Republic of Iraq

Ministry of Higher Education

& Scientific Research

Al-Muthanna University

College of Science

Department of Chemistry

The Role of Interleukin-6 and Some Biochemical Parameters in the Severity of Microbial Injury for Kidney Patients in Al-Muthanna Province

A thesis Submitted to the Council of College of Science /
Al-Muthanna University as Partial Fulfillment of the
Requirements for the Degree of Master of Science in Chemistry

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2024 A.D 1446 A.H

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سورة يوسف الآية (٧٦)

Certification of the Supervisor

I certify that this thesis which is entitled “The Role of Interleukin-6 and Some Biochemical Parameters in the Severity of Microbial Injury for Kidney Patients in Al-Muthanna Province” is done by “Anwar Aiad Gaber” under my supervision in the Department of Chemistry /College of Science /Al Muthanna University, in partial fulfillment of the requirements for the Master’s degree in chemistry.

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Dedication

To my family, especially my parents, who have supported me all the way since my childhood.

To my father ….. who has supported me all along the way since my childhood and college studies.

To my sisters and brothers, who have been a great source of motivation and inspiration.

The researcher

Anwar

Acknowledgment

First of all, gratitude and thanks be to God for giving me the power and the insistence to perform this work and achieve my goal.

I would like to express my gratitude to my supervisor, Prof. Dr. Jawad Kadhum Muraih, who suggested the topic of the research and supervised its completion, as well as for his directives and sincere and persistent effort in following up on the research steps. I would like to thank the Deanship of the College of Science at the University of Al-Muthanna, with special thanks to the head of the Department of Chemistry, Dr. Azal Shakir Waheeb, for her valuable help.

I would also like to express my thanks to Dr. Wissam Sajid Hashim, Dr. Hussein Thaer Abd All Abbas, and Sadq Abd Al Ameer for their help, especially during the course of inspecting. A special thanks to all the patients who have assisted me.

My grateful thanks to the laboratory staff of Al Rahma Centre and El Emel Centre for their cooperation and assistance throughout indwelling with them at Al-Hussein Teaching Hospital.

Finally, my sincere appreciation and love for my family, especially my father, may God have mercy on him, begging God to protect them for me.

Table of contents

List of Tables

List of Figures

List of abbreviations

Abbreviation	Details
ADAM10	A Distintegrin And Metalloprotease10
ADAM17	A Distintegrin And Metalloprotease17
AH	Arterial Hypertension
AKI	Acute Kidney Injury
ASPs	Antimicrobial Stewardship programs
BI	Bacterial Infection
Bp	Blood Pressure
BUN	Blood Urea Nitrogen
CALC-1	Calcitonin 1
CBC	Complete Blood Count
CD4+	Cytotoxic T lymphocyte
CD8+	Cytotoxic T lymphocyte
CKD	Chronic Kidney Disease
CLC	Cardiotrophin-Like Cytokine
CNTF	Ciliary neurotrophic factor
CRF	Chronic Renal Failure
CRP	C-reactive protein
CSS	Cytokine Storm Syndrome
CT-1	Cardiotrophin 1
CVD	Cardiovascular Disease
Da	Daltons
DCs	Dendritic Cells
DM	Diabetes Mellitus
DNA damage	DeoxyriboNucleic Acid damage
Egfr	Estimation of Glomerular Filtration Rate
Enos	Endothelial Nitric Oxide Synthase
ERK	Extracellular Signal-Regulated Kinase

ESCKD	End-stage Chronic Kidney Disease
ESRD	End-stage Renal Disease
FasL	Fas Ligation
FFAs	Free Fatty Acids
FPG	Fasting Plasma Glucose
GDM	Gestational Diabetes Mellitus
GFR	Glomerular Filtration Rate
GP130	Glycoprotein 130
HAS	Human Serum Albumin
HB	Hemoglobin
HbA1c	Glycated Hemoglobin
HD	Hemodialysis
HF	Heart Failure
IDDM	Insulin-dependent Diabetes Mellitus
IL-1β	Interleukin-1 Beta
IL-6	Interleukin-6
IL-6R	Interleukin-6 Receptor
IL-6Rα	Interleukin-6 Receptor Alpha
IL-6Rβ	Interleukin-6 Receptor Beta
IR	Insulin Resistance
JAK	Janus Kinase
JAK1	Janus Kinase 1
JAK2	Janus Kinase 2
KDIGO	Kidney Disease Improving Global Outcomes
LIF	Leukemia inhibitory factor
MAPK	Mitogen-Activated Protein Kinase (MAPK)
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
mIL-6R	Membrane Interleukin-6 Receptor
MODY	Maturity onset diabetes of the youn

MPC-1	Monocyte Chemoattractant Protein-1
MPV	Mean Platelet Volume
mRNA	Messenger RiboNucleic Acid
OGTT	Oral Glucose Tolerance Test
OSM	Oncostatin M
PCT	Procalcitonin
PD	Peritoneal dialysis
PI3K	Phosphoinositide3-kinase
PKC	Protein Kinase C
PMA	Phorbol-12-Myristate-13-Acetate
RA	Rheumatoid Arthritis
RANKL	Receptor Activator of Nuclear Factor Kappa B Ligand
RBCs	Red Blood Cells
RBG	Random Blood Glucose
RDW	Red Blood Cell Distribution Width
SAA	Serum Amyloid A
sGP130	Soluble Glycoprotein 130
sGP130-FC	Soluble Glycoprotein 130-FC
SH2	Src Homology 2
SHP2	Src Homology 2 Phosphatase 2
SIL-6R	Soluble Interleukin-6 Receptor
SIRP1	Signal Regulatory Protein 1
SOCS	Suppressors Of Cytokine Signaling
SOCS1	Suppressor of Cytokine Signaling 1
SOCS3	Suppressors Of Cytokine Signaling 3
STAT	Signal Transducer and Activator of Transcription
STAT 3	Signal Transducer and Activator of Transcription 3
sTNFRI	Soluble Tumor Necrosis Factor Type1
sTNFRII	Soluble Tumor Necrosis Factor Type2
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus

TF	Transfer Factor
TGF	Transforming Growth Factor
Th17	T-helper 17
TLRs	Toll-like receptors
TNF-α	Tumor Necrosis Factor Alpha
TYK2	Tyrosine Kinase 2
UV Radiation	Ultraviolet Radiation
3'UTR	3' untranslated region
VE-cadherin	Vascular Endothelial (VE)-cadherin
VEGF	Vascular Endothelial Growth Factor
VI	Viral Infection
WBCs	white Blood Cells
WHO	World Health Organization

Abstract

Interleukin-6, discovered in 1986, is one of the most studied cytokines in kidney disease. It makes inflammation worse by activating B cells that affect the production of hepatic acute phase proteins. This study deals with the effect of some demographic factors on kidney patients with or without diabetes mellitus who have had bacterial or viral infections. The subjects are 120 patients, divided into six groups.

The first four groups have 80 patients with chronic renal failure with a bacterial or viral infection based on previous medical reports, laboratory tests, and clinical examinations by consultant nephrologists. The patients are 40 years of age and older and were admitted to the Al-Hussein Teaching Hospital in the Al Muthanna Government during the period from January 2023 to the end of August 2023. The results were compared with 40 subjects (20 subjects with diabetes mellitus and 20 healthy subjects with an age group of 40 years and up) as a control group. Blood samples were withdrawn to analyse IL-6, PCT, CRP, renal function test, albumin, WBC, lymphocytes, platelets, Cl, K, and Na.

In this study, it was found that the level of IL-6 was high in patients with chronic renal failure with or without diabetes mellitus with a bacterial or viral infection, but it was higher in patients with a bacterial infection with or without diabetes. The same is shown for CRP. There was an increase in PCT in patients with chronic renal failure with or without diabetes mellitus with a bacterial infection. There was an increase in the levels of urea, creatinine, Na^+, K^+, and Cl^-but a decrease in the levels of albumin, WBC, lymphocytes, and platelets in patients.

Chapter One
Introduction&
Literature review

1. Introduction & Literature Review

1.1. Introduction

Many different types of cells in the body, including immune cells, create interleukins (IL-6), which belong to a class of protein molecules that are classified as cytokines. When it comes to the immune defense system, IL-6 is a key player in the cytokine network. Recent research has linked the IL-6 pathway to both normal and abnormal immune modulation. where it is routinely used as a window into the state of a disease and how it will respond to treatment. Acute infection, persistent inflammation, obesity, and physiological stress all trigger IL-6 secretion [1-4].

The inflammatory effects of IL-6 may be either pro- or anti-inflammatory. Through its ability to prevent bacterial infection, stimulate epithelial cell proliferation, and block epithelial cell death, IL-6 serves as an anti-inflammatory. [5]. Cytokine storm is a condition in which numerous immune active molecules, including chemokine's and cytokines, are released from the immune system at extremely high concentrations. In contrast, unchecked production of IL-6 results in pro-inflammatory activity. The etiology of arthritic illnesses is underpinned by the release of immune-related chemicals, such as cytokines, which may lead to complications such as multiorgan failure or even death [6].

Procalcitonin (PCT) is a prohormone the thyroid gland secretes. Procalcitonin (PCT) is located on the CALC-1 gene on chromosome 11, a 116-amino-acid polypeptide. IL-6, Tumor Necrosis Factor-a, and IL-1 induce PCT production in extrathyroidal tissue in response to bacterial infection. PCT is bacterial-specific since its synthesis is inhibited during most viral infections due to an increase in interferon-γ production[7-8].

