, and such organism was predicted to be responsible for 7% of all bacteraemic episodes in neutropenic patients with cancer in a 10-year research. In this community, *coagulase-negative staphylococci* are regularly detected as skin commensals, and when isolated in blood cultures, they are frequently viewed as a contaminant. These organisms, on the other hand, may be responsible for clinically severe nosocomial bacteremia, particularly in patients with intravascular devices and immunocompromised states. Biofilm generation has a role in pathogenesis in this group of organisms, which is the single most common cause of blood stream and central venous catheter (CVC)-related bloodstream infections. Despite the fact that it is frequently regarded as having a low virulence(Worth and Slavin, 2009), Among patients with gram-positive bacterial BSIs *methicillin-resistant Staphylococcus aureus* (MRSA) BSI was detected, and *methicillin-sensitive S. aureus* BSIs were detected (Muennichow *et al*., 2018).

Gram-negative bacteria, especially *Escherichia coli, Pseudomonas aeruginosa, and Klebsiella* spp., were the most commonly isolated group of bacteria among cancer patients until the 1990s, when a shift to gram-positive bacteria occurred (Kara *et al*., 2015). The bacteria responsible for BSI in patients with neutropenia and hematologic malignancies is *Pseudomonas aeruginosa* (Zhao *et al*., 2020).

2.7.6. Diagnosis of bacterial infections

Microbiological growth in blood cultures is still the gold standard for diagnosing bacteremic infections, which can take up to 48–72 hours depending on the facility, and antibiotic susceptibility tests may be available even later. In complex clinical circumstances with a high risk of misdiagnosis, doctors must assess the existence of bacteremic infections. In most cases, antibacterial medications that are ineffective against pathogenic bacteria are given while waiting for two days to confirm their suspicions, resulting in illness growth and deterioration. Furthermore, excessive or incorrect antimicrobial treatment might raise the risk of adverse effects in patients, as well as increase expenses and promote microbial resistance (Gu *et al*., 2020).

2.7.6.1. Biomarkers of the sepsis diagnosis

CRP levels rise within 24 hours and are higher in practically all cases of inflammation and infection, including low albumin levels, high glucose , procalcitonin , IL-6, and D-Dimer levels, all of which could indicate the presence of blood stream infections . IL-6 and D-Dimer are useful indicators for determining the severity of an illness (Ma *et al.*, 2020). Synthesized in the liver and secreted in response to interleukin 6 , C-reactive protein (CRP) is commonly used to diagnose and follow patients in several infectious scenarios or other systemic inflammatory disorders . CRP was shown to precede the occurrence of fever in patients with BSI . There is some evidence that it may serve as a surrogate marker preceding fever, sepsis and blood-stream infections in immunocompromised patients (Shimony *et al*., 2020).

2.7.6.2. Blood cultures

Blood culture requires relatively large sample volumes, only detects culturable pathogens and reflects a limited range of bacteria in a sample. Furthermore, only 10–30% of febrile neutropenia blood cultures are positive, but 50% of septic shock blood cultures are positive (Gyarmati *et al.,* 2016). However, persistent BSI yields false-negative results, possibly because of antimicrobial therapy, and has not been evaluated for microorganisms other than *S. aureus* (Fernández-Cruz *et al*., 2013). In adults, microbe density in peripheral blood can be as low as 10 germs per milliliter, whereas in children, it can be as high as 100 bacteria per milliliter. In theory, blood cultures have enough sensitivity to detect these small amounts of microorganisms; however, because density varies throughout the course of disease, blood culture diagnostics do not always yield positive results; therefore, in patients with suspected sepsis, culturing sufficient amounts of blood is recommended (Abedelnasser *et al*., 2020).

Blood cultures have a variety of advantages. They've been used in clinical practice for over a century and are well-integrated into clinical workflow and guidelines. Second, semi-automated culture technologies have made microbiological laboratory management much easier, resulting in less time spent doing so. Finally, isolate and identify a variety of bacterial and fungal diseases (Abedelnasser *et al*., 2020).

2.8. Antibiotics susceptibility

2.8.1. Uses of antibiotics

Antibiotics are drugs that destroy or slow bacteria's growth. Antibiotics are one type of antimicrobial, which also includes antiviral, antifungal, and antiparasitic medications. Antibiotics are microorganism-produced or derived compounds (i.e. bugs or germs such as bacteria and fungi). Alexander Fleming

created the first antibiotic in 1928, marking a watershed moment in medical history. Antibiotics are one of the most commonly recommended drugs in today's medicine, and some antibiotics are bactericidal, which means that they kill bacteria. Other antibiotics are 'bacteriostatic,' which means they prevent bacteria from multiplying. Each sort of antibiotic has a varied effect on various microorganisms. An antibiotic, for example, may prevent a bacterium from converting glucose into energy or constructing its cell wall. Instead of replicating, the bacterium dies when this happens. Broad-spectrum antibiotics that can be used to treat a wide range of infections, while others, known as 'narrow-spectrum antibiotics,' are only effective against a few species of bacteria (Bayarski, 2006).

β-Lactam antibiotics, such as penicillin, were first used in clinical practice in the 1940s to after getting FDA approval, treat bacterial illnesses caused by human pathogenic bacteria . Infections such as bacteremia caused by *Streptococcus pneumoniae* were the major cause of death prior to the antibiotic era (El Salabi et al., 2013).

2.8.2. Antibiotics sensitivity

Of the gram- positive organisms identified, vancomycin and linezolid were most frequently associated with susceptibility. In contrast, gram- negative organisms were most frequently susceptible to cefepime, meropenem, and gentamycin. Cefepime and vancomycin were the most commonly used empiric antibiotics overall (Ali *et al.*, 2017).

Pathogen isolation is also required for phenotypic susceptibility testing, which allows clinicians to begin treating patients with targeted antibiotics. On the other hand, blood culture diagnostics has limitations: detection is limited to

infections that can grow in blood cultures. In blood culture medium, *Legionella* spp. and *Bartonella* spp., for example, do not grow well. Furthermore, antimicrobials can stifle growth, making it possible for essential germs to go undetected after starting antimicrobial medication. Most importantly, many practitioners believe that because blood culture diagnosis takes time, data is accessible too late to advise treatment. (Abedelnasser *et al*., 2020).

Using fluoroquinolones to prevent infection during chemotherapy has been studied extensively. Oral ciprofloxacin, norfloxacin, or enoxacin has been shown to lower the risk of gram-negative bacterial septicemia. Gram positive septicemia has been observed to be reduced when fluroquinolones with an extended spectrum against gram positive bacteria, such as levofloxacin, are used, or when an antibiotic effective against gram positive bacteria is added. Though there is concern regarding the formation of drug-resistant germs as a result of the antibiotics' prophylactic (Rahman and Khan, 2009).

Colistin, a long-abandoned antibiotic because of its neurological and renal toxicity, has been reintroduced because of its efficacy against MDR gram-negative bacteria, particularly carbapenemase manufacturers. Indeed, colistin has been found to be beneficial in the treatment of specific bacteremia caused by MDR bacteria in hematological patients when taken alone or in conjunction with other antibiotics (Lalaoui *et al*., 2019).

Vancomycin-resistant Enterococcus faecium (VRE) colonization has major consequences for individuals undergoing induction therapy for acute myelogenous leukemia. Empirical antibiotic regimens that exclude carbapenems and include VRE coverage may be beneficial in reducing the risk of VRE BSI in febrile neutropenic patients with acute myelogenous leukemia (Ford *et al*., 2015).

2.8.3. Antibiotics resistance

Antibiotics are incredibly useful in medicine, but bacteria can develop resistance to them, and these bacteria are microorganisms that are resistant to antibiotics. When bacteria are repeatedly exposed to the same antibiotics, the germs might evolve and become resistant to the treatment (Bayarski, 2006).

Antibiotics are utilized in human treatment and agriculture all over the world. Antibiotics are either unnecessary or doubtful in many circumstances. Antibiotic use has been linked to bacterial resistance, included *Methicillin-resistant Staphylococcus aureus*, *vancomycin-resistant enterococci*, and gram-negative rods such as *Enterobacteriaceae* and *Pseudomonas aeruginosa* are the most frequent resistant bacteria in hospitals. *S. aureus* that is intermediate in vancomycin and resistant to vancomycin has only lately been discovered, posing a new treatment challenge. Penicillin- and macrolide-resistant pneumococci emerged in the community several decades ago and are now found all over the world. Community-acquired methicillin-resistant *S. aureus* has lately become a problem in a number of nations, producing skin infections as well as serious illnesses. Resistance to co-trimoxazole in Escherichia coli has modified the standard of care for urinary tract infections, which are one of the most prevalent reasons for doctor visits (Beović, 2006).

Antimicrobial resistance (AMR) pathogens cause over 2 million infections and over 23 000 deaths each year. AMR kills approximately 25 000 people in Europe Each year. Resistance factors have recently emerged in the United States (carbapenem-resistant *Klebsiella pneumoniae*), India, and other parts of the world (bacteria with the plasmid-mediated *blaNDM-1* gene that confers carbapenem resistance), The global breadth of the problem, as well as the significance of greater global surveillance (*Escherichia coli* with the plasmid-mediated mcr-1 gene

that confers colistin resistance, originally reported in China), are highlighted. Culture is still used significantly in antimicrobial susceptibility testing. As a result, broad-spectrum antibiotic therapy is frequently started before this essential information is discovered (Marston *et al*., 2016).

Patients and those who had previously used quinolones, piperacillin/tazobactam, or carbapenems had a higher likelihood of developing Multidrug resistance – *Pseudomonas aeruginosa* blood stream infection (MDR-PA BSI) , according to univariate analysis. MDR-PA BSI was linked to a significantly higher mortality rate, and a considerable number of patients with MDR-PA or CR-PA BSI had ineffective first treatment. Patients who had previously received antibiotic therapy were more likely to develop PA BSI caused by MDR or CR bacteria; thus, avoiding antibiotic misuse may prevent antibiotic resistance by permitting more careful use of the few available antimicrobial drugs (Zhao *et al*., 2020).

2.8.3.1. Causes of antibiotics resistance

Antimicrobial drugs are widely available without a prescription from a doctor or other trained health practitioner in many developing countries, resulting in excessive use. In both cases, there is a widespread belief that antibiotics are "wonder medications" that can quickly cure any sickness. Other considerations include the presence of immunocompromised individuals (e.g., Acquired Immunodeficiency syndrome (AIDS) patients, cancer patients, or transplant recipients), invasive surgical procedures, and clinical therapy severity, a number of factors can influence the emergence and spread of highly antibiotic-resistant nosocomial infections, including the length of stay in the hospital. Antibiotics are

not only overused, but they are also overused incorrectly (inadequate dose, poor adherence to treatment guidelines) (Prestinaci *et al*., 2015).

2.8.3.2. Mechanism of antibiotics resistance

A number of factors have been blamed for the growth in bacterial resistance to antimicrobial medications used in clinical settings, which has led in the emergence of multi-drug resistant strains.

1. Antibiotic resistance mediated by efflux pumps. Efflux is one of the most common ways for bacteria to discharge antimicrobials from their cells.
2. Antibiotic resistance and outer membrane permeability Antibiotics can be applied in two different methods,the lipid-mediated pathway and porin diffusion in general penetrate the outer membrane and reach the cytoplasmic membrane. Tetracycline and quinolone antibiotics, for example, utilize both methods to enter the cell. Hydrophobic antibiotics use the lipid-mediated approach to enter the Gram-negative bacterial outer membrane, while hydrophilic antibiotics employ the porin-mediated pathway. The outer membrane bilayer allows hydrophobic antibiotics including gentamicin, kanamycin, erythromycin, rifamycin, fusidic acid, and cationic peptides to enter the cell (El Salabi *et al*., 2013).
3. Carbapenem resistance is nearly entirely induced by the development of *Klebsiella pneumoniae* carbapenemase (KPC), an enzyme that hydrolyzes all -lactam antimicrobial drugs. KPC is encoded by the *blaKPC* genes, which are found on transferable plasmids that also carry genes giving resistance to other antibiotic classes. Antimicrobial therapy options that are effective against CRE are quite limited, and patients with invasive *carbapenem-resistant Enterobacteriaceae* (CRE) infections have a significant fatality rate (Satlin *et al*., 2013).

4. Antibiotic resistance is a basic mechanism that includes not only genetic and mechanistic roots, but also the formation of bacterial biofilms (BBFs):

Both intrinsic and acquired antibiotic resistance are influenced by the genetic basis of resistance. Intrinsic resistance refers to a bacteria's innate antimicrobial sensitivity, which is influenced by biological characteristics such as structure and metabolic function. Antibiotic-resistant gram-negative (G-) bacteria, such as *E. coli*, are resistant to neomycin , but *Streptococcus mutans* is gram-negative (G+) bacteria are less susceptible to streptomycin than *Staphylococcus aureus* . The intrinsic drug resistance of bacteria is mostly due to a gene discovered on the bacteria's chromosome and passed down from generation to generation with precision. Acquired resistance occurs when an antibiotic-sensitive organism develops resistance through the acquisition of genes or mutations (Su *et al*., 2020).

Chapter Three
Materials and Methods

Chapter Three: Materials and Methods

3.1. Materials

3.1.1. Kits

The Kits that used in the current study are listed in table (3-1).

Table (3-1): Kits of the Study

NO	Kits	Company	Country
1	IL-6 Kit (CLIA)	Snibe	Germany
2	CRP Kit	Boditech	Korea
3	D-Dimer Kit	Biomerieux	France
4	Random blood sugar, ALT, AST, ALP , GGT , Albumin , Direct Bilirubin , Cholesterol, Triglyceride, HDL, LDL, LDH Kit	DIRUI	Chine
5	PT kit	BIOLABO	France
6	AST FOR GRAM NEGATIVE	BIONMERIEUX	France
7	AST FOR GRAM POSTIVE	BIONMERIEUX	France
8	GN card	BIONMERIEUX	France
9	GP card	BIONMERIEUX	France
10	Gram Staining kit	VSI	Iraq

3.1.2.Chemicals

The chemicals that used in the present study are listed in table (3-2).

Table (3-2): Chemicals that uses in the study

NO	chemicals	Company	Origin
1	Iodine	Juman	Jordan
2	Ethanol	Rihana Al-Warith	Iraq
3	ABO Reagents	AFCO	Jorden

3.1.3. Culturing media

The culturing media of present study were listed in table (3-3).

Table (3-3): culturing media of study

NO	Media	Company	Origin
1	Blood Agar	OXOID	United Kingdom
2	Macconkey Agar	BIOMARK	India
3	Brain Heart Infusion broth	OXOID	United Kingdom

3.1.4. The culturing Media

3.1.4.1. Blood agar

Suspend 40g in 1 liter of distilled water, then bring it to a boil until it totally dissolves. For sterilization, autoclave at 121°C for 15 minutes, then Cooling this agar to 45-50°C adds 7% of sterile defibrinated blood.

3.1.4.2. MacConkey Agar

Suspended 51.55g of medium in 1000 mL of water, which was then distilled. Heat to boiling with gently swirling to completely dissolve the agar for 15 minutes in an autoclave at 15 ibs (121 °C) Cool to 45-50 °C without cooking over, then pour into sterile petri dishes. The medium's surface should be dry before inoculation.