Procalcitonin has gained popularity as a diagnostic tool for bacterial infections and sepsis in recent years. Blood PCT levels can go up within a few hours of inflammation and usually reach their highest point within 24 to 48 hours. This makes them more specific than other common lab tests like leukocytosis, increased band cells, and C-reactive protein (CRP). Although PCT elevations are very weak or not at all connected with viral infections, The cytokines produced during viral infections are mostly responsible for this since they inhibit the synthesis of tumor necrosis factor-alpha (TNF-a). Therefore, serum PCT levels are an excellent indicator for distinguishing bacterial from viral illnesses [9].

C-reactive protein (CRP) is a biomarker of inflammation and a mediator of the acute-phase response. Cytokines that cause inflammation, like interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF), tell the liver to make CRP. When levels of CRP go up, it means that proinflammatory cytokines are supporting an ongoing inflammatory process. When levels of these cytokines go down, it usually means that the inflammatory process is ending. Diverse CRP isoforms have diverse biological effects; some activate the complement system, induce phagocytosis, and promote apoptosis, while others delay apoptosis and enhance the chemotaxis and recruitment of circulating leukocytes to sites of inflammation. The C1q molecule in the complement pathway is activated by CRP, which then leads to the opsonization of pathogens and an active role in the immunological response to infection [10].

In patients with CKD, kidney function progressively declines over a period of months to years. Chronic renal disease is characterised by the progressive replacement of healthy kidney structures with fibrotic tissues. The eGFR is determined by the patient's height, weight, gender, and serum creatinine level; CKD is diagnosed when the eGFR is

less than 60 ml/min/1.73 m2. The GFR steadily decreases from the beginning of CKD until end-stage renal disease is reached [11- 12].

Chronic kidney disease (CKD) progresses to its last, irreversible stage, which is known as end-stage renal disease (ESRD). This stage is characterised by a steady decrease in kidney function that ultimately results in kidney failure. ESRD is linked to a worse quality of life, death at an earlier age, and increased expenses for the whole healthcare system [13]. Loss of kidney function is linked to the failure to properly eliminate several types of uremic toxins. They are both the cause and the effect of CKD because of their biological activity [14].

Blood serum albumin levels are often checked as a biomarker for inflammation and nutritional (malnutrition or over nutrition) status in regular clinical settings. Importantly, prior research has implicated both dietary and inflammatory states as potential contributors to renal disease development. While some researches have failed to discover a clear link between low blood albumin and CKD, other studies have linked low albumin levels to a higher risk of renal dysfunction in either the general population or women specifically [15].

In humans, urea is the primary metabolite of dietary protein because of its high nitrogen content. The kidneys process it by dissolving it in the blood, transporting it, and then releasing it in the urine. Creatinine is the steady-state byproduct of creatine phosphate breakdown, which is secreted from skeletal muscle. The glomerulus filters it, and the proximal tubules secrete a tiny quantity into the glomerular filtrate. Estimating progression, prognosis, and the need for dietary restrictions in renal disease due to type 2 diabetes may be done using serum creatinine and blood urea nitrogen values [16].

Diabetes mellitus is a metabolic disorder in which decreased insulin production and/or activity in target tissues leads to persistently high blood sugar levels or hyperglycemia. Diabetes mellitus is the most prevalent metabolic disease. By 2045, it is projected that 700 million individuals worldwide would have DM (10.9% of the adult population). In 2030, diabetes is expected to overtake smoking as the seventh leading cause of death, according to the WHO [17-19].

Oxidative damage at the DNA, protein, and lipid levels induces cell necrosis or apoptosis when hyperglycemia persists over an extended period of time. The insulin signal transduction system is disrupted by hyperglycemia, leading to increased glucose absorption by fat or muscle cells and reduced glucose production in the liver. Hyperglycemia may be prevented by its early diagnosis and proper management, which includes pharmacological therapy since these pathways produce cellular pathological damage and microvascular and macrovascular problems [20].

According to the 2016 report from the United States Renal Data System, diabetes is one of the primary causes of ESRD, accounting for more than a third of all cases. In people with diabetes, chronic inflammation has been linked to the onset and development of renal disease. Type 2 diabetes mellitus is also a leading cause of renal failure. In people with type 2 diabetes, chronic kidney disease (CKD) affects almost half [21].

One of the most often ordered blood tests by doctors is called a complete blood count (CBC), which measures and analyses several cellular components in the blood, including white blood cells (WBCs), red blood cells (RBCs), and platelets. If white blood cell (WBC) counts are high, it may indicate an acute or chronic infection, if they are low, it may indicate leukemia, if hemoglobin (Hb) levels are low, it may indicate anemia, and if

platelet counts are low, it may indicate liver cirrhosis. However, prior research has demonstrated that the CBC components may be used to predict cancer, CVD, arteriosclerosis, type 2 diabetes, and metabolic syndrome risk [22].

1.2. Literature Review

1.2.1. Interleukin-6 (IL-6)

After its discovery in 1986 as a B cell stimulatory factor initiating IgG production, interleukin-6 (IL-6) was found to be a pleiotropic cytokine that regulates a wide variety of physiopathological processes, including cell proliferation, survival, migration, invasion, metastasis, angiogenesis, inflammation, and metabolism. While monocytes and macrophages account for the vast majority of IL-6 production, other cell types, including T cells, B cells, hepatocytes, endothelial cells, fibroblasts, keratinocytes, mesangial cells, adipocytes, and even certain tumor cells, are capable of producing IL-6 either constitutively or in response to stimulation [5], [23-24].
In response to microbial stimulation, monocytes/macrophages (MO/M) release IL-6 [25].

Many illnesses, including autoimmune disorders, infections, and malignancies, have been linked to elevated IL-6 levels. The typical range for IL-6 in the human body is 7 pg/mL. Acute increases in IL-6 levels may occur in response to infection or inflammation. With a median blood level of 189,000 pg/mL, IL-6 in septic shock patients is 1,000 times greater than in those with meningitis (200 pg/mL) or bacteremia (200 pg/mL) [5].

1.2.1.1. Interleukin-6 in infection

Weakness, fever, muscular discomfort, and other symptoms are all caused by both bacterial and viral diseases. Differentiating between these two kinds of infections as soon as possible is crucial for effective treatment and a positive prognosis. Antibiotics are often used to treat bacterial infections, however they have been shown to be ineffective against viral infections and may even lead to the spread of antibiotic resistance. Acute inflammatory responses caused by viral and bacterial infections are characterized by an increase in pro-inflammatory cytokines and chemokines, which may leak into the bloodstream and cause systemic cytokine storms, which can cause multiorgan dysfunction [26].

To-llike receptors (TLRs) are involved in innate immunity by recognising pathogens such as bacteria, viruses, fungi and activating the nuclear factor kappa B (NF-kB) signaling pathway to produce IL-6 and other inflammatory cytokines. Intriguingly, IL-1 and TNF production stimulates IL-6 generation as well [27].

Increases in IL-6 following invasion by viruses or bacteria are rapid and short-lived. After a bacterial infection has set in, the amount of IL-6 quickly increases, reaching a peak after only 2 hours; this rise is correlated with the severity of the infection. One of the reliable markers of stress reactions, IL-6 is rapidly elevated in response to viral infection and inflammation. It may play a significant role in adaptive immune response by stimulating the differentiation of naive CD4+ T cells into effector T cells and activating B cells to produce antibodies. In response to inflammation, IL-6 levels rise sooner and remain elevated for longer than those of other cytokines like C-reactive protein (CRP) and procalcitonin (PCTs) [5], [25], [28].

1.2.1.2. IL-6 family of cytokines

All members of the interleukin-6 (IL-6) cytokine family share the same glycoprotein 130 (gp130, IL6ST) receptor signalling subunit. This includes IL-6, IL-11, IL-27, IL-31, ciliary neurotropic factor (CNTF), leukaemia inhibitory factor (LIF), cardiotrophin 1 (CT-1), cardiotrophin-like cytokine (CLC), and oncostatin M (OSM). The specificity of a cytokine is determined by its specific cell-surface receptor, which has a limited distribution and dimerizes with the ubiquitously expressed gp130 subunit. This specific arrangement is what makes some cell types more sensitive to particular cytokines [3].

In addition to activating mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK), all IL-6-related cytokine receptor complexes transduce intracellular signals via the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway.-protein kinase B (PKB)/protein kinase Akt signalling [29]. STATs enter the nucleus upon activation and turn on genes dependent on their environment [30].

STATs also induce the suppressors of cytokine signalling (SOCS), which, through a negative feedback loop, inhibit IL-6 family signalling by binding to tyrosine-phosphorylated JAK and tyrosine-phosphorylated gp130. It has been noted that some members of the IL-6 family present an affinity to more than one specific receptor and can induce the same or different physiological outcomes [3].

Patients with kidney diseases, such as diabetic nephropathy, glomerulonephritis, and obstructive nephropathy, have been found to have increased levels of IL-6 cytokine family members in their renal tissue. Members of the IL-6 cytokine family are expressed

and secreted by podocytes, endothelial cells, mesangial cells, and tubular epithelial cells in the kidney. Signalling through IL-6 cytokine family members can increase tubulointerstitial fibrosis, affect cell differentiation, or stimulate cell proliferation in these cell types [31].

Members of the IL-6 cytokine family display a wide range of both beneficial and pathogenic effects, earning them the moniker "double-edged sword". Often, pathogenic results occur when signalling goes beyond a certain point. IL-6, for instance, promotes the damaging inflammatory response and acts via its soluble receptor to increase expression in injured kidneys, but it also protects the kidney from further acute injury [32].

1.2.1.3. IL-6 receptor complex

The active IL-6 receptor complex is made up of two subunits, an 80-kD type 1 cytokine receptor (IL-6Rα) and a 130-kD signal-transducing receptor (IL-6Rβ); IL-6Rα is expressed exclusively in certain cell populations, whereas IL-6Rβ is expressed by every cell type [33-34]. A variety of mechanisms, such as internalization, recycling, and proteolysis, are responsible for keeping the same level of IL-6R at the cell surface [35].

Hepatocytes, muscle cells, epithelial cells, and several immune cell subsets (T cells, B cells, monocytes, macrophages, and megakaryocytes) are the primary cell types that express the IL-6R. Based on their unique gene expression profiles, only these cells will respond to IL-6 via the classical signaling route. Notably, almost all cells express gp130, with granulocytes being the only observed exception [36]. Therefore, the IL-6R needs a signal-transducing receptor in order to activate intracellular signaling cascade [37]. Homodimerization of gp130 is triggered by the assembly of the IL-6/IL-6R complex at

sites II and III of IL-6. Transmembrane protein Gp130 has six extracellular domains, a transmembrane segment, and an intracellular domain [37-38].

The process of dimerization of gp130 leads to the initiation of Janus kinases (Jaks) activation. These Jaks are initially bound to gp130 in an inactive state, but upon dimerization, they become active and proceed to phosphorylate themselves as well as specific tyrosine residues of gp130 [39]. Inside the cell, the tyrosine phosphorylation of gp130 provides a docking site for the STAT transcription factors, which are phosphorylated by the Jaks, translocate as dimers into the nucleus, and induce the transcription of target genes [40].

The suppressor of cytokine signalling 3 (SOCS3) is an example of one of these targets; it inhibits Jak/STAT signalling by binding to a membrane-proximal tyrosine residue of gp130 and also to the Jaks themselves [41]. Because inflammation and cancer growth are linked to dysregulated and extended activation of Jak/STAT signalling, this regulation mechanism is crucial [35]. Mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) route, phosphoinositide 3-kinase (PI3K)/AKT pathway, and Src kinase/YAP pathway are all examples of activated signal cascades [42-43].

1.2.1.4. Soluble IL-6R and GP130

Many cytokines have soluble receptors that serve as agonists or antagonists of cytokine signaling, making them crucial regulators of inflammatory events. To counteract the effects of their ligands, the soluble receptors for interleukin-1 beta (sIL-1RII) and tumor necrosis factor-alpha (sTNFRI and sTNFRII) are called antagonists. The sIL-6R, on the other hand, activates cell types that express the signal transducer protein gp130 but

lack mbIL-6R expression, thereby amplifying IL-6-mediated signaling. Not all cell types respond to IL-6 because not all cell types express IL-6R on the cell surface. Macrophages, neutrophils, specific T-cells, and hepatocytes are all examples of such cells. Unlike the IL-6R, gp130 expression is ubiquitous [44].

The IL-6/sIL-6R complex binds to IL-6 with high affinity and exerts an agonistic effect on cells expressing gp130. Trans-signaling refers to the activation of cells that only express gp130 through the IL-6/sIL-6R complex, whereas classic-signaling refers to the activation of cells through the mbIL-6R in complex with IL-6 [45-46].

Lymphocyte trafficking into the inflamed area is regulated by chemokine expression, which is in turn regulated by gp130 activation via trans-signaling. In addition to its role in regulating adhesion molecule expression on endothelial cells, IL-6 trans-signaling also promotes T-cell proliferation during colon cancer development. The sIL-6R can be produced via two distinct pathways. Metalloprotease activity is required for the first step, which is the proteolytic cleavage of the mbIL-6R. For the second, a splice variant of IL-6R-mRNA is transcribed that lacks the protein's transmembrane and cytosolic domains [47]. ADAM proteases are type-I transmembrane proteins that play an important role in the limited proteolysis (shedding) of many cytokine receptors. [48-49].

ADAM10 and ADAM17 are the most closely related of the many ADAM proteases (the human genome contains 25 ADAM genes), and they share a large number of substrates [47]. Both ADAM17 and ADAM10 have been shown to bind to the IL-6R. Slow constitutive IL-6R shedding appears to be mediated by ADAM10, while rapid IL-6R proteolysis is triggered by ADAM17 upon proper activation. [50]. The phorbol ester phorbol-12-myristate-13-acetate (PMA), a well-characterized activator of protein kinase

C(PKC), can induce ADAM17 activation and subsequent cleavage of the IL6R. The pro-inflammatory cytokines IL-1 and TNF-, the bacterial toxins streptolysin O and hemolysin A, the removal of cellular cholesterol, and the proteasome inhibitor bortezomib can all activate ADAM17 [47].

It is worth noting that a soluble form of the signal transducer protein gp130 (sgp130) was also detected in the circulation at relatively high concentrations (100-400 ng/ml in human plasma). Alternative splicing, rather than restricted proteolysis, is the primary mechanism by which Sgp130 is generated. Because of its ability to bind to the circulating IL-6/sIL-6R complex, sgp130 blocks IL-6-mediated trans-signaling. sgp130 has no effect on canonical signaling through the mbIL-6R. Signaling for other IL-6-type cytokines, such as LIF and OSM, was inhibited at 100-1000-fold higher concentrations, whereas signaling for CNTF and IL-27 was unaffected. This suggests that sgp130 is specific for the IL-6/sIL-6R complex [47].

1.2.1.5. The structure of IL-6

IL-6 is a member of the interleukin family and was found to be a secreted 26 kD protein. Single-chain glycoprotein IL-6 has a receptor binding site at its C-terminus (amino acids 175-181) and consists primarily of four-helices [51]. In addition to its helical structure at the C-terminus, which is involved in binding to the receptor, its tertiary structure consists of four helixes containing 184 amino acids. Human IL-6 is coded for by a gene that spans chromosome 7 and includes four introns and five exons. Human IL-6 precursor contains 212 amino acids; after the N-terminus, including 28 amino acids, is removed, the resulting protein, mature IL-6, has 184 amino acids [52-53].

The IL-6 gene in humans is 65% similar to the IL-6 gene in mice, whereas the amino acid sequence is only 42% similar. Rat IL-6 shares a 93% amino acid identity with mature mouse IL-6 and a 58% amino acid identity with human IL-6 [53-54].

The cytokine interleukin-6 (IL-6) has three receptor binding sites; one is for the IL-6 binding receptor protein (IL-6R), and the other two are for the signal-transducing protein (gp130). Cell-cell communication is initiated when IL-6 binds to its receptor. Two types of interleukin-6 receptors (IL-6R) exist: IL-6R (also known as CD126 or gp80) and IL-6R (also known as CD130 or gp130). Of the two, IL-6R is mostly located on the cell surface of hepatocytes, neutrophils, macrophages, and certain lymphocytes and has a molecular weight of 80 kDa. After glycosylation, gp130's molecular weight can swing between 100 to 130 kDa. It is expressed on the surface of virtually all cells and performs a signal transduction role in the body. These cells include the heart, kidney, spleen, liver, lungs, placenta, and brain. Homodimerization of gp130 and the initiation of signal transduction are initiated when IL-6 binds to IL-6R and then to gp130 to form a trimer [53], [55-56].

1.2.1.6. Functions of IL-6

1.2.1.6.1. Acute phase response

One of the key mediators of acute phase reactions is interleukin-6 [57]. Since hepatocytes express significant levels of IL-6R and gp130, it was often believed that IL-6 only affected the liver. However, it has become increasingly obvious that IL-6 does not act exclusively on the liver [27].

Interleukin-6 (IL-6) functions as an acute phase protein, augmenting the inflammatory response within the human body. The majority of its effects are primarily

mediated by the liver, where it undergoes processing and initiates an inflammatory cascade, leading to the production of various proteins such as C-reactive protein (CRP), serum amyloid A (SAA), fibrinogen, haptoglobin, and α1-antichymotrypsin. Interleukin-6 (IL-6) additionally induces a decrease in the concentrations of albumin, zinc, and iron via diverse mechanisms [34].

C-reactive protein (CRP) is an example of a pattern recognition molecule since it recognises and binds to certain cellular and viral surface antigens. C-reactive protein (CRP) that is coupled to a ligand acts as an opsonin and can initiate the classical complement cascade [58].

The measurement of serum levels of acute phase proteins is a common practise in clinical settings, where it is frequently used to establish a correlation between these protein levels and the extent of inflammation. In an in vitro setting, hepatocytes exhibit a response similar to other cytokines in the IL-6 family, resulting in the production of acute phase proteins. However, studies have demonstrated that mice lacking IL-6 display a significantly compromised acute phase response. Furthermore, the inhibition of the IL-6 receptor in individuals diagnosed with rheumatoid arthritis (RA) leads to a decrease in the levels of acute phase proteins. This observation suggests that IL-6 plays a crucial role as a cytokine in initiating the acute phase response of the liver [59].