3.1.4.3. Brain heart infusion broth

The media is made up of a base of brain heart infusion broth and a supplement of 35 % (v/v) glycerol. It was placed in 5 mL tubes, autoclaved, cooled, and kept at 4°C until needed. The goal of employing this medium was to maintain the isolate alive at 20 °C for as long as possible.

3.1.5. Apparatuses

The apparatuses used in this work are listed in table (3-4).

Table (3-4): Devices of the study

NO	Devices and Tools	Company	Origin
1.	MEGLUMI 800	Snibe	Ireland
2.	Autoclave	Labtech	Korea
3.	BACT\ALERT 3D	BIONMERIEUX	France
4.	Sensitive balance	Kern	germany
5.	Centrifuge	ROTOFIX 32 A (Hettich)	Germany
6.	Fum Hood	FASTER Bio 4s	Italy
7.	Incubator	Gallenkamp	England
8.	Microscope	Olympus	Japan
9.	Refrigerator	LG	Korea
10.	Deep freeze	ALS	Italy
11.	Swelab	Swelab Alfa Plus Standard	Sweden
12.	Shaker incubator	Gallenkamp	England
13.	Vitek 2- compact	BIONMERIEUX	France
14.	Mini vidas	BIOMERIEUX	France
15.	Auto chemistry analyzer	Biobased	China
16.	Water Distling	GEL	Germany
17.	BR-501 BILIRUBIN METER	APEL	Japan
18.	Humanclot junior	Human	Germany

3.1.6. Equipment

The equipment of current study are listed in table (3-5).

Table (3-5): The tools of the study

NO	Devices and Tools	Company	Origin
1.	Micropipettes	Micropipettes	Germany
2.	Inoculating loop	Loop Shandon	England
3.	Gloves	Mumu plus +	Malaysia
4.	Mask	Disposable 3-layer Mask	China
5.	Watte Cotton Pleats	Alsalama	Iraq
6.	Diposable syring 5 ml	EASYMED	China
7.	Disposable syring 10 ml	ULTRA HEALTH	China
8.	Tourniquet	Voltaren	China
9.	Gel tube	Vaccum blood collection tubes	Iraq
10.	EDTA tube	Vaccum blood collection tubes	Iraq
11.	Glass PT tube	JIANGUS XINKANG MEDICAL INSTRUMENT CO	Spain
12.	Blood culture bottle	BACT\ALERT FA PLUS	USA
13.	Petri dish	AFCO	Jorden
14.	Slide	MMK	China
15.	Cover slide	MMK	China
16.	Glass wear	AFCO	Jorden

3.2. Methods

3.2.1. Study Design

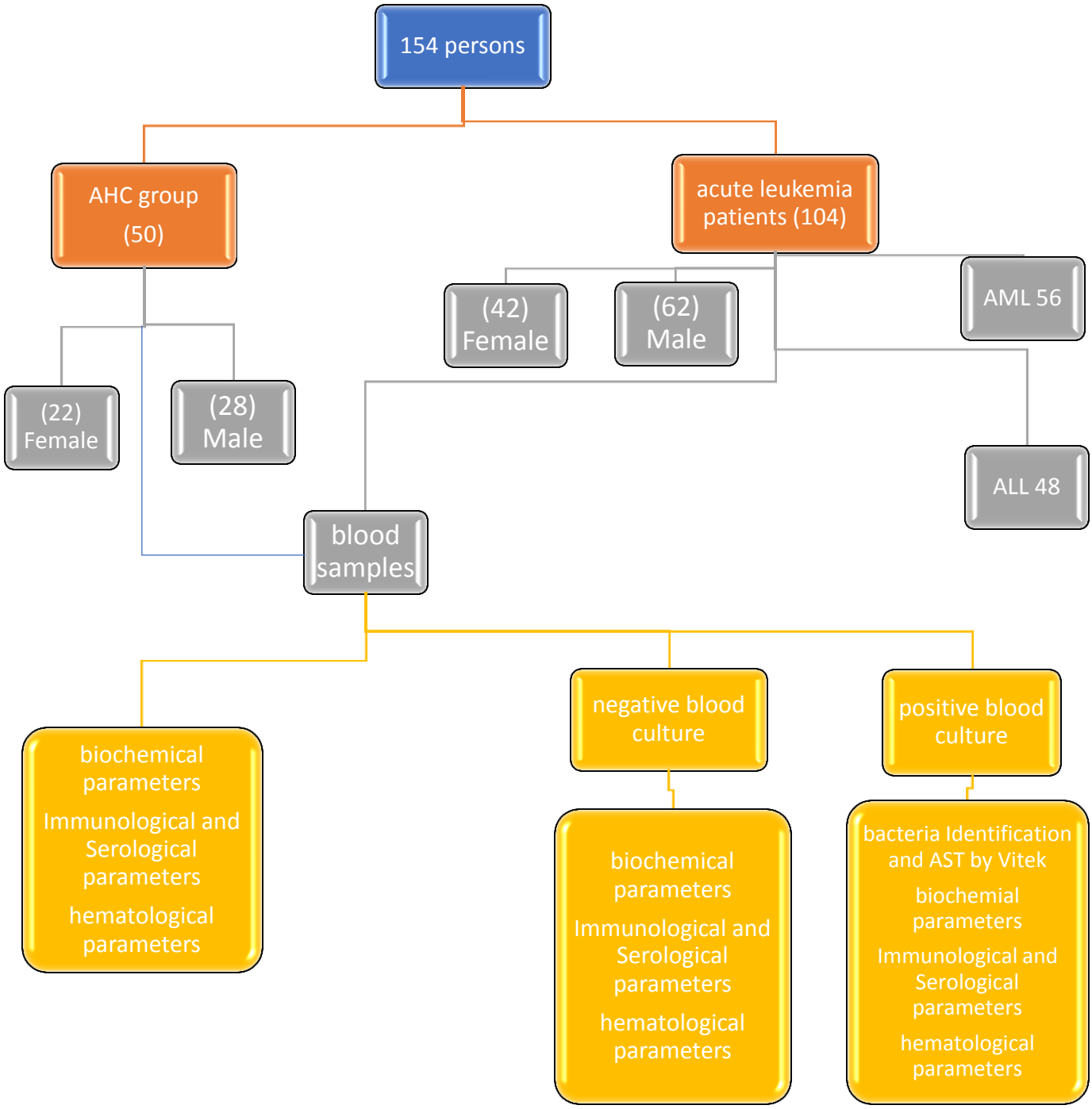

Figure (3-1) : Study design

3.2.2. Patients

A case-control study of patients with acute leukemia was conducted. In the Imam Hussein Center For Oncology and Hematology / Karbala Health Directorate during the period from October 2021 to May 2022. One hundred four patients were diagnosed with acute leukemia new and old cases by hematopathologist doctor and information patients file in the center , and all of the patients were adults, in addition their age ranged between (18- 80) years, of both sexes.

3.2.2.1. Questionnaire

There was a lot of vital information and data collected from the patients, such as their names , age, blood group , chronic disease , fever suffer , lymph nods swollen , take antibiotic , take chemotherapy , type of acute leukemia and subtype of disease as showed in appendix 1.

3.2.2.2. Ethical management of studies

The research followed the guidelines set forth by the Department of Clinical Laboratories at the University of Karbala's College of Applied Medical Sciences for dealing with biological substances and dangerous microorganisms. After acquiring the necessary authorization from the hospital administration and patients, The samples for this investigation were taken from patients at the Karbala Health Directorate's Imam Hussein Center For Oncology and Hematology.

3.2.2.3. Collection samples

A total of 10 milliliters of blood flowed through the veins of acute leukemia patients were collected. Nutusi et al. performed an important blood culturing process that should be followed (Ntusi *et al*., 2010).

1. The patient's identity had been verified, and the patient's identity had been inquired about. Look on the wall above the bed or in the patient's records to double-check identify.
2. The method was explained to the patient, as well as the plans' details. Frequently, verbal approval was obtained.
3. Blood culture bottles, syringe (10 mL), sharps waste disposal container, as needed for a blood culture, sterile gloves, tourniquet, adhesive strip, povidone iodine or alcohol solution (or other acceptable skin disinfectant), and sterile pack with cotton/gauze swabs were collected.
4. A tourniquet was applied, and a suitable vein was selected. Hands were cleaned with soap and water or disinfected with alcohol. After that, the hands were cleaned or rubbed until fully dry. The gloves were put on with sterility in mind.
5. In an aseptic procedure, the puncture site was cleansed with povidone or an alcohol solution. For 1 to 2 minutes, the disinfectant was allowed to dry. The blood culture site was covered with a green sterile cover with an opening.
6. A needle was gently inserted into the patient's blood vein, resulting in a blood sample of at least 10 milliliters (adults). If the vacutainer equipment was employed, the blood culture would be the first blood specimen taken.
7. The tourniquet had been undone. From the puncture wound, the syringe and needle were withdrawn. A dry swab was used to clean the puncture site, and

pressure was administered. If blood was not extracted directly into the culture bottle using the vacutainer method, inoculate blood into the culture bottle after cleaning the lid of the blood culture container with an alcohol swab. Before collecting blood for additional tests, inoculate the blood culture tube. There's a lot to do between obtaining blood samples and inoculating the blood culture container.

8. The blood culture container was gently turned to mix the blood and culture material (Avoided shake vigorously).
9. The blood culture vial was delivered to the laboratory as quickly as possible. At the same time, 2 mL of blood was deposited at room temperature in a gel tube (2 mL) and allowed to coagulate for at least fifteen minutes before centrifugation at 2500 rpm. The serum was then split into epindrops. The leftover blood sample (1.5ml) was placed in an EDTA tube and shaken for at least fifteen minutes, and (1.5 ml) blood sample was put in the sodium citrate tube and quickly centrifuged at 2500 rpm at least fifteen minutes to obtain of plasma to estimate (PT , D-D)(Arif *et al*., 2021) .

3.2.3. control group

People were apparently healthy and selected from the general population in university and relatives.

3.2.4. Estimate Liver Function Tests

3.2.4.1. Alanine aminotransferase (ALT)

Principle : This method has been optimized and adjusted in accordance with the International Federation of Clinical Chemistry (IFCC). The rate of change in absorbance at λ=340 nm in spectrophotometer is proportional to the activity of alanine aminotransferase (Burtis, 1999).

3.2.4.2 Aspartate aminotransferase (AST)

Principle: This method has been improved and changed in accordance with the International Federation of Clinical Chemistry (IFCC).The rate at which the absorbance changes at λ=340 nm is proportional to the activity of aspartate aminotransferase (Tietz *et al*., 1995).

3.2.4.3. Alkaline Phosphatase (ALP)

Principle Colorless p-nitrophenol is transformed to 4-nitrophenoxide under alkaline conditions, resulting in a bright yellow tint. Its strength is proportional to the sample's alkaline phosphatase activity (Burtis, 1999)**.**

3.2.4.4.Gamma-glutamyl transferase (GGT)

Principle : The IFCC technique is a system that was developed by the International With the kinetic technique,

The rate of formation of 5-amino-2-nitrobenzoate, as measured by colorimetry, is directly related to the activity of -glutamyltransferase (Schumann and Klauke, 2003).

3.2.4.5.Albumin

Principle : Bromocresol green (BCG) forms with albumin, in succinate buffer (acid medium), a coloured complex. The colour intensity of the formed complex measured by spectrophotometer at 630 nm is proportional to albumin concentration in the sample (Rifai, 2017).

3.2.4.6. Total Protein (TP)

Principle: The biuret reaction is used in this method. In an alkaline solution, protein forms a colored compound with cupric ions. The protein concentration is related to the color intensity (Rifai, 2017).

3.2.4.7.Direct Bilirubin (DB)

Principle : The method uses vanadate as an oxidizing agent and is based on chemical oxidation. Conjugate (direct) bilirubin is oxidized to biliverdin in the presence of detergent and vanadate in an acidic solution. The yellow color of bilirubin changes to a green color that is characteristic of biliverdin as a result of this oxidation event. As a result, measuring the absorbance before and after vanadate oxidation can be used to determine the direct bilirubin concentration in the sample (Burtis, 1999).

3.2.4.8. Lactate dehydrogenase (LDH)

Principle: The oxidoreductase Lactate Dehydrogenase (LDH) catalyzes the interconversion of lactate and pyruvate. When LDH-containing tissues are affected by disease or injury, the cells release LDH into the bloodstream, where it is detected in higher-than-normal quantities. As a result, LDH is frequently used to assess the presence of tissue or cell damage. The non-radioactive colorimetric

LDH assay is based on the reduction of the tetrazolium salt MTT to a reduced form of MTT with an absorption maximum at 565 nm in a NADH-coupled enzymatic process. The intensity of the purple color produced is related to the activity of the enzyme (Stentz *et al*., 2010).

Assay Protocol

A kinetic reaction is used in this test. The addition of working reagent to samples should be rapid, and mixing should be brief but thorough, to guarantee a similar incubation time. It is recommended that you use a multi-channel pipettor. At room temperature or at 30°C, assays can be carried out.

Reagent Preparation

Raise the temperature of the reagents to room temperature. 14 µL MTT Solution, 8 µL NAD Solution, 8 µL PMS Solution, and 170 µL Substrate Buffer are mixed for each 96-well experiment to make the working reagent. It's best to do a fresh reconstitution.

Assay Procedure

Procedure using 96-well plate:

1. Fill wells of a transparent flat bottom 96-well plate with 200 µL H2O (ODH2O) and 200 µL Calibrator (ODCAL) solution.
2. Fill the sample wells with 10 µL of sample and 190 µL of Working Reagent. To combine, tap the plate a few times.
3. On a plate reader, read OD565nm (ODSO) and then again after 25 minutes (ODS25).

Procedure using cuvette:

1. Pour 50 µL of sample into 1-cm cuvettes.
2. Add 950 µL of Working Reagent to the samples. Mix for a few seconds.
3. Read the OD565nm of the sample immediately after mixing (ODSO) and again after 25 minutes (ODS25).
4. Calibrator and OD565nm for 1 mL water (ODH2O) (ODCAL).
1. If the LDH activity of the samples exceeds 200 IU/L, dilute the samples in water and repeat the experiment (Stentz *et a*l., 2010) .

Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline Phosphatase (ALP), Gamma-glutamyl transferase (GGT), Albumin, Total Protein (TP), and Direct Bilirubin (DB) , Lactate dehydrogenase (LDH) , were automatically tested in a BIOBASE auto chemistry analyzer using the approach of (Young, 1997).

3.2.4.9. Estimate Total Serum bilirubin (TSB)

Principle: The reaction between bilirubin and diazotised sulfanilic acid produces azobilirubin, which is colored in an 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. Dimethyl sulfoxide is used in this phase (DMSO). The absorbance of azobilirubin produced in this way is proportional to the bilirubin concentration and is measured at 550 nm (530-580) (Walters and Gerarde, 1970).

Manual Procedure

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
Fill the cuvette halfway with distilled water and drain thoroughly. Read all of one run's blanks first, then all of the assays, with a well-draining cuvette between each tube. However, DO NOT RINSE WITH WATER, since this may result in streaks on the cuvette. When adding the specimen, mix thoroughly and set a timer. Compare blanks to absorbance at 550 nm (530-580). TB: after more than 3 minutes at 37°C or more than 5 minutes at room temperature, take a reading. DB: take a reading at 37°C for exactly 3 minutes or 5 minutes at room temperature.		

1. Manual procedure performances should be validated by the user.
2. Proposals for Kenza applications and other applications are available upon request.
3. Paediatric Specimen: double the volume of the sample by 5.

TSB was measured automatically in the BR-501 (BILURUBIN METERT).

3.2.5. Estimation the level of C- reactive Protein (CRP)

Agglutination occurs when CRP in a sample reacts with anti-CRP antibody that has been sensitized to latex particles. This agglutination is measured as a change in absorbance (572 nm), with the size of the change related to the amount of CRP in the sample. The actual concentration is then calculated using interpolation from a calibration curve derived from known concentration calibration.

CRP was determined automatically in the BIOBASE auto chemistry analyzer using the method of (Young, 1997, Arif *et al*., 2021).

3.2.6. Estimation of D-Dimer

D-Dimer was measured automatically in the VIDAS® D-Dimer Exclusion II™ (DEX2) .

Procedure :

1. For the sample, use one "DEX2" strip and one "DEX2" SPR® from the kit. After the appropriate SPRs have been withdrawn, make sure the storage pouch has been carefully resealed.
2. The sample test part for this test is 200 liters.
3. Place the "DEX2" SPRs and "DEX2" strips in the instrument's proper locations. Check that the color labels on the SPRs and the STRs match the assay code.
4. The results of the assay are ready in 20 minutes. Remove the SPRs and STRs from the instrument once the assay is finished.
5. Transfer the utilized SPRs and STRs to a suitable recipient (Raymond III and Rico-Lazarowski, 2009).

3.2.7. Estimate IL-6

Principle: The IL-6 assay is a sandwich chemiluminescence immunoassay. The sample (or calibrator/control, if applicable), buffer, anti-IL-6 monoclonal antibody-labeled ABEI and magnetic microbeads coated with another anti-IL-6 monoclonal antibody are properly combined and incubated to produce sandwich complexes. The supernatant is decanted after precipitation in a magnetic field, and then a wash cycle is done. The start 1+2 are then added to start the chemiluminescent process. A photomultiplier measures the light signal as relative

light units (RLUs), which are proportional to the amount of IL-6 in the sample (or calibrator/control, if appropriate) (Kishimoto, 2010).

Procedure:

1. The user loads the desired reagents
2. The sample are loaded
3. Desired work-list is input either through LISOR manually and choose IL6
4. Press start and wait for the results.

3.2.8. Estimation of physiological parameters

3.2.8.1. Complete Blood Count (CBC)

The procedure was followed by Blum in the swelab device

1. In the first step, the samples were at room temperature.
2. It was ten times inverted by hand till it was suspended.
3. If the samples are barcoded, it was run as if it were a regular patient (Caps lock was disabled).
4. After placing the sample on the analyzer, the RUN button was hit. After all of the samples had been evaluated, the results were printed.
5. To print the information, "Stored Data" was selected.
6. The output button was pressed.
7. Remove all marks by pressing "Mark," "All Clear," and then "Cancel."(Arif et al., 2021).

3.2.8.2. Determination of ABO Blood Group

For each part of the white porcelain support, a drop of donor or recipient blood is mixed with anti-A, anti-B, and anti-D separately (Arif *et a*l., 2021). The ABO and RhD blood types can be determined by physically seeing the agglutination or blood clumping pattern. The test is quick and inexpensive, taking

only 5–10 minutes to conduct and requiring only a little amount of blood typing reagents (Mujahid and Dickert, 2016).

3.2.9. Diagnosis of Bacteria

3.2.9.1. Blood Culture Samples

Blood was taken from an arm vein and put into blood culture flasks. The BacT/ ALERT® 3D system (bioMeriéux, Marcy l'Etoile, France) was utilized for the initial examination of the blood cultures(Arif *et al*., 2021). The bacteria were collected and inoculated onto blood agar plates (BAP; Asan Pharmaceutical Co., Ltd., Seoul, Korea) and MacConkey agar plates (Becton Dickinson, Sparks, MD, USA) before being incubated at 35°C in a 5% CO2 atmosphere (Ha *et al*., 2018).

3.2.9.2. Conventional workflow of positive blood cultures

Following a positive signal from the BacT/ALERT® 3D Device, Gram staining was conducted, after that, the bacteria are cultured on a solid agar medium. The colonies on the agar plates were used for identification and antibiotic susceptibility testing (AST) using the commercial automated Vitek2 system (bioMeriéux) after an overnight incubation period. The ID and AST values produced using this method served as a benchmark against which the institution's methods could be compared (Ha *et al*., 2018).

1. After primary organism isolation, minimal treatment is required using a simple homogenous inoculum.
2. Insert the inoculum into the VITEK® 2 Cassette at the Smart Carrier StationTM.
3. The VITEK® 2 Card and the sample are linked via a barcode.
4. Once the Cassette has been loaded, the gadget will handle the incubation and results readout (Arif *et al*., 2021).

VITEK® 2 Compact is a biochemically based automated microbiological identification tool with 48 biochemical attributes that is extensively used in clinical laboratories (Książczyk *et al*., 2016).VITEK® 2 Compact can identify microorganisms for up to 4 hours. Each well evaluates the metabolic performance of a strain, including its capacity to acidify, alkalize, Enzymatically hydrolyze substrates, as well as bacterial proliferation in the presence of inhibitors. Fluorescence-based sensors are used to track bacterial growth and metabolic changes in the microwells(Arif *et al*., 2021). Bacterial incubation conditions, such as media composition and pH, influenced the outcomes of biotyping and biochemical-based techniques (Książczyk *et al*., 2016). A sterile microloop was used to collect a few colonies from a pure culture that had grown for 18 to 24 hours on blood or macconkey agar. Using a VITEK® 2 DensiChek (bioMérieux, Warszawa, Poland), a bacterial culture was calibrated to the McFarland Turbidity Standard of 0.5–0.63 in 3 mL of a 0.45 % sodium chloride solution (Arif *et al*., 2021). The GP card was placed on the cassette and placed in the instrument if the gram stain was negative; otherwise, the GN card was placed on the tape and placed in the instrument if the gram stain was positive. To avoid turbidity changes, the duration between suspension preparation and card filling was shorter than 30 minutes. At 35.5 1 °C, the cards were incubated. After each card was withdrawn from the incubator, colorimetric measurements were obtained automatically every 15 minutes. After 10 to 18 hours of incubation, the findings were read (Morka *et al*., 2018).

3.2.10. Determination of antibiotic susceptibility

Antibiotic susceptibility testing determines the antibiotic susceptibility of a bacterial isolate. After being vaccinated, the cards were placed in the Vitek 2

automatic reader-incubator. I followed the manufacturer's instructions for infecting and analyzing identification and susceptibility cards, which I detail below. The volume and density of microorganisms injected into the Vitek cards were checked using colony counts (Bazzi *et al.*, 2017).

- The bacteria has been exposed to antibiotics, and the examination will indicate whether it can grow in the presence of the antibiotics.
- The doctor receives the Minimum Inhibitory Concentration (MIC), which is a measure of a microorganism's sensitivity or resistance to an antibiotic.
- Antibiotic susceptibility testing was used to identify microorganisms that were resistant to antibiotics. The results of antibiotic resistance testing are used by clinicians to properly identify the best treatment options for the infection and the specific patient(Arif *et al*., 2021).

3.3. Statistical analysis

The data was analyzed using SPSS to determine Chi-square, T test (one tail) at significance levels of (0.01 and 0.05), and Correlation (r**)**.

Chapter Four
Results and Discussion

Chapter Four: Results and Discussion

4.1. The Study Sample

104 new cases of acute leukemia patients (AL) , 62 patients (59.62%) were males and 42 patients (40.38%) were females, in addition 48 (46.15%) patients were diagnosed as acute lymphoblastic leukemia (ALL) and 56 (53.85 %) were diagnosed as acute myeloid leukemia (AML), 16 with bacterial infection and 88 without bacterial infection . The study sample also include 50 healthy persons , 28 persons (56%) were male and 22 persons (44%) female.

4.2. General features of acute leukemia patients

The statistical analysis of table (4-1) revealed in the significant differences ($P < 0.05$) between male and female in the Acute Leukemia patients group. However, there were high significant differences ($P< 0.001$) in all age groups of patients , results indicated that the most age group affected by leukemia is (40-59), with a percentage of 38.46%.While The least affected is the age group less than 20 years, as its rate was 11.54%.Also the results in the same table showed AML were high incidence than ALL (53,85%, 46.15%), respectively . While no significant differences($P > 0. 05$) between subtypes of acute leukemia .

Table (4-1): General features of Acute Leukemia patients

Factors		Numbers	Percentage(%)	*P value*
Gender	**Male**	62	59.62	0.049 *
	Female	42	40.38	
Age (years)	**< 20**	12	11.54	0.00098**
	20 – 39	30	28.85	
	40 – 59	40	38.46	
	60 – 79	22	21.15	
Type of Leukemia	**AML**	56	53.85	0.432
	ALL	48	46.15	
Subtypes of Leukemia (AML)	**M0**	4	7.14	0.246
	M1	8	14.29	
	M2	6	10.71	
	M3	16	28.57	
	M4	12	21.43	
	M5	10	17.86	
Subtypes of Leukemia (ALL)	**B-ALL**	30	62.5	0.0832
	T-ALL	18	37.5	

* means significance differences (P <0.05) ** means high significances differences (P <0.001)

In males in each age-group, with the exception of infant ALL , with an overall male: female ratio of about 1.3:1 (Henderson, 1990). Males had greater global leukemia rates than females, with a total M/F ratio of 1:4, which was consistent with the current study (Mjali *et al*., 2019, Miranda-Filho *et al*., 2018). Previous study that referred to Acute leukemia (AL), both myeloblastic (AML) and lymphoblastic (ALL), and lymphomas are more common These studies suggest that female gender may serve as a favorable risk factor in AML, which is consistent with a publication reporting on younger patients with AML(Acharya *et al*., 2018). Despite the fact that both males and females received chemotherapy throughout their cancer treatment, female survivors had a larger risk of cardiorespiratory fitness impairment than male survivors (Caru *et al*., 2019).

Both types of acute leukemia are highly linked to age, although in opposite directions. AML is more frequent in the elderly than ALL, which peaks in childhood. As a result, the median age at diagnosis for AML is 67 years old, while the median age for ALL is 14 years old (Fiegl, 2016). Disagreements with recent EUROCARE-5 study based on cancer registries from 27 European countries that compared the outcomes of 4617 adolescents and young adults diagnosed with acute lymphoblastic leukemia (ALL) aged 15 to 39 years to 15 089 children aged 0 to 14 years diagnosed between 2000 and 2007(Trama *et al*., 2016). According to the distribution of subtypes of leukemia by age group, ALL was the most common type of leukemia among the younger age groups, accounting for 87.9% of leukemia cases among children under the age of ten years . AML was identified in 32.6 % and 31.9 % of patients in the age groups between ranges 31–40 years and 61–70 years, respectively (Mjali et al., 2019). Also, the median age of acute leukemia diagnosis is 68, with 55.54 % of those diagnosed being 65 or older (Howlader *et al*., 2019).

Acute lymphocytic leukemia (ALL) occurs approximately five times more frequently than acute myelogenous leukemia (AML) (Belson *et al*., 2007). In another study indicated to the annual number of new cases/100,000 was 1.7 for ALL and 4.0 for AML in the US , and similar rates are observed in other industrialized countries such as Germany with 5.2 new AML cases and 1.6 ALL cases in 2010 (Fiegl, 2016). disagreement with previous study was referred to ALL more incidence than AML, the American Cancer Society estimated that 13,800 cases of acute myelogenous leukemia (AML) and 6000 cases of acute lymphoblastic leukemia (ALL) were diagnosed in the United States in 2012(Appelbaum, 2020).

The French-American-British (FAB) group has identified eight AML variants , including three with predominantly granulocytic differentiation (M1, M2, and M3), two with at least 20% monocytic precursors (M4, M5), one with a high proportion of erythroblasts (M6), and a more recently recognized and rare variant with a predominance of megakaryoblasts (M7). In addition, the FAB group has described M0, a type of AML with low myeloid differentiation that cannot be diagnosed purely on the basis of morphologic or cytochemical criteria and requires immunohistochemical staining (Bennett *et al.*, 1991). This is agreements with study that documented B cell precursor ALL is the most frequent subtype of ALL, which affects people over the age of 50 years (Pui *et al*., 1993). Classifies ALL into precursor B-cell (85%) or T-cell (15%) subgroups that are reminiscent of normal stages of lymphoid maturation(Hunger and Mullighan, 2015).

4.3. Common bacterial infections in acute leukemia patients

Results in table (4-2) showed no significant differences ($p < 0.05$) between Bacterial types that isolated from Leukemia's patients , in which gram positive were the most bacterial species in leukemia patients than gram negative, *Staphylococcus hemolyticus* was the most bacterial species isolated from leukemia patients with a percentage of 37.5%,%, while the other three bacterial species were equal in proportions and they were 12.5% for each of *Enteroccocus casseliflavus* , *Staphylococcus warneri* and *Staphylococcus hominis*. However *Klebsiella pneumoniae* with 25%.

Table (4-2): Common bacterial species that isolated from acute leukemia patients

Bacterial type		No. (%)	*P value*
Gram positive bacteria	***Staphylococcus haemolyticus***	6 (37.5)	0.40601
	Staphylococcus warneri	2 (12.5)	
	Staphylococcus hominis	2 (12.5)	
	Enteroccocs casseliflavus	2 (12.5)	
Gram negative bacteria	***Klebsiella pneumonia***	4 (25.0)	

* means significance differences (P <0.05) ** means high significances differences (P <0.001)

Gram-positive microorganisms were the most common blood isolates (75.8%) (Bochud *et al*., 1994). Certan studies showed that *Coagulase-negative staphylococci* and *Streptococcus viridans* accounted for more than half (57.6%) of all blood isolates in acute leukemia (AL) patients (Madani, 2000). In addition , previous study show that gram negative bacteria accounted for 78 % of the total isolates, whereas gram positive bacteria accounted for 22 % In acute leukemia patients, the most prevalent pathogens were *Escherichia coli* (43%), *Staphylococcus aureus* (22%), *Pseudomonas aeruginosa* (17.4%), and *Klebsiella pneumonia* (17.4%) (Karanwal *et al*., 2013). While study of hospital-onset bacteremia in ICUs, was led by *P. aeruginosa* (22.2%), *Enterobacter* spp (22.2%), *K. pneumoniae* (17.8%), *E. coli* (15.6%), and *Serratia marcescens* (11.1%) (Sligl *et al*., 2006). A s well as other study indicated that gram-negative rods (GNRs) accounted for 59.6 % and gram-positive cocci (GPCs) for 34.4 % of BSI, in which Four pathogens were involved in relapsing bloodstream infection (R-BSI) : *Escherichia coli, Pseudomonas aeruginosa, coagulase-negative staphylococci*, and *Streptococcus viridans* (Cattaneo *et al*., 2014).