1.2.1.6.2. Immune Response

In particular, the impact of IL-6 on the immune system is intriguing since it has an impact on both innate and acquired immunity. In terms of innate immunity, IL-6 is in charge of maturing the inflammatory infiltrate and encouraging neutrophil migration and infiltration by mononuclear cells. In terms of acquired immunity, IL-6 also exhibits its

activity both on T-cells and on B-cells, serving as a chemoceptor for monocytes at the site of inflammation. With regard to the latter, it exerts a differentiative effect on active plasma cells, raising serum gamma-globulin levels. In fact, Castelman's illness, which responds to treatment with an anti-IL-6, shares both of these symptoms [27].

The role of IL-6 in T-cells is especially important because it is linked to a wide range of diseases. IL-6 primarily affects CD4+ T-cell differentiation, namely by promoting Th17 differentiation while suppressing T-reg differentiation. Th17 differentiation helps suppress inflammation and boosts di-erentiation by encouraging IL-6 production. TNF, IL-1, IL-17, IL-21, and IL-22 are only some of the cytokines released by Th17 cells that promote inflammation and a fibrotic response in the tissue [60].

By blocking transforming growth factor (TGF), IL-6 suppresses T-reg cell production. Under the correct circumstances, IL-6 can operate as an autoinflammatory mediator, impairing the body's ability to recognise self and promoting fibrosis and inflammation instead. Its relevance in numerous autoimmune illnesses has been proven, and it is now a common target of treatment [51], [61].

1.2.1.6.3. Bone Homeostasis's

The stages of inflammation, regeneration, and remodeling are all necessary for a broken bone to mend properly. Evidence from the mouse femur osteotomy model indicates that interleukin-6 (IL-6) plays a crucial role in bone healing by reducing inflammation, immune cell recruitment, and bone regeneration during the early phase while disrupting bone formation and remodeling throughout the repair phase [62]. However, bone loss occurs due to persistent inflammation. Essential for osteoclastogenesis, receptor activator

of nuclear factor kappa B ligand (RANKL) is induced by inflammatory cytokines like interleukin-6 (IL-6) [63].

In the bone marrow, IL-6 acts as a guide for cell differentiation, encouraging the development of neutrophils and megakaryocytes and, in conjunction with IL-3, increasing the dierentiation of megakaryocytes in platelets. Indeed, IL-6 production is linked to anemia, like many other inflammatory agents; its effects on hepatocytes include the in vitro generation of hepcidin, however, this has not been verified in vivo [27].

1.2.1.6.4. Blood Vessels

Vascular permeability enhancement is a protective process that allows immune cells to enter tissues, eliminate infections, and repair tissue damage. This also paves the way for the transportation of immune-related proteins like cytokines, antibodies, and complements to areas of inflammation. The major protein responsible for mediating the adhesion of neighboring cells by hemophilic binding is vascular endothelial (VE)-cadherin, and its disintegration results in leakage in the blood vessels. Since gp130 is expressed by endothelial cells but IL-6R is not, IL-6/sIL-6R trans-signaling induces endothelial cells to promote VE-cadherin phosphorylation and internalization [64].

Inflammatory cytokines, such as interleukin-6 (IL-6), have the ability to stimulate the production of vascular endothelial growth factor (VEGF) from adipose tissue or other cellular sources. Additionally, these cytokines can cause the phosphorylation and internalization of VE-cadherin in endothelial cells [59].

Moreover, edema is exacerbated by a decrease in liver albumin due to IL-6. In severe cases of acute systemic inflammation, such as those seen in sepsis or cytokine-

releasing syndrome, extreme hyperpermeability causes a shock-like vital condition. In this example, IL-6 levels are associated with outcome. The IL-6 trans-signaling inhibitor sgp130-Fc increased survival in a cecal ligation and puncture sepsis model [65].

1.2.1.6.5. Coagulation System

Inflammation causes macrophages to secrete IL-6-induced tissue factor [66]. The coagulation system is activated by TF, which triggers the extrinsic coagulation pathway. After prothrombin has been activated, thrombin is made, which cleaves fibrinogen to fibrin and initiates fibrin clot formation via activation of factors VIIa and Xa. Human trials of recombinant IL-6 showed that the protein stimulated coagulation by increasing levels of thrombin-antithrombin III complexes and the prothrombin activation fragment F1 + 2 [67].

1.2.1.7. IL-6 Signaling pathways

Classical signaling, trans-signaling, and trans-presentation signaling are the major mechanisms by which IL-6 signals are transmitted [5].

1.2.1.7.1. IL-6 Classic Signaling

Many cytokines, including IL-6, have a classical signaling system in which all receptor components are located on the same cell surface, also known as a cis-signaling (classical) system [68]. Classical IL-6 signaling occurs when IL-6 binds to the IL-6R on cells' membranes. Hepatocytes, neutrophils, monocytes, and T cells are the primary cell types that express mIL6R and benefit from the physiological functions mediated by IL-6 [69-70].

When interleukin-6 (IL-6) binds to its particular receptor, interleukin-6 receptor (CD126), an IL-6/IL-6R complex is formed, leading to homodimerization of the signal component gp130 (CD130). The intracellular domain of IL-6R is only 82 amino acids long and cannot transmit signals on its own. In comparison, gp130 is 277 amino acids long and has a phosphorylation site-rich cytoplasmic domain[68]. Homo-dimerization of gp130 and subsequent phosphorylation of tyrosine residues in the cytoplasmic portion of gp130 initiate IL-6 intracellular signaling by activating cytoplasmic Janus kinases (JAKs: JAK1, JAK2, and TYK2) [59].

The downstream signaling molecules, namely the signal transducer and activator of transcription 3 (STAT3), STAT1, and SH2 domain-containing protein-tyrosine phosphatase 2 (SHP2), are recruited to the tyrosine-phosphorylated motifs of gp130. The JAKs phosphorylate STAT3 and STAT1, leading to their translocation to the nucleus and subsequent generation of the transcriptional output. The SHP-2 protein is responsible for the activation of the Ras-MAP kinase pathway. The intracellular signaling of IL-6 is modulated by molecules that either inhibit or promote its activity. The STAT3 protein is responsible for the activation of negative feedback molecules, namely suppressor of cytokine signaling 1 (SOCS1) and SOCS3 proteins. The protein known as Suppressor of Cytokine Signaling 1 (SOCS1) interacts with and exerts inhibitory effects on Janus kinase (JAK). The protein suppressor of cytokine signaling 3 (SOCS3) forms a complex with the glycoprotein 130 (gp130) receptor and acts as an inhibitor of the SHP2 signaling pathway. The STAT3 protein is known to activate the expression of the Arid5a molecule through a positive feedback mechanism. Arid5a, in turn, selectively enhances the stability of Stat3 mRNA by binding to the 3' untranslated region (3'UTR) of the Stat3 gene, thereby

amplifying the STAT3 signaling pathway. The magnitude of the IL-6 response is determined by negative or positive feedback mechanisms [59], [68].

1.2.1.7.2. IL-6 Trans-signaling

Trans-signaling can also occur when IL-6 binds to the serum-bound soluble version of the IL-6 receptor (sIL-6R). Cells that express gp130 can still be activated by the IL-6/sIL-6R complex even in the absence of membrane IL-6R[71-72]. The generation of sIL-6R occurs via proteolytic cleavage of mIL-6R by members of the metalloprotease gene family, namely ADAM10 and ADAM17, or through direct secretion subsequent to the translation of alternatively spliced mRNAs [71].

In humans, both ADAM17 and ADAM10 appear to stimulate sIL-6R secretion, whereas in mice, only ADAM10 has been linked to sIL-6R synthesis and secretion. Apoptotic pathways (such as DNA-damage, UV radiation, and Fas ligation) as well as phorbol-esters and the cytokines IL-1 and TNF- activate ADAM10 and ADAM17 [69], [73]. The interaction between interleukin-6 (IL-6) and soluble IL-6 receptor (sIL-6R), followed by the binding of this complex to the gp130 receptor on tissue cells. The transduction of IL-6/sIL-6R signaling follows a comparable pathway to that of classical IL-6R signaling. The utilisation of sIL-6R offers an additional benefit as it facilitates the binding of circulating IL-6, thereby significantly prolonging the half-life of IL-6 [69].

Furthermore, the soluble interleukin-6 receptor (sIL-6R) plays a role in the interaction between leukocytes and vascular endothelium, leading to the production of monocyte chemoattractant protein-1 (MCP-1) by the endothelial cells. MCP-1 is a crucial chemokine that controls the infiltration of monocytes and macrophages into the vascular wall [74].

Later research verified that sIL-6R was significantly elevated in the blood of patients with inflammatory illnesses such as rheumatoid arthritis and chronic inflammatory bowel disease. Importantly, sIL-6R has been shown to induce carcinogenesis in chronic inflammation-associated cancers such as colitis-associated cancer [75].

There are consistently high amounts of sIL6R (25-75 ng/mL) in human serum, and these concentrations increase by a factor of two to three during inflammation. Several disorders, such as bipolar disorder and significant depression, are associated with increased levels of circulating soluble IL6R. The extent to which trans-signaling occurs depends on the IL-6 to sIL6R/IL-6 ratio [73].