4.3.1. Antibiotics susceptibility test

4.3.1.1. Antibiotics susceptibility of Gram positive bacteria that isolated from acute leukemia patients

The statistical analysis for Antibiotics susceptibility in table (4-3) revealed to that gram positive bacteria sensitive to 11 antibiotics and resistance to 9 antibiotics

Table (4-3): Antibiotics susceptibility of Gram positive bacteria that isolated from acute leukemia patients

Gram positive bacteria	Sensitivity (100%)	Resistance (100%)
Staphylococcus haemolyticus ; S. warneri ; S. hominis ; Enteroccocs casseliflavus	1. Linezolid 2. Nitrofurantoin 3. Trimethoprim/sulfamethoxazole 4. Tigecycline 5. Doxycycline 6. Minocycline 7. Ofloxacin 8. Ceftaroline 9. Gatifloxacin 10. Streptomycin 11. Daptomycin	1. +Azithromycin 2. Cefalexin 3. Cefixime 4. Cefpirome 5. Clarithromycin 6. Cefdinir 7. Amikacin 8. Kanamycin 9. Ceftizoxine

4.3.1.2. Antibiotics susceptibility of Gram negative bacteria that isolated from acute leukemia patients

The results of table (4-4) showed that gram negative bacteria were resistance to all antibiotics .

Table (4-4): Antibiotics susceptibility of Gram negative bacteria that isolated from acute leukemia patients

Gram positive bacteria	Sensitivity (100%)	Resistance (100%)
Klebsiella pneumonia	No	1. Gentamycin 2. Trimethoprim/sulfamethoxazole 3. Cefapime 4. Ceftazidime 5. Levofloxacin 6. Ciprofloxacin 7. Imipenem 8. Meropenem 9. Ticarcillin/Clavulanic acid 10. Amoxicillin 11. Ampicillin 12. Ampicillin/sulbactam 13. Amoxicillin/clavulanic acid+ 14. Piperacillin/sulbactam 15. Piperacillin/tazobactam 16. Cefadroxil 17. Cefuroxime 18. Cefuroxime Axetil 19. Cefazolin 20. Cefpodoxime 21. Ceftriaxone 22. Cefixime 23. Nalidixic Acid 24. Tobramycin 25. Ertapenem 26. Cefotaxime 27. Norfloxacin 28. Fosfomycin 29. Nitrofurantoin

Enterococci, especially vancomycin-resistant strains, have also been noted as a significant cause of mortality in AML patients receiving hematopoietic stem cell transplantation (Vydra *et al.*, 2012). Quinolone prophylaxis did not increase the incidence of gram-positive bacteraemia, and there were no significant variations in the number of patients getting infections caused by organisms resistant to quinolones, according to those findings (Gafter-Gvili *et al*., 2012). All *coagulase-negative Staphylococci* isolated from bloodstreams of acute leukemia patients were methicillin-resistant and fluoroquinolone-resistant. Ampicillin resistance was found in *Enterococcus faecalis* isolates. Vancomycin and teicoplanin were active in vitro against two of the three *Enterococcus faecium* isolates (66,6%). Resistance to fluoroquinolones was also full among *Corynebacterium spp*. strains, and it was 78 % in *Escherichia coli* strains that were extended spectrum beta-lactamases (ESBL) producers in 12.1 percent of the time throughout the consolidation phases (De Rosa *et al*., 2013) . Multi drugs resistance (MDR) organisms were commonly isolated in BSI in AL .The following gram-negative bacilli were considered to be MDR: 1) extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae*, 2) AmpC cephalosporinase hyperproducing *Enterobacteriaceae*, 3) MDR strains of non-fermenting GNB such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Stenotrophomonas maltophilia* . MDR gram-positive organisms included methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VRE) (Garcia-Vidal *et al.*, 2018).

4.4. Blood groups

Table (4-5) showed that no significant differences (P > 0.05). in blood group A in both controls and patients based on statistical analysis. High significance differences (P <0.001) were detected in blood groups B,AB,O, in comparsion

between AHC and patients groups with acute leukemia, while high significance differences (P <0.001) were found in all blood groups of study groups.

Table (4.5): The Blood Groups of the study sample.

Blood Groups	AHC	Leukemia's patients	Total	P value
A	54.55% 24 48%	45.45% 20 19.23%	44	0.546
B	14.29% 4 8%	85.71% 24 23.08%	28	0.00016 **
AB	0.0% 0 0.0%	100% 10 9.62%	10	0.0000 **
O	30.56% 22 44%	69.44% 50 48.07%	72	0.00097 **
Total	50	104	154	
P value	0.00001 **	0.00001 **		

* means significance differences (P <0.05) ** means high significances differences (P <0.001)

ABO blood groups are associated with altered risk of a number of malignancies and diseases, There is an increased proportion of B and O blood groups in Hodgkin's lymphoma and ALL, respectively. While was no significant difference in the distribution of blood groups among AML patients (Vadivelu *et al.*, 2004). this close to results of current study . There is also agreement with previous studies that show that ALL has a higher proportion of O blood group and lower proportions of A and B blood categories. It also demonstrates that AML patients have a higher proportion of the A blood group(Alavi *et al*., 2006). Another study showed a significant association between ALL and ABO blood

group and showed that blood group AB was associated with a higher risk of ALL (Tavasolian *et al.,* 2014) .

4.4.1. Blood Groups of Leukemia's Patients

All blood groups had significant differences in acute leukemia patients with and without bacterial infection, according to the statistical analysis showed in table (4-6) , but patients without bacterial infection appear to have higher significance differences than patients with infection.

Table(4-6): Blood Groups of Leukemia's Patients

Blood Groups	Leukemia's Patients Without Bacterial Infection N (%)	Leukemia's Patients With Bacterial Infection N (%)	Total	P value
A	18 (90 %)	2 (10 %)	20	0.00035 **
B	20 (83.33 %)	4 (16.67 %)	24	0.001 **
AB	10 (100 %)	0 (0.00 %)	10	0.00666 *
O	40 (80 %)	10 (20 %)	50	0.00002 **
Total	**88**	**16**	**104**	**0.00001 ****
P value	**0.00006 ****	**0.00944 ***	**0.00001 ****	

* means significance differences (P <0.05) ** means high significances differences (P <0.001)

A person's blood group may have an impact on disease pathophysiology, Especially in the case of sepsis and its coagulation and immunological connections. As a result, they hypothesized that patients with blood group O sepsis are more likely to die, and that this effect is stronger in severe septic shock groups due to more severe coagulation disruption (Hasegawa *et al.,* 2020). Consistent with the findings of a prior study Many blood groups operate as receptors for poisons, parasites, and germs, allowing them to colonize, invade, and avoid host defense mechanisms. False receptors, such as blood groups, can impede binding to target tissue. Finally, microorganisms can induce antibodies to be produced against blood type antigens, such as ABO, therefore antibodies to ABO-active antigens are part

of the innate immune system's defense against certain bacterial infections and enveloped viruses . Furthermore, the results in Table (4.6) are consistent with a previous study that found that septic patients with blood type B had reduced endothelium damage , and a small reduction in mortality. The exposure is, however, unmodifiable (Itenov *et al*., 2021)**.** Another studies indicated that blood group A is independently associated with acute kidney injury (AKI) risk in critically ill patients with trauma or severe sepsis of European descent, suggesting a role for ABO glycans in AKI susceptibility(Reilly *et al*., 2015).

4.5.Immunological and Serological parameters

4.5.1. White blood cells (WBC)

The results of table (4-7) showed that high significant differences ($P < 0.05$) in the mean of WBCs count in acute leukemia patients compared to AHC group , in which the mean count of WBC for acute leukemia patients and controls reached to 12.350 and 6.792 10^3/ µl, respectively. The mean of WBCs count increased insignificantly ($P < 0.05$) for Leukemia's patients infected with bacteria than if they were not infected with bacteria, as the mean of WBC was 14.823 and 11.903 10^3/ µl, respectively.

Table (4-7) : The number of WBC(10^3/ µl) of the study groups .

Patients groups		**AHC**	**P value**
Infection	**Mean ± SD(10^3/ µl)**	**Mean ± SD**	
Without bacterial infection	11.903 ± 2.133	6.792 ± 1.346	0.0001**
With bacterial infection	14.823 ± 2.799		0.0001**
Total	**12.350 ± 2.235**	**6.792 ± 1.346**	**0.0001****
P value	**0.0001****		

* means significance differences (P <0.05) ** means high significances differences (P <0.001)

Acute leukemia , a bone marrow condition that develops when an aberrant white blood cells continues to duplicate itself indefinitely. These cells don't do

what they're supposed to do, which is fight infections. They hinder the generation of other normal blood cells in the marrow as they amass, resulting in anemia, bleeding, and recurrent infections. The leukemic cells move through the blood stream over time, dividing and sometimes forming tumors and causing damage to organs including the kidney and liver (Joshi *et al*., 2013). Agreement with study that referred to Leukopenia is not typically regarded a normal reaction to infection, despite the fact that both leukocytosis and leukopenia have been considered systemic inflammatory response syndrome criteria. Within the sepsis, they wanted to assess the prognostic value of leukopenia as a marker of sepsis-defining hematological organ failure. In patients with probable infection, they expected that leukopenia is Leukocytosis linked to an increased risk of death (Belok *et al.*, 2021). The current accordance with another study that indicated total white blood cells (WBCs) drop modestly in the elderly, according to another study. The count of WBCs increases in response to an acute infection, and it increases dramatically in sepsis. There have been some findings that a higher number of WBCs can be a predisposing factor for bacteremia. There is apparently a link between neutrophilia and leucopenia and an increased mortality risk in the elderly(Aminzadeh and Parsa, 2011).

4.5.2. C-Reactive Proteins (CRP)

As indicated in the statistical analysis of table (4-8) , the mean of CRP of patients with acute leukemia was substantially higher ($P < 0.005$) than the AHC group , which reached to 45.031 and 11.666 mg\I , respectively. In addition the mean of CRP was 58.987 and 42.494 mg\I in infected not infected patients respectively , and the statistical analysis revealed insignificant increased ($P > 0.05$) in patients with bacterial infection.

Table (4-8): the level of CRP (mg\I) in patients and AHC groups

Patients groups		AHC	P value
Infection	**Mean ± SD(mg\I)**	**Mean ± SD**	
Without bacterial infection	42.494 ± 36.025	11.666 ± 6.024	0.0001 **
With bacterial infection	58.987 ± 44.743		0.0001 **
Total	**45.031 ± 37.731**	**11.666 ± 6.024**	**0.0001 ****
P value	**0.1081**		

* means significance differences (P <0.05) ** means high significances differences (P <0.001)

Changes of plasma CRP levels can be useful in the diagnosis of bacterial infection (Adnet *et al*., 1996). In which CRP levels were substantially greater in acute leukemia patients with normal temperatures than in the AHC group.

This means that even when their temperature is normal, leukemia patients are always infected, inflamed, and have a neuroendocrine system dysfunction. Some leukemia patients have a high CRP level, indicating that they were infected with bacteria or that they were inflamed by the disease itself (Han et al., 2007). Agreement with previous study demonstrated that the CRP levels in the blood have been linked to the severity of infection(Povoa *et al.,* 2005).Also it is study showed CRP is a valuable biomarker for monitoring therapy response (Cho and Choi, 2014).

4.5.3. proinflammatory cytokine Interleukin -6 (IL-6)

Table (4-9) shows the levels of IL-6 in studies groups , there were high significant differences (P < 0.05) in the levels of IL-6 in acute leukemia patients compared to the AHC group , which reached to (36.498 and 3.059) pg/Ml , respectively. Also statistical analysis revealed significances differences (P < 0.05) in the level of IL-6 in infected patients compared not infected with bacteria , as well as the mean of IL-6 was (76.748 and 29.180) pg/Ml , respectively.

Table (4-9): The level of IL-6 (pg/Ml) of the study group .

Patients groups		AHC	P value
Infection	**Mean ± SD(pg/Ml)**	**Mean ± SD**	
Without bacterial infection	29.180 ± 6.103	3.059 ± 0.797	0.0001**
With bacterial infection	76.748 ± 11.110		0.0001 **
Total	**36.498 ± 7.240**	**3.059 ± 0.797**	**0.0001****
P value	**0.0001 ****		

* means significance differences (P <0.05) ** means high significances (P <0.001)

Inflammatory cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-1 (IL-1), tumor necrosis factor– (TNF), IL-6, C-X-C motif chemokine 12 (CXCL2), and C-C motif chemokine ligand 3 (CCL3) can be produced by AML blasts, which reduce the colony-forming potential of normal CD34+ cells and induce endosteal endothelial remodeling and progenitor depletion (Duarte *et al*., 2018) . Consistent with the findings of a previous investigation dysregulated cytokine expression, which is a common feature of chronic inflammation and auto-inflammatory disorders, may potentially play a role in the progression of hematological malignancies. Interleukin-1 (IL-1), Tumor necrosis factor alpha (TNF-), and Interleukin-6 (IL-6) have all been identified as important pro-inflammatory cytokines that affect hematopoietic cell function and promote inflammatory disorders (Mirantes *et al.*, 2014). Another study shows clinically significant increase in IL-6 levels have recently been shown to be in the range of 5-25 pg/mL in physiologically normal circumstances and up to 1000 pg/mL in sepsis patients (Franco *et al*., 2015).

4.6.Hematological parameters

4.6.1. D-Dimer

The statistical analysis for D-dimer in table (4-10) revealed that a substantial increase (P< 0.05) in patients when compared to AHC groups , as the mean levels of D-dimer for patients and AHC groups were (1586.492 and 219.451) ng /ml, respectively. As the mean for D-Dimer (1942.305 and 1521.798) ng /ml,

respectively, significant increased (P < 0.05) in infected patients and non-infected respectively .

Table (4-10) : D-Dimer (ng/ml) level in patients and AHC group

Patients groups		AHC	P value
Infection	**Mean ± SD(ng/ml)**	**Mean ± SD**	
Without bacterial infection	1521.798 ± 210.717	219.451 ± 15.992	0.0001**
With bacterial infection	1942.305 ± 256.233		0.0001**
Total	**1586.492 ± 217.481**	**219.451 ± 15.992**	**0.0001****
P value	**0.0001****		

* means significance differences (P <0.05) ** means high significances differences (P <0.001)

It has been revealed that, at the time of initial diagnosis, the plasma level of D-dimer was elevated in most patients, irrespective of the type of acute leukemia. However, the initially elevated plasma level of D-dimer was significantly lower when complete remission had been achieved. Furthermore, in the majority of cases of relapse or resistance to chemotherapy, a further increase of D-dimer level is commonly observed (Cielińska *et al*., 2000). According to a study, D-dimer (DD) and other coagulation indicators are drastically elevated during sepsis, especially when disseminated intravascular coagulation occurs (DIC).

Therefore , DD has been looked into as a potential risk indicator in infected patients(Goebel *et al*., 2010). It also agrees with a prior study that found septic patients with poor DD and a high mortality risk would benefit from a customized drug aimed at lowering clotting activation and/or enhancing fibrinolysis. DIC is a serious sepsis complication that increases the risk of death. D-dimer is the most often used fibrin-related marker for DIC diagnosis . Coagulation and fibrinolysis, on the other hand, have an impact on DD levels. The death rate was higher in individuals with severe sepsis and normal DD. In sepsis, normal DD is thought to hide a DIC type with substantial fibrinolysis inhibition (Semeraro *et al.*, 2019). certain literatures disagreement with current results about the correlation between

D-Dimer and sepsis . Although ,increased DD values have been associated with worse clinical outcomes in some studies, others failed to confirm such findings, revealing that the prognostic value of DD may be modest or poor in sepsis patients(Yin *et al.,* 2013). Notably, a recent study has also demonstrated that sepsis patients with DD values within the normal reference range had a nearly 4-fold higher risk of dying than those with DD concentration modestly or markedly increased(Semeraro *et al.,* 2019).

4.6.2. Platelets

Results in table (4-11) demonstrated that a significant decreases ($P < 0.005$) in the PLT count in patients compared to AHC groups , which reached to 132.826 and 257.04 (**µ**l) , respectively. As the mean count of PLT was (110.125 and 136.954) **µ**l, respectively, in infected and non-infected patients respectively , with no-significant differences ($P > 0.05$).

Table (4-11): PLT (µl) count in patients and AHC groups .

Patients groups		**ACH**	**P value**
Infection	**Mean ± SD(µl)**	**Mean ± SD**	
Without bacterial infection	136.954 ± 103.106	257.04 ± 62.334	0.0001**
With bacterial infection	110.125 ± 95.166		0.0001**
Total	**132.826 ± 101.946**	**257.04 ± 62.334**	**0.0001****
P value	**0.3353**		

* means significance differences (P <0.05) ** means high significances differences (P <0.001)

Acute leukemia is a commonly seen malignant tumor in the hematopoietic system. And It often causes abnormal bleeding and subsequently leads to death. The mechanism of bleeding causes by leukemia is complex and involves leukemic cells infiltration in the vessel wall, reduction in platelet production, and

coagulation/anticoagulation dysfunction. A quantitative reduction and qualitative dysfunctioning of platelets are the leading causes of bleeding in AL(Qian and Wen-jun, 2013). The results of current study was agree with other study that indicated Platelets secrete a number of factors that can potentially both promote and retard leukemic cell growth; thus, their effects are likely to be highly contextually dependent on leukemia type and receptor expression, stage of disease, and the leukemic microenvironment (Yan and Jurasz, 2016). In another study were close to present results and indicated to platelets, as important effector cells in both haemostasis and inflammation, are implicated in sepsis etiology and contribute to sepsis consequences, according to a certain studies. Platelets trigger hyperinflammation, disseminated intravascular coagulation, and microthrombosis, all of which contribute to multiple organ failure. In addition platelet buildup and activity are important factors in the development of sepsis-related consequences such acute lung injury and acute kidney injury, also Platelet activation readouts could be used as early sepsis indicators, and platelet inhibition in septic patients appears to be an essential target for immune-modulating therapy(de Stoppelaar *et al*., 2014). As a result of their involvement in both inflammation and thrombosis, platelets contribute to an excessive inflammatory host response during sepsis and enhance the onset and progression of sepsis. On the other hand, platelets have a receptor- and organ-dependent ability to reduce inflammation and promote tissue repair. As a result, the outcome is governed by the balance of platelet pro-inflammatory and anti-inflammatory functions(Assinger *et al.*, 2019).

4.7.Biochemical parameters

4.7.1. Alanine Transaminase (ALT)

As indicated in table (4-12) , there were significant differences ($P< 0.05$) in the concentration of ALT in acute leukemia patients compared to AHC groups ,

which reached to (40.656 and 21.796) IU/L , respectively. There was an insignificant decrease (P > 0.05) in infected and non- infected patients , as the mean of ALT (38.881 and 40.978) IU/L , respectively.

Table (4-12): ALT (IU/L) of the study groups

Patients groups		AHC	P value
Infection	**Mean ± SD(U/l)**	**Mean ± SD**	
Without bacterial infection	40.978 ± 4.627	21.796 ± 1.209	0.0001**
With bacterial infection	38.881 ± 3.549		0.0001**
Total	**40.656 ± 4.464**	**21.796 ± 1.209**	**0.0001****
P value	**0.0884**		

* means significance differences (P <0.05) ** means high significances differences (P <0.001)

Hepatomegaly is a common sign of leukemia, although the initial laboratory data revealed an elevated alanine aminotransferase (ALT) of 492 IU/l, acute liver failure as the first symptom is unusual (Gu *et al.*, 2019). This is consistent with previous research Hematological malignancies (HM) frequently necessitate ICU hospitalization, and acute respiratory or renal failure become independent risk factors for death. Despite the fact that HM patients accumulate risk factors, data on acute liver damage (ALD) is sparse (Van de Louw *et al*., 2021). Also it was agrees with another study that showed . Increased total bilirubin (TBIL) or alanine transaminase (ALT) levels are the gold standard for diagnosing Sepsis-associated liver damage (SALI) (Dou *et al*., 2019).

4.7.2. Aspartate Aminotransferase (AST)

The statistical analysis of Table (4-13) revealed that there were significant differences (P< 0.001) in the concentration of AST in patients compared to AHC group , with the mean reached to (35.530 and 20.273) IU/L , respectively. But tha level in infected and non - infected patients , show insignificant differences (P > 0.05).

Table (4-13) : AST (U/l) levels in patients and AHC group .

Patients groups		AHC	P value
Infection	**Mean ± SD(U/l)**	**Mean ± SD**	
Without bacterial infection	33.799 ± 28.707	20.273 ± 5.556	0.0013*
With bacterial infection	45.055 ± 45.217		0.0003 **
Total	**35.530 ± 31.789**	**20.273 ± 5.556**	**0.001 ** **
P value	**0.1940**		

* means significance differences (P <0.05) ** means high significances differences (P <0.001)

Levels of AST and ALT in septic patients in the septic group were statistically substantially higher than in the non-septic groups from the first day after surgery, according to another study. This difference persisted in AST until Day 4 (p values varied from 0.002 to 0.006)(Durila *et al*., 2012).Agreements with the results of previous study identified a link between AST and disease in some studies, but also found a link between AST (liver disease) and anti-leukemic medication in others. The pathogenesis of acute liver failure (ALF) in these patients was first assumed to be related to extensive infiltration by malignant cells, as hepatic outflow blockage was ruled out. The mainly and significantly elevated AST levels are more consistent with ischaemia (or acute drug toxicity) (Anderson *et al.*, 2001). A few studies have shown that Gemtuzumab ozogamicin (GO) therapy is associated with increased rates of hepatotoxicity, resulting in fatal hepatic VOD in some patients. Therefore, GO should be avoided in patients with pre-existing hepatic pathology, in order to decrease the risk of veno-occlusive disease (VOD) (Tsimberidou *et al.*, 2006). Results of current study showed no connection between patients and sepsis and weren't agreement with previous literature . AST levels were found significantly higher in septic when compared to the control group (Ersoy *et al*., 2007).

4.7.3. Alkaline phosphatase (ALP)

According to the results of statistical analysis in Table (4-14) , the decrease in level of ALP in patients was no significantly (P > 0.05) compared with AHC group , as the mean of ALP for acute leukemia patients and controls (92.738 and 105.157)IU\L, respectively. In the same, the results showed that the mean ALP (91.721 and 92.922), respectively. insignificantly differences (P > 0.05) between infected and non-infected bacteria patients .

Table (4-14): ALP (IU/L) level in patients and AHC

Patients of Leukemia		**Control**	**P value**
Infection	**Mean ± SD(U/l)**	**Mean ± SD**	
Without bacterial infection	92.922 ± 32.414	105.157 ± 80.42	0.2095
With bacterial infection	91.721 ± 26.830		0.5156
Total	**92.738 ± 31.504**	**105.157 ± 80.42**	**0.1714**
P value	**0.8893**		

* means significance differences (P <0.05) ** means high significances differences (P <0.001)

According to a certain studies, hepatomegaly, which is caused by leukemic infiltration of the liver, is more common in ALL patients than in AML patients. Monocytic leukemias are the most common type of AML to involve extramedullary infiltration, which includes the liver. Some factors could explain why these AL variants have higher ALP activity(Merza *et al*., 2010). previous study referred that the level of ALP in the serum of AL patients was found to be significantly higher than that of the control group which is consistent with current results . Individuals with ALL had significantly greater total serum levels than patients with AML. ALP levels can be significantly elevated in leukemic patients

with liver infiltration, and these levels are related to the amount of liver involvement(Al Rawi, 2001). In these study we have found that increased cellular alkaline phosphatase activity in leukemic cells at diagnosis was significantly associated with a higher risk of relapse, or treatment resistance, and mortality (Rico *et al.,* 2019). The role of intestinal ALP to detoxifying bacterial lipopolysaccharide (endotoxin) in animal models in vivo and the augmentation of ALP activity following treatment of human cells with inflammatory stimuli in vitro imply that ALPs have a host defense function. The activity of ALP in human plasma (mainly tissue-nonspecific ALP; TNAP) on lipopolysaccharide and other microbial compounds, on the other hand, has not been investigated (Pettengill *et al*., 2017).

4.7.4. Gamma-glutamyl Transferase(GGT)

The statistical analysis of Table (4-15) revealed that there were significant differences (P< 0.05) in the mean of GGT in compared to AHC group , with the mean of GGT for leukemia patients and AHC (71.109 and 56.052) IU/L, respectively. When comparing infected patients with non- bacterial infected , the mean level of AST (77.655 and 69.918) U/l show insignificant differences rise (P > 0.05).

Table (4-15): GGT (IU/L) level in study groups .

Patients group		**AHC**	**P value**
Infection	**Mean ± SD**	**Mean ± SD**	
Without bacterial infection	69.918 ± 45.195	56.052 ± 18.518	0.0403*
With bacterial infection	77.655 ± 40.458		0.0043*
Total	**71.109 ± 44.402**	**56.052 ± 18.518**	**0.0228***
P value	**0.5241**		

* means significance differences (P <0.05) ** means high significances differences (P <0.001)

Liver failure due to ALL was related to the rapid and critical response to treatment; one week after taking prednisone, liver test readings were practically normal, except for bilirubin and GGT. Laboratory findings in ALL frequently show an increase in serum transaminase activities but bilirubin, GGT and alkaline phosphatase are usually normal or only slightly elevated at the time of diagnosis, however jaundice is uncommon (Felice *et al*., 2000). previous studies showed that elevation of the liver enzymes such as AST, ALT, ALP, GGT in leukemic patients due to infiltration of the leukemic cell that leads to liver damage, while other studies demonstrated limited effect of leukaemia in the liver functions, As a result, the goal of this study was to determine the levels of AST, ALT, ALP, GGT, TP, ALB, and GLB in leukemic individuals (Shimizu, 2008). This contradicts the findings of one study, which found a link between the presence and durability of increased GGT in relatives and disease .GGT elevation were also associated with Symptomatic venous thromboembolism (VTE) is an unpredictable and life-threatening complication of therapy for acute lymphoblastic leukemia (ALL*)* (Mateos *et al*., 2019).

4.7.5. Serum Albumin (SA)

The results of table (4-16) shows revealed that there were high significant differences (P< 0.001) in the concentration of Albumin in patients compared to AHC group , with the mean of Albumin for Leukemia patients and AHC (42.069 and 47.294) g/l, respectively. As the mean of Albumin (41.813 and 42.115) g/l, respectively, When patient with bacterial infection were compared to those without bacterial infection, there was a non-significant decrease (P > 0.05).

Table (4-16): Albumin (g/l) level of studied groups .

Patients group	AHC	P value

Infection	Mean ± SD(g/l)	Mean ± SD	
Without bacterial infection	42.115 ± 8.211	47.294 ± 3.765	0.0001**
With bacterial infection	41.813 ± 7.673		0.0003**
Total	**42.069 ± 8.095**	**47.294 ± 3.765**	**0.0001****
P value	**0.8916**		

* means significance differences (P <0.05) ** means high significances differences (P <0.001)

There was a significant association between outcome and serum albumin levels at diagnosis for AML patients, those with higher levels faring better than those with (SA) levels less than 30 g/L. Although lower SA levels were associated here with higher Body Mass Index(BMI) , the latter parameter had not impact on overall survival (OS) (Filliatre- Clement et al., 2019). certain studies indicate that plasma albumin (PA) decrease is an important biomarker for imminent bacteremia in adult patients with AML(Gradel *et al*., 2020). Previous studies performed that patients with AL also had lower levels of albumin (Wang *et al.,* 2002). The current data confirmed an association between low admission serum albumin levels and mortality (Kendall *et al*., 2019). This is in conformity with a study that was published clinical evidence that two additional characteristics (fever and serum albumin) that we have found significant in these study, have been previously recognized as having prognostic influence in AML (Sanz *et al.*, 1988).

4.7.6. Total serum Bilirubin (TSB)

Table (4-17) revealed that there was significant difference (P < 0.05) in the level of TSB in patients compared to AHC group , with the mean of TSB reached to 0.503 and 0.4032 (mg/dl), respectively. The results of the same Table revealed that the mean of TSB (0.500 and 0.504, respectively) decreased insignificantly differences (P > 0.05) in infected and non- infected bacteria patients .

Table (4-17): Total Bilirubin (mg/dl) level of patients and AHC .

Patients group	AHC	P value

Infection	Mean ± SD (mg/dl)	Mean ± SD	
Without bacterial infection	0.504 ± 0.369	0.4032 ± 0.133	0.0648
With bacterial infection	0.500 ± 0.338		0.0981
Total	**0.503 ± 0.301**	**0.4032 ± 0.133**	**0.0266***
P value	**0.9679**		

* means significance differences (P <0.05) ** means high significances differences (P <0.001)

The most clinically significant drug-related toxicity that used to treat AML, observed in clinical studies was liver injury, defined as elevation of levels of serum aminotransferase enzymes and/or bilirubin. These signs of liver injury occurred approximately 1-2 weeks after treatment and were self-limited in most cases(Leopold *et al*., 2002). previous study that referred to almost all antineoplastic agents have some degree of hepatotoxicity, and the liver injury is usually due to direct, intrinsic toxicity. The typical manifestation is an elevation in liver enzymes or bilirubin during therapy that reverses rapidly with stopping treatment or dose modification (Halegoua-De Marzio *et al.*, 2013). This contradicts a prior study that found a link between high total bilirubin and poor prognosis in individuals with protracted sepsis (Yamano *et al.*, 2016). another study pointing to elevated serum bilirubin levels within 72 hours of admission are associated with an increased risk of mortality in patients with severe sepsis and septic shock (Patel *et al*., 2015).

4.7.7. Direct Bilirubin (DB)

Table (4-18) revealed high significant differences (P< 0.001) in patients with compared to AHC group , as the mean of DB for patients and AHC (0.177 and 0.0936) mg /dl, respectively. As the mean for DB (0.110 and 0.190) mg /dl, respectively, high significant differences decreased (P < 0.001) in patients with bacterial infection compared to patients without bacterial infection.

Table (4-18): Direct Bilirubin (mg/dl) level of studied groups .