1.2.1.7.3. Trans-presentation signaling

Trans-presentation of interleukin-6 (or IL-6) is a kind of IL-6 cluster signaling. To participate in IL-6 cluster signaling, a donor cell must in trans deliver IL-6 to a recipient cell through its own membrane-bound IL-6Rα. For instance, SIRP1+ DCs (DC2) are able to carry out this trans-presentation by loading IL-6 on their IL-6R prior to IL-6R being displayed on the cell surface [76].

The donor cell's IL-6R/IL-6 complex can only be detected by the recipient cell's gp130 if the two cells are in close proximity to one another. To take up an IL-6 signal via trans-presentation, it is not necessary for the receiving cell to express IL-6R, as is the case with trans-signaling [77].

In contrast to the first two signal aspects, downstream T cell signaling is initiated by IL-6 binding to mIL-6R expressed on immune cells, which then forms a complex with gp130 on T helper 17 (TH17) cells. Dendritic cell-bound mIL-6R and IL-6 are delivered to

T cells with the gp130 receptor, phosphorylating STAT3 in T cells, and setting off T cell activation [78]. The observation of this mechanism in human models has not yet been documented [79].

1.2.2. Chronic kidney disease (CKD)

The kidney plays a crucial role in human health. The kidneys play a crucial role in excretion and osmoregulation. To put it simply, the kidneys and excretion systems remove waste and toxins from the body. If the illness is diagnosed early and the right treatments are initiated, the patient can live for a long time despite having impaired kidney functioning. However, it is typical for the patient's health to worsen and the nephron count to drop precipitously over time. Therefore, the patient's life is in jeopardy due to an increase of dangerous substances in the blood. Kidney failure that has progressed to its last stage is said to be terminal [80].

Chronic kidney disease (CKD) is characterized by impaired renal function, as measured by a glomerular filtration rate (GFR) of less than 60 mL/min per 1.73 m2, or by the presence of indicators of kidney damage, or by both, and persisting for more than 3 months. Albuminuria, urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology, structural abnormalities detected by imaging, and a history of kidney transplantation are all considered markers of kidney damage according to 2012 guidelines from Kidney Disease Improving Global Outcomes (KDIGO) [81] .

Diabetes, metabolic syndrome, obesity, arterial hypertension (AH), and cardiovascular disease (CVD) are all examples of non-communicable diseases that are strongly linked to the development of chronic kidney disease (CKD).The prevalence of

CKD has increased by almost 30% since 1990; this rise is correlated with increasing treatment costs attributable to renal replacement therapy (RRT) and the prolonged use of dialysis for patients with end-stage renal disease (ESRD). RRT currently serves about 2.5 million people, but that number is predicted to rise to 5.4 million by 2030 [82].

Diagnosis is typically made by estimating GFR using many available equations or, less frequently, by measuring GFR by exogenous markers because patients are generally asymptomatic or have non-specific symptoms such lack of appetite, pruritus, and fatigue. Renal biopsies aid in diagnosis as well, typically revealing glomerular sclerosis, tubular atrophy, and interstitial fibrosis [83].

The inflammatory response is an essential and normal defense mechanism. Through a series of stages assisted and coordinated by cytokines, chemokines, and acute-phase proteins, it is responsible for the migration of immune system cells to the stimulus target site. This solves the issue and allows business as usual to resume in an emergency situation. However, tissue damage and fibrosis may result from chronic inflammation. Therefore, it has been linked to several ailments, chronic kidney disease included [84].

1.2.2.1. Staging of Chronic kidney disease

The criteria for the diagnosis of CKD were established in 2002 by the Kidney Disease Outcomes Quality Initiative (KDOQI) recommendations. Previous definitions of nephropathy had been replaced by the newer classifications, which placed more emphasis on identifying the disease in its earliest stages and relied on a variety of poorly specified descriptive factors [85]. CKD is defined as structural or functional impairment for three months or more, as per the KDOQI recommendations and subsequent Kidney Disease Improving Global Outcomes (KDIGO) adjustments. Chronic kidney disease (CKD) is

typically divided into "stages" based on the patient's glomerular filtration rate (GFR) and albuminuria. Kidney disease is classified into five stages by GFR, with an extra three for each stage identified by albuminuria. Classification in CKD staging predicts renal survival, therefore the combination of GFR (CKD stages, I-V) and albuminuria (A1-3) thresholds takes on added prognostic value. However, the benefit of CKD categorization in forecasting the progression of nephropathy and, most importantly, in establishing an effective preventative strategy is severely constrained by three issues: lack of consensus on an age-adjusted CKD staging system, assessment of albuminuria, and GFR calculation methodologies [86].

1.2.2.2. Glomerular Filtration Rate

The estimation of glomerular filtration rate (eGFR) is a widely utilized clinical assessment to evaluate an individual's renal function and to classify the severity of kidney disease in the event of renal impairment. The outcomes of glomerular filtration rate (GFR) estimation are expressed in milliliters per minute per square meter (mL/min/m^2).The glomerular filtration rate (GFR) is directly associated with the flow rate per unit area across the glomeruli, which are the filtering structures within the kidneys. The glomerulus is a complex arrangement of capillaries situated at the proximal end of a nephron within the renal system. The process of blood filtration occurs as the blood traverses the capillary walls by means of the glomerular filtration barrier. Subsequently, the filtrate proceeds to enter the renal tubule within the nephron[87].

Reduced blood flow or fewer active nephrons can both lead to a drop in GFR. The rate of progression of kidney disease and its classification as either acute or chronic can be established by a single or numerous diagnostic tests [88]. The kidneys are not functioning

as they ought to if the GFR is low. According to estimated GFR, clinicians can determine the severity of renal disease and arrange a course of treatment. In order to determine the best medicine dosage, glomerular filtration rate is frequently needed[87].

1.2.2.3. End-stage kidney disease

End-stage renal disease (ESRD) represents the final stage (stage 5) of Chronic Kidney Disease (CKD), wherein the kidneys are functioning at a filtration capacity of 15% or less. The decline in filtration capacity is linked to a diverse array of complications, including hypertension, anemia, malnutrition, bone disease, neuropathy, and a diminished quality of life. The management of end-stage renal disease encompasses not only dialysis or renal replacement therapy, but also entails fluid and dietary regulation, medication administration, and active involvement in scheduling treatment [13].

Patients with ESRD need close observation since prompt referral to a renal transplant program or dialysis treatment is crucial for their survival. The mortality rate of ESRD patients is higher than that of the general population [89].

1.2.2.4. Dialysis

Dialysis is a procedure for purifying the blood by removing waste products and excess fluid. In the case of renal failure, it is a prosthetic kidney that performs the same functions. Dialysis cannot replace kidney function in its entirety, although it can control certain of the kidney's functions through diffusion and ultrafiltration. When the glomerular filtration rate (GFR) is less than 15 ml/min/1.73 m2, a patient is diagnosed with chronic renal failure (CRF) [90]. Dialysis can be either hemodialysis (HD) or peritoneal dialysis

(PD). HD is often performed at outpatient dialysis centers three times a week, whereas PD can be done by the patient at home or in any other sterile setting [91].

1.2.2.4.1 Hemodialysis

Patients with end-stage renal disease (ESRD) often undergo hemodialysis, an extracorporeal blood-cleansing treatment, to get rid of the uremic poisons that have built up in their bodies. Electrolytes, including potassium, sodium, phosphate, and calcium, are all kept in check by hemodialysis as excess fluids are flushed out of the body. The process of hemodialysis consists of the following: A dialyzer (an artificial kidney with as many as 15,000 hollow fiber membranes) is attached to a dialysis machine, and the patient's blood is pumped out through a vascular access and filtered. After being treated, the blood is reintroduced to the patient's circulatory system. Toxins with molecular weights of less than 500 Daltons (Da) can be effectively removed from ESRD patients' blood with this treatment, along with a negligible quantity of the middle-weight molecules (MW 500–32,000 Da). Through the use of semipermeable membranes and other separation techniques, including diffusion and ultrafiltration, excess blood pressure is used to push water and solutes through the membrane and into the dialysate side of the system. On the other side of the membrane, dialysate is used to treat the patient [92].

Hemodialysis is a process wherein urea and other low molecular weight compounds are exchanged from the patient's blood into an electrolyte and pH balanced dialysis solution through the use of an extra-corporal filtering/dialysis membrane. Depending on factors such remaining kidney function, protein intake, body size, and tolerance for fluid clearance, the frequency and length of dialysis treatment can vary. Hemodialysis is performed three times weekly, with each session lasting three to four

hours on conventional dialysis machines and significantly less time on high efficiency or high-flux dialysis machines [93].

1.2.2.4.2 Peritoneal dialysis

Patients with chronic kidney disease (CKD) have the option of undergoing peritoneal dialysis (PD), a kind of renal replacement therapy that can be performed at home [94]. PD is less expensive than hemodialysis and has a similar survival rate; it also protects the remaining kidney function better and removes solutes and fluid more gradually. Despite PD's efficacy in treating ESKF, it is still under prescribed. Infections, including peritonitis and a lack of catheter patency, are likely to blame for the inefficiency and short lifespan of PD. Therefore, PD treatment may be discontinued after only a short period of time. Long-term PD patients are most concerned about the dialysis fluid's biocompatibility, or its ability to maintain the peritoneal membrane's native anatomical and functional properties. It is possible that neoangiogenesis, inflammation, and fibrosis will develop after the peritoneal membrane has been exposed to the very un-physiological composition of typical PD fluids for an extended period of time. Increased transport of low-molecular-weight solutes is a hallmark of peritoneal injuries of this type [95].

1.2.2.5. Risk factors of chronic kidney disease

Chronic kidney disease (CKD) is characterized by a complex and varied set of risk factors. It has been hypothesized that common risk factors, such as longer duration of diabetes, hypertension, impaired metabolic regulation, smoking, obesity, and hyperlipidemia, enhance the likelihood of diabetic complications. The kidneys are more vulnerable to damage and impairment when blood pressure (BP) and glucose levels are

kept low. Similarly, some contextual factors have been demonstrated to be positively associated with CKD. These include age, smoking, and body mass index [95-96].

Patients with type 2 diabetes mellitus (T2DM) and chronic heart failure (HF) have an elevated chance of developing chronic kidney disease (CKD), which is associated with an increased risk of death and a decrease in quality of life. Patients with preexisting CKD frequently also suffer from type 2 diabetes and/or heart failure. The complex relationship between myocardial, vascular, and renal injury closely overlaps in conventional cardiovascular (CV) and unique kidney-specific (anemia, malnutrition, altered bone mineral metabolism, etc.) risk factors, and strongly links these conditions pathophysiologically. Patients of all HF phenotypes commonly observe a deterioration in kidney function, which is attributed in large part to the aforementioned risk factors [98].

Recent research has linked acute kidney injury (AKI) to either a worsening of CKD or the onset of CKD in those who previously did not have the disease [82].

1.2.2.6. IL-6 and Chronic kidney disease

One of the most extensively researched cytokines in kidney illness, IL-6 is well recognized for its pro-inflammatory effects, such as B-cell activation and induction of hepatic acute phase proteins. However, it is also involved in metabolic, regenerative, and neurological processes [99].

The presence of elevated plasma interleukin-6 (IL-6) levels is frequently observed in patients with chronic kidney disease (CKD). This phenomenon is primarily attributed to heightened production as a consequence of oxidative stress, chronic inflammation, and fluid overload. In addition, the diminished renal function plays a role in the accumulation

of IL-6 by reducing its clearance. In patients with end stage renal disease (ESRD), both therapeutic hemodialysis and peritoneal dialysis have been observed to elicit inflammatory responses and enhance the production of interleukin-6 (IL-6). Interleukin-6 (IL-6) has been found to expedite the advancement of chronic kidney disease (CKD) through its dual role of exacerbating renal injury and instigating associated complications, notably chronic vascular disease (CVD). The evidence supports the notion that IL-6 plays a significant role in initiating endothelial injury primarily by downregulating the expression of endothelial nitric oxide synthase (eNOS) and adiponectin, which is an adipokine known for its anti-atherogenic properties. Furthermore, the administration of recombinant IL-6 has been shown to worsen the progression of atherosclerosis. These findings provide insight into the potential contribution of IL-6 to the heightened occurrence of cardiovascular disease (CVD) in individuals with chronic kidney disease (CKD). The presence of an elevated interleukin-6 (IL-6) level in individuals with chronic kidney disease (CKD) is not solely a result of the disease itself. Rather, it plays a crucial role as a catalyst for the advancement of CKD and its associated complications[24].

All of the kidney's cell types (podocytes, mesangial, endothelial, and epithelial) produce IL-6. Given the apparent harmful net effect of IL-6 in renal cells, it is generally agreed that IL-6 plays a significant role in the initiation or advancement of CKD. It has been established that increased levels of systemic IL-6 are present even in the earliest stages of CKD, and that these levels are an independent predictor of mortality in the latter stages of the disease. Elevated IL-6 levels may be a symptom of CKD rather than an independent pathogenic cause, as impaired function has been linked to decreased renal clearance of IL-6 [100]. The mesangial proliferation in mesangial proliferative glomerulonephritis is induced by IL-6, and increased levels of IL-6 in the urine and the

kidneys are associated with poor outcomes. While 'traditional' signaling blockade of IL-6 and IL-6 R and inhibition of the 'trans' signaling pathway with sgp130Fc, as well as antibodies targeting other members of the IL-6 cytokine family, have both been used in preclinical and clinical investigations, they have yielded conflicting findings [101].

while many other cytokines have been shown to have a role in the onset or progression of chronic kidney disease, targeting IL-6 specifically for anti-inflammatory intervention in CKD looks to be a promising route to follow. Despite this, there are no IL-6 inhibitors approved for use in CKD, and clinical attempts to suppress IL-6 in CKD have been limited. Canakinumab had no positive effect on kidney function, but the CANTOS trial provided indirect evidence that patients with CKD and elevated IL-6 levels are a subgroup that benefits greatly from intervention to reduce inflammation and thus reduce their risk of cardiovascular disease [102].

1.2.3. Diabetes mellitus

Diabetes mellitus encompasses a collection of disorders pertaining to the metabolism of carbohydrates, characterized primarily by the presence of persistent hyperglycemia. This condition arises from impairments in either insulin secretion, insulin function, or a combination thereof. The presence of metabolic abnormalities in diabetes can be attributed to the diminished production of insulin and/or the resistance of target tissues to insulin. The disease primarily impacts skeletal muscles and adipose tissue, as well as the liver, specifically targeting insulin receptors, the signal transduction system, and/or effector enzymes or genes [103].

Polyuria, polydipsia, weight sometimes accompanied by polyphagia, and a generalized feeling of fuzziness in the eyes are all signs of high blood sugar. It can also

increase a person's vulnerability to some infections and slow their growth. Consequences that pose an immediate risk to human life due to untreated diabetes [102-103].

Indeed, this illness is marked by a high degree of familiarity, and its prevalence varies among ethnic groups, from the black and Hispanic to the members of certain minority groups in the United States and Canada, such as the American Indian and Alaska Native[105].

1.2.3.1. Types Diabetes mellitus

Type 1 diabetes (T1D) is an autoimmune disease that occurs when T lymphocytes specifically target and destroy insulin-producing -cells in the pancreas. The medical term for type 1 diabetes is insulin-dependent diabetes mellitus (IDDM).In children, this form of diabetes accounts for 5- 10% of all cases [18].

Type 1 diabetes (T1D), formerly known as "juvenile diabetes" due to its prevalence among children, has been recognized as a prevalent chronic condition. However, it is important to note that T1D can now be diagnosed across all age groups, highlighting its evolving clinical presentation. The aforementioned condition typically manifests predominantly during the age range of 5 to 7 years and also during or around the onset of puberty. The medical condition is distinguished by the body's absolute incapacity to generate insulin, a vital anabolic hormone responsible for facilitating the utilization of glucose by the body's cells for energy. Significantly, insulin plays a crucial role in facilitating the transportation of glucose into muscle and adipose cells. It also promotes the storage of glucose as glycogen in the liver and facilitates the synthesis of fatty acids. Additionally, insulin stimulates the uptake of amino acids and hinders the breakdown of fat in adipose tissue. Furthermore, it promotes the uptake of potassium into cells [106].

Type 2 Diabetes Mellitus (T2DM) is one of the most prevalent metabolic disorders in the world, and its development is predominantly due to a combination of two main factors: defective insulin secretion by pancreatic -cells and the inability of insulin-sensitive tissues to respond to insulin. Therefore, the molecular mechanisms involved in the synthesis and release of insulin, in addition to the insulin response in tissues, must be tightly regulated. Therefore, defects in any of the involved mechanisms can result in a metabolic imbalance that contributes to the pathogenesis of type 2 diabetes [107].

Type 2 Diabetes Mellitus (T2DM) has historically been known as non-insulin-dependent diabetes or adult-onset diabetes. It is characterized by insulin resistance, which can gradually escalate to absolute resistance. However, in recent years, there has been a growing recognition of reduced B-cell function as a significant issue in T2DM [108].

Patients diagnosed with Type 2 Diabetes Mellitus (T2DM) commonly exhibit prominent features such as obesity or an elevated body fat composition, primarily concentrated in the abdominal area. In this pathological state, the adipose tissue contributes to the development of insulin resistance (IR) through a multitude of inflammatory mechanisms. These mechanisms encompass heightened liberation of free fatty acids (FFAs) and dysregulation of adipokines. The primary contributing factors to the epidemic of Type 2 Diabetes Mellitus (T2DM) encompass the escalating worldwide prevalence of obesity, sedentary behaviors, high-calorie dietary patterns, and the aging of populations. These factors have collectively resulted in a fourfold increase in both the incidence and prevalence of T2DM [107].

The pancreas (both β-cells and α-cells), liver, skeletal muscle, kidneys, brain, small intestine, and adipose tissue all play a role in the progression of type 2 diabetes

[109]. This condition is often asymptomatic or manifests with only subtle symptoms in its earliest stages. This means that it is extremely challenging to make a precise estimate of the number of people who are afflicted by the disease because it may go untreated for a long time. Diagnosis is made in the absence of symptoms if either the fasting plasma glucose (FPG) or the oral glucose tolerance test (OGTT) is greater than or equal to 200 mg/dl or if the glycated hemoglobin (HbA1c) is greater than or equal to 6.5%. The diagnosis of diabetes is made when blood glucose levels are over 200 mg/dl, regardless of the presence or absence of symptoms [105].