Patients groups	AHC	P value

Infection	Mean ± SD (mg/dl)	Mean ± SD	
Without bacterial infection	0.190 ± 0.039	0.0936 ± 0.026	0.0001**
With bacterial infection	0.110 ± 0.030		0.0383*
Total	**0.177 ± 0.036**	**0.0936 ± 0.026**	**0.0001****
P value	**0.0001****		

* means significance differences (P <0.05) ** means high significances differences (P <0.001)

Patients with acute leukemia (AML/ALL) commonly present with elevated aminotransferases along with hyperbilirubinemia. This is likely due to hepatic injury from leukemic infiltrates .bilirubin increase in response to chemotherapeutic drugs during treatment of acute leukemia. Liver function test should be regularly evaluated during the treatment of patients with leukemia (Islam *et al*., 2020). There are similarities to a prior study that demonstrates levels of bilirubin and other associated parameters were higher for the sepsis group, only sepsis related organ failure (SOFA) score and bilirubin levels were correlated. Because bilirubin is already a SOFA parameter, this correlation was not considered as clinically significant (Tutak *et al.*, 2014). Also the current results agree with previous study that referred to Sepsis was also associated with development of jaundice secondary to intrahepatic cholestasis. bilirubin serum levels were increasing, reaching the peak of 18.41 mg/dL of total and 15.67 mg/dL of direct bilirubin (Piwowarczyk *et al.*, 2019). Certain studies too indicated to the presence of significant conjugated hyperbilirubinemia, although a rare presenting feature in ALL, can require modification of the induction therapy protocol (Segal *et al*., 2010).

4.7.8. Total Protein (TP)

Table (4-19) revealed that there were significant differences (P< 0.001) in the level of TP in patients compared to AHC group , as measured by the mean of TP for Leukemia patients and controls (67.914 and 75.662) g/l, respectively. In

infected and non- infected Patients with bacteria an insignificant differences decrease (P > 0.05) in TP (65.496 and 68.353) g/l, respectively.

Table (4-19): Total Protein (g/l) level of patients and AHC groups .

Patients of Leukemia		Control	P value
Infection	**Mean ± SD(g/l)**	**Mean ± SD**	
Without bacterial infection	68.353 ± 10.989	75.662 ± 5.762	0.0001**
With bacterial infection	65.496 ± 10.199		0.0001**
Total	**67.914 ± 10.873**	**75.662 ± 5.762**	**0.0001****
P value	**0.3361**		

* means significance differences (P <0.05) ** means high significances differences (P <0.001)

Reduced total protein and albumin levels were shown to be prevalent in 38.1 % and 28.5 % of hematological malignancies, respectively (Turedi *et al*., 2010). The current results disagree of previous study that indicate to the patients with ALL had lower serum total protein (Koskelo *et al.*, 1991). Another study that showed Hypoproteinemia is significantly correlated with fluid retention and weight gain, development of acute respiratory distress syndrome (ARDS) and poor respiratory outcome, and mortality in patients with sepsis (Mangialardi *et al.*, 2000). Certain study that emphasized that plasma protein levels display reasonably predictable changes in response to acute inflammation, malignancy, trauma, necrosis, infarction, burns, and chemical injury (O'Connell et al., 2005).

4.7.9. Lactate Dehydrogenase (LDH)

Table (4-20) shows that there were significant differences (P< 0.001) in the level of LDH in patients compared to the AHC group , with the mean reached to (712.098 and 163.617) U/L, respectively. As the mean of LDH (634.112 and 726.277) U/L, respectively, When infected and non- infected patients ,there was a substantial decrease (P< 0.001).

Table (4-20) : LDH (U/L) level of studies groups .

Patients groups		AHC	P value
Infection	**Mean ± SD (U/L)**	**Mean ± SD**	
Without bacterial infection	726.277 ± 81.622	163.617 ± 39.28	0.0001**
With bacterial infection	634.112 ± 67.853		0.0001**
Total	**712.098 ± 79.4289**	**163.617 ± 39.28**	**0.0001****
P value	**0.0001****		

* means significance differences (P <0.05) ** means high significances differences (P <0.001)

In ALL, LDH levels were markedly elevated (Kornberg and Polliack, 1980) The current study was agree with results that correlation between LDH with acute leukemia. Agreements with previous study that referred increased plasma LDH levels are commonly seen in patients with severe sepsis. It is a marker of cell injury which reflects the degree of tissue damage (Zein *et al.*, 2004). Also in other study that confirmed the Elevation of Lactate dehydrogenase activity in acute leukemia patients was reflecting the increase rate of aerobic glycolysis. Lactate dehydrogenase can be used as independent prognostic marker not only in diagnosis of acute leukemia but also, in classification of acute leukemia (Walaa Fikry, 2017).

Another study that connection between LDH and sepsis , and there is other study indicate to Serum LDH is probably associated with 28-day mortality in patients with sepsis (Lu *et al.*, 2018).

4.8. The Correlations between parameters of the study

4.8.1. The correlation coefficient between study parameters in leukemia's patients without bacterial infections .

Table (4-21) shows the results of statistical analysis, which revealed a significant association (P<0.01) between CRP and IL-6 ,also, as well as a positive correlation (0.612). At the same time, there was a significant (P< 0.01) association between ALT and AST, as well as a positive correlation (0.766 and 0.670) between

IL-6 and direct bilirubin . Albumin and total protein had significant correlations at ($P<0.01$), with positive correlations which reached to (0.698). In addition , there was positive correlation (0.669) between LDH and GGT . Albumin with age,CRP,IL-6 had negative significant correlation (-0.545,-0.566,-0.575) .

Table 4-21: The correlation between parameters (that have significance effects) in leukemia's patients without bacterial infections .

	Age	WBC	CRP	IL-6	D-Dimer	PLT	ALT	AST	GGT	Albumin	Direct Bilirubin	Total Protein	LDH
Age	1	-0.211	0.357	0.343	0.210	0.006	0.035	-0.020	-0.080	-0.545 *	0.409	-0.324	-0.104
WBC	-	1	0.050	-0.049	0.261	- 0.151	-0.035	0.201	-0.121	-0.136	-0.131	-0.271	0.389
CRP	-	-	1	0.612**	0.062	-0.296	-0.038	0.032	-0.128	-0.566*	0.316	-0.482	-0.006
IL-6	-	-	-	1	0.023	-0.344	0.011	-0.054	-0.024	-0.575*	0.670**	-0.419	-0.004
D-Dimer	-	-	-	-	1	-0.095	-0.022	-0.037	0.164	-0.209	0.046	-0.053	0.269
PLT	-	-	-	-	-	1	-0.095	-0.056	-0.178	0.468	-0.323	0.319	-0.241
ALT	-	-	-	-	-	-	1	0.766**	0.397	0.076	0.115	0.211	0.439
AST	-	-	-	-	-	-	-	1	0.075	0.020	0.069	0.028	0.382
GGT	-	-	-	-	-	-	-	-	1	0.036	0.036	0.378	0.669**
Albumin	-	-	-	-	-	-	-	-	-	1	-0.514*	0.698**	-0.052
Direct Bilirubin	-	-	-	-	-	-	-	-	-	-	1	-0.360	0.030
Total Protein	-	-	-	-	-	-	-	-	-	-	-	1	0.111
LDH	-	-	-	-	-	-	-	-	-	-	-	-	1

* The correlation is significant at 0.05 level (2-tailed) ** The correlation is significant at 0.01 level (2-tailed)

The positive correlation between CRP with IL-6, among older adults with AML, the relationships between TNFα-R1, CRP, and IL-6 with change in physical and emotional health during treatment warrants further investigation. CRP levels increased from baseline to weeks 1–3, , and decreased from weeks 1–3 to follow-up. IL-6 levels decreased from baseline to weeks 1–3, then increased from weeks 1–3 to follow-up (Loh *et al*., 2020). In the current study, an over-production of IL-6 is observed in patients with M5 subtype acute leukemia, suggesting that is involved in the pathogenesis of acute monoblastic leukemia, probably as a viability factor for tumor cells (van der Schoot *et al.*, 1989). Patients who developed B-cell precursor ALL had significantly lower C-reactive protein (CRP) and higher levels of IL6 (Søegaard *et al*., 2018).

AST with ALT , several mechanisms have been proposed to explain the etiopathogenesis of acute hepatic failure in leukemia, including comorbidity with viral infections, particularly HBV, sepsis, autoimmune hepatitis, or hypoxia and ischemia caused by leukemic cell infiltration that results in obstruction of hepatic blood flow, or hypoxia and ischemia caused by leukemic cell infiltration that results in obstruction of hepatic blood flow. In the example described here, hepatoprotective medication was started while the results of the bone marrow biopsy were awaited, and the ALT, AST, and TBIL levels gradually dropped. After a biopsy revealed massive aggregates of blasts, low-dose dexamethasone was started, and serum levels of ALT, AST, and TBIL decreased rapidly, accompanied by a significant improvement in the patient's physical state(Gu *et al.*, 2019). Accordance with one study that showed Pegasparaginase (PEG-Asp), commonly used in acute lymphoblastic leukemia (ALL), is associated with elevated transaminases. Treatment of acute hepatotoxicity is limited to case studies reporting success with levocarnitine (LC) (Trang *et al*., 2020). The current results was agreement with other study referred

to the National Cancer Institute (NCI) common toxicity criteria (CTC) are a safety feature that guide choice of dose in clinical trials, but for asymptomatic toxicities involving bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and treatment-associated mortality in acute myeloid leukemia (Veatch *et al*., 2013).

IL-6 with direct bilirubin (DB) , positive correlations were observed between the serum bilirubin and IL-6 following allogeneic hematopoietic stem cell transplantation in acute leukemia (Min *et al.*, 2001)**.** It was reported in bone marrow transplant patients increased levels of TNF-a, IL-6 and CXCL-8 correlated with hepatic or renal dysfunction as evaluated by increased bilirubin and creatinine in plasma (Ferrà *et al*., 1998).

Albumin with total protein . The lower plasma protein binding in relapsed patients appears to be explained primarily by lower serum albumin concentrations, given the correlation we found between teniposide binding and serum albumin. These patients had significantly lower serum albumin values after undergoing 2-9 months of second remission therapy of ALL (Petros *et al.*, 1992).

The negative correlation Albumin with Age, CRP and IL-6, the ratio of C-reactive protein to albumin (CAR) is a simple and effective prognostic marker in patients with AML. It could be an additional prognostic factor that help further precise the current risk stratification of non-M3 AML, particularly for patients in intermediate risk stratification and those aged ≤ 65 years and those who did not undergo Hematopoietic stem cell transplant (HSCT) (Dou *et al.*, 2022). Similarly, the IL-6 levels in leukaemia/lymphoma (ATL) patients were significantly higher and were significantly correlated with decreased serum albumin (Yamamura *et al*., 1998).

4.8.2. The correlation coefficient between study parameters (that have significance effects) in leukemia's patients with bacterial infections

The current results in table (4-22) revealed that there was a strong significant correlation between Age and WBC at (P<0.01), as well as an positive correlation (0.639). There were also strong significant correlations between IL6 and WBC (P<0.01), significant correlations between IL6 and Age (P<0.05), and positive correlations (0.529, 0.767), respectively. While there were strong positive associations between CRP and D-Dimer (P<0.01), there were also significant positive correlations (0.634). There were high significances correlations at (P<0.01) between AST , WBC ,IL6 and D-dimer significances correlations at (P<0.05), there were positive associations (0.910, 0.718, 0.566),respectively. While there were significant correlations between GGT and ALT (P<0.05) and positive correlation (0.540). There were high significant differences correlations at (P<0.01) between Albumin and PLT, as well as positive correlations (0.644), respectively, in the same Table. Direct bilirubin and D-Dimer, PLT and ALT had a strong significant association (P<0.01) and (P<0.05), respectively, as positive, inverse, and positive correlation (0.630, -0.689, and 0.537). Also, there was a strong significant correlation (P<0.01) between Total Protein and IL6, PLT, as well as inverse and positive correlations (-0.697, 0.789), respectively. At the same time, there was a significant (P<0.01) association between LDH and WBC, IL6, D-Dimer, and AST, as well as positive correlation (0.834, 0.618, 0.726, and 0.957), respectively.

Table 4-22: The correlation between parameters (that have significance effects) in leukemia's patients with bacterial infections .

	Age	WBC	CRP	IL-6	D-Dimer	PLT	ALT	AST	GGT	Albumin	Direct Bilirubin	Total Protein	LDH
Age	1	0.639**	0.086	0.529*	0.007	0.043	0.218	0.459	-0.320	-0.221	-0.115	-0.103	0.471
WBC	-	1	0.081	0.767**	0.231	-0.293	0.389	0.910**	0.136	-0.110	-0.122	-0.305	0.834**
CRP	-	-	1	0.462	0.634**	-0.296	-0.167	0.312	-0.275	-0.426	0.416	-0.226	0.445
IL-6	-	-	-	1	0.122	-0.473	0.243	0.718**	-0.052	-0.640**	0.042	-0.697**	0.618**
D-Dimer	-	-	-	-	1	-0.381	0.181	0.566*	-0.021	0.068	0.630**	0.139	0.726**
PLT	-	-	-	-	-	1	-0.476	-0.477	-0.339	0.644**	-0.689**	0.789**	-0.389
ALT	-	-	-	-	-	-	1	0.525*	0.540*	-0.320	0.537*	-0.285	0.360
AST	-	-	-	-	-	-	-	1	0.229	-0.159	0.227	-0.290	0.957**
GGT	-	-	-	-	-	-	-	-	1	0.041	0.104	-0.223	0.078
Albumin	-	-	-	-	-	-	-	-	-	1	-0.470	0.864**	-0.038
Direct Bilirubin	-	-	-	-	-	-	-	-	-	-	1	-0.279	0.249
Total Protein	-	-	-	-	-	-	-	-	-	-	-	1	-0.121
LDH	-	-	-	-	-	-	-	-	-	-	-	-	1

* The correlation is significant at 0.05 level (2-tailed) ** The correlation is significant at 0.01 level (2-tailed)

The positive correlation between Age with WBC, in patients with (AML) may be present with early complications from sepsis or leukemic infiltration. Benefits from early in-intensive care unit (ICU) hematological management was evaluated in 42 adults with newly diagnosed AML with hematological risk of early death (age 46 years, French–American–British [FAB] M4/5 58%, leukocytes 103 × 10^9/L) first admitted to the ICU without immediate life support (early-ICU) (Lengliné *et al*., 2012)**.** The previous studies that indicated that to the elderly, total white blood cells (WBCs) drop slightly. The number of WBCs increases in response to an acute infection, and it increases dramatically in sepsis. There have been some findings that a higher number of WBCs can be a predisposing factor for bacteremia. There is apparently a link between neutrophilia and leucopenia and an increased mortality risk in the elderly (Aminzadeh and Parsa, 2011).Another study showed Leukopenia is not typically regarded a normal reaction to infection, despite the fact that both leukocytosis and leukopenia have been considered systemic inflammatory response syndrome criteria. Within the sepsis, they wanted to assess the prognostic value of leukopenia as a marker of sepsis-defining hematological organ failure. In patients with probable infection, it was predicted that leukopenia would be linked to a higher risk of death than leukocytosis (Belok *et al*., 2021).