Gestational diabetes mellitus (GDM) is a medical condition that occurs during pregnancy and is characterized by high blood sugar levels. is a prevalent prenatal condition characterized by impaired glucose tolerance that manifests for the first time during pregnancy. Its occurrence affects approximately 9–25% of pregnancies globally, although specific rates may vary depending on the characteristics of the study population and the diagnostic criteria employed. Gestational diabetes mellitus (GDM) is distinguished by the presence of impaired glucose tolerance, which arises from maternal pancreatic beta-cell dysfunction. This dysfunction leads to an inadequate production of insulin, thereby compromising the regulation of glucose homeostasis throughout the duration of pregnancy [110].

Monogenic diabetes syndromes (including neonatal diabetes and maturity-onset diabetes of the young (MODY)), diseases of the exocrine pancreas (including cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (including with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation) are all examples of other types of diabetes [111].

1.2.3.2. Diagnostic of Diabetes Mellitus

Untreated DM can cause serious problems, but an early diagnosis of diabetes can lessen or even eliminate these risks. Diagnosing pre-diabetes and diabetes typically requires a battery of biochemical testing [112].

The Fasting Plasma Glucose Test (FPG) involves the measurement of glucose levels in the blood after a period of fasting, which entails refraining from consuming any food or beverages, with the exception of water, for a minimum of 8 hours prior to the test. Individuals diagnosed with diabetes typically exhibit a fasting glucose concentration equal to or exceeding 7.0 mmol/L. If an individual exhibits a plasma glucose level of ≥7.8 mmol/L after a duration of 2 hours following the consumption of 75 g of glucose, it can be concluded that the individual is experiencing impaired glucose tolerance [112-113].

Tolerance to glucose via mouth The oral glucose tolerance test (OGTT) evaluates how effectively cells absorb glucose following a predetermined dose of sugar. It is common practice to administer 75 g of glucose orally to a suspect, wait 2 hours, and then measure their plasma glucose level. A person is considered to be diabetic if their plasma glucose level is over 11.1 mmol/L. Diagnosing pre-diabetes and diabetes with this test [18].

The HbA1c test can be used to identify diabetes, with a 6.5% cutoff level being indicated for diagnosing purposes. It has been hypothesized that HbA1c is a more accurate gauge of how well diabetics are managing their blood sugar levels than fasting blood sugar levels. Patients with type 2 diabetes have a glycosylated hemoglobin level of 48 mmol/mol or more (≥6.5 DCCT%) [112].

Traditional methods of determining a person's glycemic status have relied on random blood glucose, a direct measure of glucose levels in the blood. However, there are a number of factors, including nutrition and physical and emotional stress, that can cause glucose levels to fluctuate. Random plasma glucose levels more than or equal to 200 mg/dl (11.1 mmol/L) in patients exhibiting signs of hyperglycemia or hyperglycemic crisis [113-114].

1.2.4. Procalcitonin (PCT)

Non-hormonal propertied calcitonin, also known as procalcitonin (PCT), consists of 114 to 116 amino acids [116].

In contrast to bacterial infections, viral infections reduce levels of the inflammatory serum marker procalcitonin (PCT). It rises and falls more rapidly during an infection than C-reactive protein (CRP), another common inflammatory marker. Therefore, the test can aid in diagnosing and tracking the progression of infections of various causes. PCT is a highly specific and sensitive diagnostic for sepsis since it increases in response to bacterial infections but not to other inflammatory reactions such as viral infections, autoimmune illness, or trauma. Normal adults and children, past the newborn stage, typically release it at a low serum concentration (0.1 ng/mL). In severe BI cases, PCT levels can skyrocket from 0.5 ng/ml to 200 ng/ml. PCT levels in VI patients rarely go above 1 ng/ml. PCT has a half-life of around 24 hours. International consensus recommendations advocate PCT as a decision aid in ASPs due to its efficacy in lowering antibiotic use, especially in sepsis and lower respiratory tract infections [115-117].

Thyroid C cells produce PCT, which is then transformed to calcitonin before entering the bloodstream under normal circumstances. In response to a bacterial infection, the body's non-thyroidal tissues ramp up their PCT production [119].

1.2.5. C-Reactive Protein (CRP)

CRP is an acute-phase protein that is made by hepatocytes in response to the inflammatory cytokine interleukin 6 (IL-6). It is thought to be a sensitive biomarker of bacterial infections, cardiovascular events, and inflammatory diseases. CRP helps the immune system get rid of harmful substances by increasing phagocytosis and turning on the classical complement pathway[120]. In healthy individuals, C-reactive protein (CRP) levels in the blood are typically low (0.6 mg/dl), but they increase in response to inflammation or tissue damage. Once the inflammation or tissue damage goes away, these levels go back to normal [121].

It is known that the C-reactive protein (CRP) comes in two different shapes: the native pentameric CRP (p CRP) and the monomeric CRP (m CRP). both of which belong to the family of pentraxins. In response to stimulation by IL-6, hepatocytes produce pCRP, which is then released into the bloodstream. Research indicates that pCRP can have pro-inflammatory or anti-inflammatory effects. On the other hand, mCRP may exacerbate the inflammatory response since it has strong pro-inflammatory effects on endothelial cells, endothelial progenitor cells, leukocytes, and platelets. CRP could be directly linked to inflammation by its conversion to the pro-inflammatory form, mCRPs [121-122].

In acute bacterial infections, doctors frequently employ CRP for both the identification of the inflammatory process and the quantification of its intensity. In addition, CRP is utilized to direct antibiotic therapy and to monitor the conclusion of the

inflammatory process. C-reactive protein (CRP) concentrations have been shown to rise in patients with acute bacterial infections, and doctors frequently utilize this measure to determine whether or not a patient has a noteworthy inflammatory response [10]. By contrast, interferon α strongly suppresses IL-6-induced CRP expression in hepatocytes, which explains why viral infections only result in mild increases in CRP [124].

1.2.6. Kidney Functions Test

Accurate diagnosis, risk assessment, and select treatment that enhances clinical result, all rely heavily on biochemical indicators [125].

1.2.6.1. Urea and Creatinine

Creatinine, a chemical byproduct generated through the metabolic processes of muscles, is primarily excreted as a waste product. Additionally, it is worth noting that a lesser contribution to Creatinine production can be attributed to the consumption of meat. The kidneys, in their state of optimal health, perform the vital function of effectively filtering Creatinine and various other waste products from the bloodstream. Subsequently, the body expels these meticulously filtered waste products through the process of urination. In the event of renal dysfunction, there is a potential for the accumulation of Creatinine within the bloodstream. The serum Creatinine test is a diagnostic procedure that quantifies the concentration of Creatinine in the bloodstream, thereby offering an assessment of the renal filtration capacity. The results of the Creatinine blood test are quantified in milligrams per deciliter (mg/dl). Creatinine normal level in the blood changes from lab to lab but also between men and women, between people of different races, and as people age. Males often have higher creatinine levels than females because of their

greater muscular mass, which causes their blood creatinine levels to rise. A high serum creatinine level is an indicator that the kidneys are not functioning normally and are not filtering blood adequately; however, a temporary elevation in creatinine level can occur in response to factors such as dehydration, low blood volume, excessive meat consumption, or the use of certain drugs. When added to the diet, creatine can raise serum creatinine levels [87].

The liver produces urea, the primary nitrogenous end product of protein and amino acid catabolism, and distributes it both intracellularly and extracellularly. Renal glomeruli remove urea from the blood and reabsorb some of it together with water. Clinical indices used most often to estimate renal function are those based on serum urea concentration. It aids in distinguishing between acute renal failure and pre-renal conditions characterized by an elevated blood urea nitrogen-creatinine ratio. Since the rate of urea overproduction depends on factors outside of the kidneys, such as the food and the enzymes involved in the urea cycle, urea clearance is not a good indication of glomerular filtration rate. High levels of blood urea nitrogen (BUN) can indicate renal illness or failure, urinary tract obstruction from a kidney stone, congestive heart failure, dehydration, fever, shock, or internal bleeding. Some women experience elevated BUN levels in late pregnancy, and others get them after consuming a lot of protein. Increased BUN levels indicate advanced renal injury, while lower BUN levels reflect fluid overload. Anabolic steroid use, trauma, surgery, opiate use, starvation, and severe malnutrition all result in decreased levels [125].

1.2.7. Albumin

Albumin is a family of globular proteins, with serum albumins being the most prevalent. Serum albumin is the most prevalent protein in all vertebrate blood plasma. Before being secreted by hepatocytes, it is synthesized in the liver as pre-pro-albumin and matures in the endoplasmic reticulum and Golgi bodies. One polypeptide chain with 585 amino acids makes up the HSA molecule. The extravascular and intravascular concentrations of human serum albumin (HSA) are 35–50 mg/mL, with an approximate half-life of 19 days. Albumins, like all proteins, are soluble in water and only slightly soluble in concentrated salt solutions. Albumin's main characteristics are those of an acidic, highly soluble, and very stable protein, as it can remain stable at 60 °C for 10 hours. There are a total of 83 positively charged residues (Arg and Lys) and 98 negatively charged residues (Asp and Glu) in human serum albumin (HSA), giving it a theoretical pI of 5.12 [125-126].