IL-6 and WBC, (Antonell *et al.,* 1995) found that elevated IL-6 levels in all neutropenic patients with sepsis syndrome, corroborate. However, only the patients who died of refractory septic shock maintained high serum levels of IL-6. These data, showing an association between both septic shock and mortality, seem to be consistent with that reported in critically ill patients without leukopenia. Shows the importance of IL-6 as an important mediator of severe infection in adults with severe neutropenia. High correlation was found between IL-6 and temperature in them study as in immunocompetent patients after severe burn injury . No correlation was found

between IL-6 levels and sex, age, underlying disease. type of chemotherapy, or leukocyte or platelet count (Tilman Steinmetz *et al.*, 1995). In addition , the bacterial infection group had greater PCT, IL-6, CRP, ESR, and WBC counts than the systemic inflammatory response syndrome (SIRS) group (Jekarl *et al*., 2013). Recently, validated the diagnostic capability of IL-6 and showed that the combination of CRP and IL-6 as a panel for the early diagnosis of sepsis could enhance the sensitivity in the diagnosis of sepsis and may provide a new diagnostic strategy for sepsis patients (Shoukry *et al*., 2021).

CRP with D-Dimer . It was reported that CXCIL-8 and D-dimer levels were higher in patients with febrile neutropenia than in the other two groups. Although macrophage migration inhibitory factor (MIF) and osteoprotegerin(OPG) were higher in patients with newly diagnosed cancers, there were no differences among the three groups regarding procalcitonin (PCT) and hs-CRP values (Bilgir *et al*., 2012). It was revealed that to APL is a distinct subtype of AML, which is characterized by DIC. Among the components of the DIC criteria D-dimer and During sepsis, ESR and CRP are increased (Lee *et al.*, 2013). On the other hand , the positive correlation between of D-Dimer and CRP were disagreement with the results of current study that indicate to IL-6 and D-dimer were strongly related to all-cause mortality. Interrupting Antiretroviral Therapy (ART) may further increase the risk of death by raising IL-6 and D-dimer levels. Therapies that reduce the inflammatory response to HIV and decrease IL-6 and D-dimer levels may warrant investigation (Kuller *et al.*, 2008).

The positive correlation between AST and WBC,IL6,D-Dimer and ALT in current study was agreements with one study that conducted patients with infection are often accompanied with changes of biochemical indexes, such as aspartate

transaminase (AST). Some clinical parameters, including white blood cell count (WBC), (IL-6) and (D-D) are commonly used in diagnosing infection (Hack *et al*., 1989, Fioretto *et al*., 2008, Schwameis *et al*., 2015, El Haddad *et al.*, 2018 Shao *et al*., 2019) . Another study referred that to IL-6 significantly increased the activities of ALT and AST, and creatinine concentration in the patients with sepsis (Ding *et al*., 2014). Also, measurements of ALT, AST, ALP and CRP along with blood counts are driving toward the successful diagnosis and management of septic cases. The implementation of these diagnostic parameters around the globe may reduce the morbidity and mortality in patients (El-Nahhal and Al_Shareef, 2018).

The results of current study found a positive link between GGT and ALT, which is consistent with the results of other studies found that, ALT and GGT activities were expressed as multiples of their upper limits of normal (ULN). The R ratio was defined as the ratio of ALT activity to GGT activity, i.e. (ALT/ULN): (GGT/ULN). When the ALT or GGT values were both below the ULN, the ULN was used instead of the value. In our hospital, the ULNs for ALT and GGT were 40 IU/L and 50 IU/L, respectively. When GGT increased above 50 and the R ratio was 2 or less, liver damage was classified as cholestatic. When ALT levels rise above 40 IU/L and the R ratio rises above 2, it's considered hepatocellular. When total bilirubin was 3.0 mg/dL or above, sepsis-associated liver damage was classified as "with jaundice," and "without jaundice" when total serum bilirubin was less than 3.0 mg/dL (Kobashi *et al.*, 2013). It was indicated that to AST and ALT were promptly and significantly raised in shock liver, with early superiority of AST over ALT, modest elevation of GGT, and a rapid decline in a few days once the underlying course was rectified; these patterns have previously been documented (Geier *et al*., 2006). But the results of current study was disagreements with other study that showed of serum GGT and

AST values can be used to predict the prognosis of patients with sepsis-associated cholestasis (Oswari *et al.*, 2013).

The current data revealed a positive relationship between PLT and Albumin. It was reported in particular, recent hemorrhage, hypoalbuminemia, uremia, fever, bacteremia, are more likely to be found among patients with severe bleeding low platelets counts in AML, FAB subtype M3 patients (Friedmann *et al.,* 2002)**.** The risk of developing a serious infectious complication in the early phase of azacitidine treatment . In univariate analysis, lower neutrophil count, lower lymphocyte count, higher bone marrow blast percentage , lower platelet count , higher serum ferritin level , lower serum albumin level were identified to be associated with a significant increase in the risk of infection ($p < 0.05$) in acute leukemia patients (Mądry *et al.*, 2019).

The current findings show a positive correlation between direct bilirubin and both ALT, PLT and D-dimer. It was , which suggests that MCV, NE, WBC, PLT, HB, D-Dimer, PT, CRP, PCT, IL-6, ALB, TBIL, Cr, LAC, CysC, and BNP were statistically significant in the sepsis group compared to the control group. The diagnostic efficiency of D-dimer, CRP, and PCT is higher. PLT and IL-6 are statistically significant and have diagnostic significance when compared to the difference between the infection and systemic inflammatory response syndrome (SIRS) groups. In the comparison of Sepsis vs. Infection, WBC, IL-6, neutrophils , and TBIL, statistical differences were found. The Area under the curve (AUC) of NE was the highest among the three, at 67.6, although the specificity (95.8%) was the highest, the sensitivity (49%) was the lowest(Meng *et al*., 2020). In which thrombocytopenia is a common feature of sepsis(Levi, 2004).

Total protein with PLT and Albumin, it was reported that WBC , hemoglobin, hematocrit, platelet count, erythrocyte sedimentation rate for most patients were within the normal range (Ng *et al*., 2009).

The positive correlation between LDH and WBC ,D-Dimer, IL6 and AST was agree with previous studies conducted that there were statistic positive correlations between serum LDH and serum IL-1b, creatinine, and lactate .There was a significant statistic negative correlation between serum LDH and oxygenation index .Nevertheless, there were no significant correlations between serum LDH and serum WBC , albumin , BNP , and D-dimer (Lu *et al*., 2018) **.** A another study refers to Levels of fibulin-2, WBC, NEU%, D-dimer, IL-6, CRP and PCT were significantly higher in the infection group than in the non-infection group ($P < 0.05$) (Li *et al.*, 2022).

Conclusions and Recommendations

Conclusions

- *Staphylococcus hemolyticus* was the most prevalent bacterial species associated with acute leukemia infection.
- Most grame positive bacteria isolates were resistant to cephalexin, kanamycin, amikacin, cefdinir, clarithromycin, cefepime, ceflaxin, azithromycin and amikacin , while gram negative bacteria was resistance to all types of antibiotics.

Recommendations

- To avoid the occurrence of further resistance, a blood culturing test should be performed before any antibiotics are given to sepsis suspects.
- Conducting a study about molecular diagnosis of mutation that causes disease.
- Conducting a study about common bacterial infection of acute leukemia(ALL and AML) subtypes
- Conducting a study about Mixed-phenotype acute leukemia ,epidimiology , common bacterial infection and correlation with biochemical and immunological parameters .
- Conducting a study about the relationship between renal function tests (urea, creatinine) with bacterial infection in acute leukemia patients .
- Conducting a study about the common CD marker in acute leukemia related to bacterial infection.

Conducting a study about vitamin D defieciency and bacterial infection in acute leukemia patients.

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Appendices

Apendix 1: Questionnaire of patients

Name:		
Age:		
Sex:		
Date:		
Blood group		
Leukemia type	ALL	AML
Subtype of ALL:		
Subtype of AML:		
Antibiotics	yes	No
Chemotherapy	yes	No
Fever	yes	No
Chronic diseases		

Apendix 2: Antibiotics susceptibility profile of Gram positive bacteria by vitek (R-resistance, I-intermediate, S-sensitive).

Antibiotics	*Staphylococcus haemolyticus (1)*	*Staphylococcus haemolyticus (2)*	*Staphylococcus haemolyticus (3)*	*Enteroccocus casseliflavus*	*staphylococcus warneri*	*Staphylococcus hominis*	*Staphylococcus haemolyticus (4)*	*Staphylococcus haemolyticus (5)*	*Staphylococcus haemolyticus (6)*	*Enteroccocus casseliflavus*	*staphylococcus warneri*	*Staphylococcus hominis*	*R%*	*S%*
Benzylpenicillin	R	S	R		S	R	R	S	R		S	R	60	40
Cefoxitin screen	+	-	+		-	+	+	-	+		-	+		
Clindamycin	R	S	S		S	R	R	S	S		S	R	40	60
Erythromycin	R	R	R	S	R	R	R	R	R	S	R	R	90	10
Fusidic acid	R	S	R		S	R	R	S	R		S	R	60	40
Gentamicin	R	S	S	S	S	R	R	S	S	S	S	R	80	20
Inducible clindamycin resistance		-	-		-	-		-	-		-	-		
Levofloxacin	R	S	S		S	S	R	S	S		S	S	20	80
Linezolid	S	S	S	S	S		S	S	S	S	S		0	100
Moxifloxacin	R	S	S		S	S	R	S	S		S	S	20	80
Nitrofurantoin	S	S	S		S	S	S	S	S		S	S	0	100
Oxacillin	R	S	R		S	R	R	S	R		S	R	60	40
Rifampicin	R	S	S		S	R	R	S	S		S	R	40	60
Teicoplanin	S	S	S	S	S	R	S	S	S	S	S	R	20	80
Tetracycline	R	S	S	S	S	R	R	S	S	S	S	R	40	60
Tigecycline	S	S	S	S	S	S	S	S	S	S	S	S	0	100
Tobramycin	R	S	S		S	R	R	S	S		S	R	40	60
Trimethoprim/sulfamethoxazole	S	S	S		S	S	S	S	S		S	S	0	100
Vancomycin	S	S	S	S	S	R	S	S	S	S	S	R	20	80
Amoxicillin+	R		R		S	R	R		R		S	R	60	40
Amoxicillin/clavulanic Acid+	R		R		S	R	R		R		S	R	60	40
Ampicillin+	R		R	S	S	R	R		R	S	S	R	60	40
Ampicillin/sulbactam+	R	S	R		S	R	R	S	R		S	R	60	40
+Carbenicillin					S	R					S	R	50	50
+Azithromycin	R	R	R		R	R	R	R	R		R	R	100	0
Cefazolin					S	R					S	R	50	50
Cefalexin	R		R			R	R		R			R	100	0
Cefepime	R		R		S	R	R		R		S	R	60	40
Cefixime	R	R	R			R	R	R	R			R	100	0
Cefotaxime	R		R		S	R	R		R		S	R	60	40
Cefoxitin	R		R		S	R	R		R		S	R	60	40
Cefotetan	R		R		S	R	R		R		S	R	60	40
Cefpirome						R						R	100	0
Ceftazidime	R	R	R		S	R	R	R	R		S	R	80	20

Apendix 3: Antibiotics susceptibility profile of Gram negative bacteria by vitek (R-resistance, I-intermediate, S-sensitive)

Ceftriaxone	R		R		S	R	R		R		S	R	60	40
Ciprofloxacin	R	S	S	S	S	S	R	S	S	S	S	S	90	10
Clarithromycin	R	R	R		R	R	R	R	R		R	R	100	0
Cloxacillin	R		R		S	R	R		R		S	R	60	40
Dicloxacillin					S	R					S	R	50	50
Doripenem	R		R		S	R	R		R		S	R	60	40
Ertapenem	R		R		S	R	R		R		S	R	60	40
Doxycycline		S	S		S			S	S		S		0	100
Flucloxacillin					S	R					S	R	50	50
Imipenem					S	R					S	R	50	50
Meropenem	R	S	R		S	R	R	S	R		S	R	60	40
Methicillin					S	R					S	R	50	50
Minocycline	S	S	S		S	S	S	S	S		S	S	0	100
Ofloxacin					S	S					S	S	0	100
Cefdinir	R		R				R		R				100	0
Piperacillin	R		R		S	R	R		R		S	R	60	40
Piperacillin/tazobactam	R		R		S	R	R		R		S	R	60	40
Ticarcillin	R		R		S	R	R		R		S	R	60	40
Ticarcillin/ Clavulanic Acid	R		R		S	R	R		R		S	R	60	40
Amikacin	R					R	R					R	100	0
Kanamycin	R					R	R					R	100	0
Ceftaroline					S						S		0	100
Cefalotin					S	R					S	R	50	50
Gatifloxacin						S						S	0	100
Oxacillin MIC					S	R					S	R	50	50
Streptomycin high level				S						S			0	100
Daptomycin	S	S	S			S	S	S	S			S	0	100
Lincomycin	R	S	S				R	S	S				40	60
Norfloxacin	R	S	S			S	R	S	S			S	40	60
Ceftizoxime	R		R				R		R				100	0

Antibiotics	***Klebsiella Pneumonia (1)***	***Klebsiella Pneumonia (2)***	***Klebsiella Pneumonia (3)***	***Klebsiella Pneumonia (4)***	***R %***	***I %***	***S %***
Gentamicin	R	R	R	R	100	0	0
ESBL	-		-				
Trimethoprim/sulfamethoxazole	R	R	R	R	100	0	0
Cefepime	R	R	R	R	100	0	0
Ceftazidime	R	R	R	R	100	0	0
Levofloxacin		R		R	100	0	0
Ciprofloxacin	R	R	R	R	100	0	0
Imipenem	R	R	R	R	100	0	0
Meropenem	R	R	R	R	100	0	0
Ticarcillin\Clavulanic Acid		R		R	100	0	0

Amoxicillin	R	R	R	R	100	0	0
Ampicillin	R		R		100	0	0
Ampicillin\sulbactam		R		R	100	0	0
Amoxicillin/clavulanic Acid+	R	R	R	R	100	0	0
Piperacillin\ **sulbactam**		R		R	100	0	0
Piperacillin/tazobactam	R	R	R	R	100	0	0
Cefadroxil		R		R	100	0	0
Cefalexin		R		R	100	0	0
Cefuroxime		R		R	100	0	0
Cefuroxime Axetil		R		R	100	0	0
Cefazolin		R		R	100	0	0
Cefpodoxime		R		R	100	0	0
Ceftriaxone		R		R	100	0	0
Cefixime		R		R	100	0	0
Nalidixic Acid		R		R	100	0	0
Tobramycin		R		R	100	0	0
Ertapenem		R		R	100	0	0
Cefotaxime	R		R		100	0	0
Norfloxacin	R	R	R	R	100	0	0
Fosfomycin	R	R	R	R	100	0	0
Nitrofurantoin	R	R	R	R	100	0	0
Amikacin	R	I	R	I	50	50	0

Apendix 4:Diagnostic results of biochemical tests for Gram positive bacteria isolated from Acute leukemia patients

Tests	Staphylococcus haemolyticus (1)	*Staphylococcus haemolyticus (2)*	*Staphylococcus haemolyticus (3)*	*Enteroccocus casseliflavus*	*staphylococcus warneri*	*Staphylococcus hominis*
BGAL	-	-	-	+	-	-
APPA	-	-	-	-	-	-
PHOS	-	-	-	-	-	-
ProA	-	-	-	-	-	-
AGAL	-	-	-	-	-	-
PyrA	+	+	+	+	+	-
BGUR	+	+	+	-	-	-
TyrA	-	-	-	+	-	-
URE	-	-	-	-	-	+
ILATk	+	+	+	-	+	-
Dmal	+	+	+	+	+	+
Dman	-	-	-	+	+	-
Dmne	-	-	-	+	-	-
O129R	+	+	+	-	+	-
SAC	+	+	+	+	+	+
Dtre	+	+	+	+	+	+
AMY	-	-	-	+	+	-
LeuA	-	-	-	+	-	-
AIaA	-	-	-	-	-	-
H2S	+	+	+	-	-	-
Drib	+	+	+	-	+	-
NOVO	-	-	-	-	-	-
Draf	-	-	-	-	-	-
OPTO	+	+	+	+	+	+
PIPLC	-	-	-	-	-	-
CDEX	-	-	-	-	-	-
NC6.5	+	+	+	+	+	+
DXYL	-	-	-	-	-	-
AspA	-	-	-	-	-	-
BGURr	+	+	+	-	-	-
dSOR	-	-	-	+	-	-
LAC	-	-	-	-	-	-
SAL	-	-	-	+	-	-
ADH1	+	+	+	+	+	-
BGAR	-	-	-	+	-	-
NAG	+	+	+	+	-	-
AMAN	-	-	-	-	-	-
POLYB	-	-	-	+	-	-
MBdG	-	-	-	+	-	-
AGLU	-	-	-	+	-	+
dGAL	-	-	-	-	-	-
BACI	+	+	+	+	+	-
PUL	-	-	-	-	-	-

Apendix 4:Diagnostic results of biochemical tests for Gram positive bacteria isolated from Acute leukemia patients

Tests	Staphylococcus haemolyticus (4)	*Staphylococcus haemolyticus (5)*	*Staphylococcus haemolyticus (6)*	*Enteroccocus casseliflavus*	*staphylococcus warneri*	*Staphylococcus hominis*
BGAL	-	-	-	+	-	-
APPA	-	-	-	-	-	-
PHOS	-	-	-	-	-	-
ProA	-	-	-	-	-	-
AGAL	-	-	-	-	-	-
PyrA	+	+	+	+	+	-
BGUR	+	+	+	-	-	-
TyrA	-	-	-	+	-	-
URE	-	-	-	-	-	+
ILATk	+	+	+	-	+	-
Dmal	+	+	+	+	+	+
Dman	-	-	-	+	+	-
Dmne	-	-	-	+	-	-
O129R	+	+	+	-	+	-
SAC	+	+	+	+	+	+
Dtre	+	+	+	+	+	+
AMY	-	-	-	+	+	-
LeuA	-	-	-	+	-	-
AIaA	-	-	-	-	-	-
H2S	+	+	+	-	-	-
Drib	+	+	+	-	+	-
NOVO	-	-	-	-	-	-
Draf	-	-	-	-	-	-
OPTO	+	+	+	+	+	+
PIPLC	-	-	-	-	-	-
CDEX	-	-	-	-	-	-
NC6.5	+	+	+	+	+	+
DXYL	-	-	-	-	-	-
AspA	-	-	-	-	-	-
BGURr	+	+	+	-	-	-
dSOR	-	-	-	+	-	-
LAC	-	-	-	-	-	-
SAL	-	-	-	+	-	-
ADH1	+	+	+	+	+	-
BGAR	-	-	-	+	-	-
NAG	+	+	+	+	-	-
AMAN	-	-	-	-	-	-
POLYB	-	-	-	+	-	-
MBdG	-	-	-	+	-	-
AGLU	-	-	-	+	-	+
dGAL	-	-	-	-	-	-
BACI	+	+	+	+	+	-
PUL	-	-	-	-	-	-

Apendix 5: Diagnostic results of biochemical tests for Gram negative bacteria isolated from Acute leukemia patients

Tests	Klebsiella Pneumonia (1)	*Klebsiella Pneumonia (2)*	Klebsiella Pneumonia (3)	*Klebsiella Pneumonia (4)*
BGAL	+	+	+	+
APPA	-	-	-	-
PHOS	+	+	+	+
ProA	-	-	-	-
AGAL	+	+	+	+
PyrA	+	+	+	+
BGUR	-	-	-	-
TyrA	+	+	+	+
URE	-	-	-	-
ILATk	+	+	+	+
Dmal	+	+	+	+
Dman	+	+	+	+
Dmne	+	+	+	+
O129R	+	+	+	+
BGLU	+	+	+	+
GIyA	-	-	-	-
SAC	+	+	+	+
H2S	-	-	-	-
dTRE	+	+	+	+
BNAG	-	-	-	-
ADO	+	+	+	+
LIP	-	-	-	-
dTAG	-	-	-	-
AGLU	-	-	-	-
ODC	-	-	-	-
GGAA	-	-	-	-
AGLTp	-	-	-	-
PLE	+	+	+	+
SUCT	+	+	+	+
LDC	+	+	+	+
IMLTa	-	-	-	-
IARL	-	-	-	-
dGLU	+	+	+	+
CTT	+	+	+	+
NAGA	-	-	-	-
IHISa	-	-	-	-
ELLM	-	-	-	-
dCEL	+	+	+	+
GGT	+	+	+	+
BXYL	+	+	+	+
MNT	+	+	+	+
CMT	-	-	-	-
ILATa	-	-	-	-
OFF	+	+	+	+
BAIap	-	-	-	-
dSOR	+	+	+	+

الخلاصة

مصطلح اللوكيميا مشتق من الكلمتين اليونانيتين "leukos" و "heima" ، والتي تشير إلى خلايا الدم البيضاء الزائدة (WBC) في الجسم. تم التعرف على اللوكيميا ، التي كانت تعتبر مرضًا منفردًا ، لأول مرة في القرن الرابع تقريبًا. بحلول نهاية القرن التاسع عشر ، تم تصنيف سرطان الدم إلى أربعة أنواع فرعية: ابيضاض الدم النخاعي الحاد (AML) ، وسرطان الدم الليمفاوي الحاد (ALL) ، وسرطان الدم النخاعي المزمن ، وسرطان الدم الليمفاوي المزمن. حاليًا ، من المعروف أن تشخيص سرطان الدم يتكون من مجموعة متنوعة من الأورام المكونة للدم المعقدة والفريدة من نوعها. يمكن تمييز كل نوع فرعي بشكل أكبر من خلال الاختلافات المورفولوجية والتشوهات الوراثية الخلوية والنمط الظاهري المناعي والميزات السريرية. تؤثر هذه الخصائص المميزة على كل من التشخيص واختيار العلاج الأمثل.

المرضى الذين يعانون من سرطان الدم الحاد معرضون بشدة للأمراض المعدية بسبب العوامل المتعلقة بالمرض نفسه ، والعوامل المنسوبة إلى العلاج ، وعوامل الخطر الفردية المحددة في كل مريض. المرضى الذين يعانون من قلة العدلات الناتجة عن العلاج الكيميائي معرضون بشكل خاص لخطر كبير ، وتشمل العوامل الميكروبيولوجية العوامل الفيروسية والبكتيرية والفطرية. غالبًا ما يكون المسببات غير معروفة في المضاعفات المعدية ، على الرغم من أن تقييم المريض المناسب وأخذ العينات لهما نتائج تشخيصية وإنذارية وعلاجية. تشمل العدوى البكتيرية مجموعة واسعة من الميكروبات المحتملة ، سواء كانت سالبة الجرام أو إيجابية الجرام.

هدفت الدراسة الى تحديد الأنواع البكتيرية الاكثر شيوعًا والمسؤولة عن تعفن الدم لدى مرضى سرطان الدم الحاد ، وتحديد نمط حساسيتها للمضادات الحيوية.

أجريت هذه الدراسة في الفترة من تشرين الأول (أكتوبر) 2021 إلى آيار (مايو) 2022 في مركز الإمام الحسين للأورام وأمراض الدم / مديرية صحة كربلاء. تم إجراء دراسة الحالة على 104مئة واربعة مريضا مصابون بسرطان الدم الحاد ، ثمانية واربعون مريضا مصابين بمرض سرطان الدم الحاد(ALL) ، و ستة وخمسون مريضا مصابًا بمرض ابيضاض الدم النقوي الحاد (AML) ، ستة عشر منهم مصابًا بعدوى بكتيرية ، و ثمانية وثمانون مريضا غيرمصابِّين بالعدوى البكتيرية ، و خمسون فرداً من الاصحاء كمجموعة سيطرة. تم الحصول على عينة من الدم الوريدي بحجم 10 مل من المرضى ومجموعة الاصحاء . زرعت عينات الدم على الاوساط المحددة لذلك ، بعد ذلك تم إجراء العديد من التحليلات مثل المعايير

الكيموحيوية كاختبارات وظائف الكبد (اسبارتيت ترانزمينيز ، الانين ترانسفيريز ، الكالاين فوسفيتيز ، جاما جلوتاميل ترانسفيراز ، البومين ، البيليروبين الكلي ، البيليروبين المباشر ، البروتينات الكلية و اللاكتات ديهيدروجينيز)، المعلومات العامة (العمر ، الجنس) ، المعايير الفسيولوجية(مجاميع الدم) ، المؤشرات المناعية والمصلية (عدد كريات الدم البيض , بروتين سي التفاعلي و انترلوكين 6) ، بعض معايير الدم (دي-ديمر ، الصفيحات الدموية)، الاختبارات الميكروبيولوجية (تشخيص البكتيريا واختبارات الحساسية للمضادات الحيوية).

لقد بينت نتائج هذه الدراسة ان تراكيز المعايير للمرضى كانت :

اسبارتيت ترانزمينيز (35.530 U / l)، الانين ترانزفيريز (40.656 U / l)، الكالاين قوسفاتيز (92.738 U / l)، جاما جلوتاميل ترانسفيراز (71.109U\l) ، الألبومين (42.069) غم / لتر، البيليروبين الكلي (0.503 mg / dl)، البيليروبين المباشر (0.177 mg / dl)،(67.914g\l) بروتينات البلازما ، اللاكتات ديهيدروجينيز (712.098 U / l) ، كريات الدم البيض(12.350 10^3 / µl) ،بروتين سي التفاعلي (45.031mg\l), انترلوكين 6(36.498 pg / Ml) ، دي- ديمر (1586.492) نانوغرام / مل ، الصفيحات الدموية (132.826)ميكرولتر , وكانت فصيلة الدم الشائعة في لدى مرضى سرطان الدم الحاد المصحوب بالعدوى البكتيرية هي O ، في حين تبينت ان أكثر أنواع البكتيرية المسببة للعدوى لمرضى سرطان الدم الحاد فس عينة الدراسة هي *Staphylococcus hemolyticus* , وكانت معظم العزلات البكتيرية موجبة لصبغة جرام مقاومة لمضادات سيفالكسين ، كانامايسين ، أميكاسين ، سيفدينير ، كلاريثروميسين ، سيفيبيم ، سيفلاكسين ، أزيثروميسين وأميكاسين ، بينما كانت البكتيريا سالبة سالبة لصبغة جرام مقاومة لجميع أنواع المضادات الحيوية.

أشارت نتائج مرضى سرطان الدم الحاد غير المصحوب بعدوى بكتيرية وجود ارتباط بروتين سي التفاعلي و انترلوكين 6 وكذلك بين جاما جلوتاميل ترانسفيراز و اللاكتات ديهيدروجينيز و بعلاقة ارتباط موجبة (0.612 و 0.669) على التوالي, كما كان هناك ارتباط موجب بين الانين ترانزفيريز و اسبارتيت ترانزمينيز وانترلوكين 6 و البيليروبين المباشروقد بلغ (0.766 و 0.670) على التوالي, كما لوحظ ارتباط عند مستوى معنوية (0.01) بين الألبومين و البروتين الكلي حيث كان ارتباطًا إيجابيًا (0.698) . بينت الدراسة ايضا وجود ارتباط معنوى سالب عند (0.05) بين الالبومين والبيليروبين المباشر اذ بلغ (-0.514). كذلك كان الارتباط سالب بين الألبومين والعمر ، بروتين سي التفاعلي و انترلوكين 6 ، اذ بلغ (-0.545 ، -0.566 ، -0.575) على التوالي.

لقد اشارت نتائج دراسة مرضى ابيضاض الدم الحاد المصحوب بعدوى بكتيرية ان هناك بعض الاختلاف في معاملات الارتباط بين العمر و اعداد كريات الدم البيض حيث كان الارتباط موجبًا (0.639). وكذلك بين انترلوكين6 والعمر و WBC حيث كان الارتباط موجبا (0.529، 0.767) على التوالي. كما أن هناك علاقة ارتباط بين البروتين التفاعلي سي و دي- ديمر حيث كانت موجبة (0.634). كان هناك ارتباط بين اسبارتيت ترانزمينيز و كريات الدم البيض و انترلوكين 6 و دي – دايمر حيث كان هناك ارتباط موجب (0.910 و 0.718 و 0.566) على التوالي. كان هناك ارتباط بين جاما جلوتاميل ترانسفيراز و الانين ترانزفيريز حيث كان ارتباط موجب (0.540). وقد لوحظ الارتباط أيضًا الألبومين و الصفيحات الدموية ، حيث كان هناك ارتباط عكسي وإيجابي (-0.640 ، 0.644) ، على التوالي. كما كان هناك ارتباط بين البيليروبين المباشر و دي -ديمر و الصفيحات الدموية و الانين ترانزفيريز حيث كانت هناك علاقة موجبة وعكسية وموجبة (0.630 و -0.689 و 0.537) على التوالي بينما كان هناك ارتباط بين البروتين الكلي و انترلوكين 6 و الصفيحات الدموية : حيث توجد ارتباطات عكسية وموجبة (-0.697 ، 0.789) على التوالي. كان هناك ارتباط بين لاكتيت ديهايدروجينيز و كريات الدم البيض و انترلوكين 6 و دي - ديمر و اسبارتيتترانزمينيز حيث كان هناك ارتباط موجب (0.834 و 0.618 و 0.726 و 0.957) على التوالي.

نستنتج من نتائج الدراسة الحالية بأن أكثر الأنواع البكتيرية المسببة تجرثم الدم لدى مرضى سرطان الدم الحاد هي *Staphylococcus hemolyticus* ، وكانت معظم البكتريا موجبة لصبغة جرام وكل البكتريا السالبة لصبغة جرام مقاومة لجميع أنواع المضادات الحيوية.

جامعة كربلاء

دراسة الاصابات البكتيرية في مجرى الدم لمرضى سرطان الدم الحاد

رسالة مقدمة

الى مجلس كلية العلوم الطبية التطبيقية - جامعة كربلاء

وهي جزء من متطلبات نيل شهادة الماجستير في التحليلات المرضية

كتبت بواسطة

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بكالوريوس تحليلات مرضية/ 2016 كلية العلوم الطبية التطبيقية – جامعة كربلاء

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