1.2.8. Complete Blood Count (CBC)

Blood has many cell types and plasma components. This vital fluid delivers oxygen and nutrients to tissues and organs. Blood removes CO2, ammonia, and other wastes. It helps regulate body temperature, oxygen delivery, cell regeneration, coagulation, and immunity. RBCs, WBCs, platelets, and plasma make up blood [128].

The complete blood count (CBC), referred to as a hemogram, is an extremely useful laboratory test for diagnosing and monitoring a wide variety of health problems. The complete blood count (CBC) measures three components: (1) white blood cell (WBC) total and differential count; (2) erythrogram (RBC count, Hb determination, hematocrit,

and indices calculation; MCV, MCH, MCHC, and RDW); and (3) platelet count indices calculation (mean platelet volume (MPV)) [128-129].

1.2.8.1. White blood cells (WBCs)

White blood cells (WBC) are powerful infection fighters; they typically multiply and divide in an organized fashion in response to the needs of the human body to fight infections and other illnesses [131].

When analyzing CBC results, the WBC count is one of the most crucial indications. Neutrophils, lymphocytes, monocytes, eosinophils, and basophils are just a few examples of the many different types of white blood cells (WBCs) found in the blood. White blood cells (WBCs) play an important role in the immune system and have specialized functions depending on their kind. An increase in white blood cells (WBCs), for instance, may point to cancer or infection elsewhere in the body. A low white blood cell count (WBC) may indicate an issue with bone marrow production or represent an unwanted side effect of medication, such as chemotherapy for cancer [22].

A healthy person's percentage of different types of WBCs falls within a range. Neutrophils, for instance, can make up 40% to 80% of the body's white blood cell population, whereas lymphocytes contribute 20% to 40%, eosinophils 1% to 6%, and monocytes 2% to 10% [131].

1.2.8.1.1.Lymphocytes

Lymphocytes, which account for about 20-40% of all leukocytes, play a crucial role in the adaptive immune response [130].

Lymphocytes are types of white blood cells that have a role in the immune system of vertebrates. They can be broadly classified as either large and granular lymphocytes or tiny lymphocytes, depending on size. Large lymphocytes are identical to natural killer cells in almost every way. Lymphocytes, or small lymphocytes, are made up of T cells and B cells. While B cells create antibodies to combat foreign cells, T cells are responsible for attacking and fighting against one another. The fate of these progenitor cells is determined by their genes. This conversion does not take place in a person with leukemia, as this step is permanently arrested [132].

When there are abnormally few lymphocytes floating around in the blood, doctors call it lymphopenia. Total lymphocyte counts below the normal range for a certain age group (for example, less than 1000 cells/L in older children and adults) are diagnostic of this condition. Viral infections, chemical and physical lympho-depleting agents, autoimmune-related systemic disorders, hereditary factors, malignancies, sepsis, and other severe injuries can contribute to a dramatic drop in blood lymphocyte counts [133].

1.2.8.2. Red blood cells (RBCs)

The absolute number of red blood cells is also an important CBC result. Red blood cells (RBCs) mature in the bone marrow before being discharged into the bloodstream. Red blood cells (RBCs) are typically homogeneous in size and shape; however, situations such as iron shortage can alter their appearance. When the red blood cell count or hemoglobin level falls below the normal range, a condition known as anemia sets in. Hb, hematocrit, MCV, MCH, MCHC, and RDW are just few of the CBC components that are linked to RBC count. We describe the relationships of Hb, MCV, RDW, and CVD with metabolic disease [22].

1.2.8.2.1. Hemoglobin (Hb)

Hemoglobin (Hb) is an iron-containing oxygen-transporting metalloprotein and is the primary component of red blood cells (RBC). Hb has four heme groups, and each heme group contains an iron atom in the ferrous state (Fe^{2+}), which may bind molecular oxygen (O_2) reversibly. This results in two forms of Hb, OxyHb and DeoxyHb. RBC receive oxygen from the lungs (OxyHb) and transport that oxygen to the body's tissues (DeoxyHb) [134].

During the typical lifespan of red blood cells (RBCs), approximately 1-3% of hemoglobin (Hb) undergoes a conversion into an oxidized non-functional state, specifically ferric/met. Methemoglobin (MetHb) undergoes rapid conversion to ferrous/oxyhemoglobin (ferrous/oxyHb) by the action of MetHb reductase in the presence of nicotinamide adenine dinucleotide (NADH). During the storage of red blood cells (RBCs), the enzymatic activity of methemoglobin reductase is reduced, leading to elevated amounts of methemoglobin that remain unconverted to oxyhemoglobin. The potential rise in hemoglobin oxidation during the storage of red blood cells (RBCs) could potentially be attributed to a decline in their antioxidant capacity. This decline may subsequently result in the oxidation and degradation of membrane lipids and proteins, ultimately leading to irreversible harm to the membrane [135].

1.2.8.3. Platelets

Platelets, the smallest circulating blood cells, originate in the bone marrow and are essential for hemostasis, among other tasks. Platelet count changes, such as thrombocytopenia or thrombocytosis, can occur for a variety of causes. Inadequate or

excessive platelet production in the bone marrow, platelet consumption in the peripheral tissues, or platelet distribution within the organs can lead to thrombocytopenia or thrombocytosis. Platelet longevity is lower in conditions with greater platelet consumption, but no known circumstances extend platelet lifespan (in contrast to, for example, red blood cells) [136].

Platelets are produced and eliminated at a rate of about 1011 each day, maintaining a steady concentration in human blood of between 150 and 450×109 platelets per liter. After being activated, platelets can perform a variety of hemostasis and immunity-related jobs during their 7–10 day circulation [137].

1.3. The aim of the study

The study aimed to evaluate the roles of interleukin-6, PCT, and CRP in the different diagnoses of patients with kidney failure with or without diabetes mellitus who have had bacterial or viral infections.

Chapter Two

Materials &Method

2. Materials and methods

2.1 Study subjects

A total of one hundred and twenty (120) subjects were included in this study, divided into six groups:

A-Twenty patients with chronic kidney disease were undergoing dialysis and had a bacterial infection.

B- Twenty patients with chronic kidney disease were undergoing dialysis and had a viral infection.

C- Twenty patients with chronic kidney disease were undergoing dialysis with type 2 diabetes and a bacterial infection.

D- Twenty patients with chronic kidney disease were undergoing dialysis with type 2

E- Twenty patients with type 2 diabetes

F- Twenty healthy control participants had no signs or symptoms of any systemic disease.

In the center of Al-Kidney; the collection of samples was accomplished, in the Al-Hussein Teaching Hospital of Muthanna for the period ranging from January 2023 to the end of August 2023 (Appendix 1).

All participants who were able to comprehend the study's objectives and aims gave their informed written consent. Also, they were free and could withdraw from their participation at any time.

2.2. Inclusion Criteria

1. ESCKD patients with microbial infection (viral and bacterial)

2. Diabetes mellitus type 2 patients age ≥ 40 years (both males and females)

3. Hepatitis patients B and C.

2.3. Exclusion Criteria

1. Renal transplant patients.

2. Cardiovascular disease patients.

3. Diabetes mellitus type 1 patients age < 40 years (both males and females).

4. Cancer patients.

2.4. Methods and Procedures

2.4.1. Blood Samples Collection

Blood samples from the veins (5 mL) were withdrawn from each patients and also from the healthy control group by venipuncture with the use of disposable syringes. At room temperature, gel tubes of 5 ml capacity were left after being filled with blood. To collect sera, these tubes were centrifuged, for 10 minutes at 3000 rpm. Sera aliquots were located in Eppendorf pipe and saved in (−80℃) before to use for determination of biochemical analysis (IL-6 , PCT ,Urea , Creatinine , Albumin , K^+, Na^+, Cl^-). To accomplish complete blood count, blood of 2 ml volume was poured into anticoagulant filmed tubes; ethylene diamine tetra acetic acid type; EDTA.

2.5. Implements and Appliances

Appliances and implements depended via this study; their source such as countries and companies **(Table 2.1).**

Table (2.1) : The appliances that depended via this study.

Order	Manufacturer	Appliances	Indent
1	Fish Scientific	Centrifuge	U.S.A
2	Heidolph	Vortex	Germany
3	Brannan	stop watch	U.S.A
4	Nanjing	Getein Biotech 1100	Chain
5	Shimadzu	Refrigerator	Chain
6	Biobas	Sysmex	Japan
7	Memmert	Incubator	Germany

Table (2.2): The implements depended in the current study.

Order	Manufacturer	Implements	Indent
1	Sterile	disposable syringes	China
2	SLAMED	Micropipette (100-1000) µL	Germany
3	Eppendorf	Eppendorf tubes	Germany
4	Thermo Fisher scientific	Eppendorf tube Rack	USA
5	ALS	gel tubes	China
6	ALS	Plain tubes	China
7	ALS	EDTA coated tubes	China
8	Broche	Gloves	Malaysia
9	Unisef	Cool ice box	Russia

2.6. Chemical and Biological material

The materials utilized in this study are given below, along with the nation and firm from which they came they came in **Table (2.3)**

Table(2.3): Materials used in the current study.

NO.	Materials	Company	Source
1	Urea Kit	Randox	United Kingdom
2	Creatinine Kit	Randox	United Kingdom
3	IL-6 Fast Test Kit	Nanjing	China
4	PCT Fast Test Kit	Nanjing	China
5	Albumin Kit	Randox	United Kingdom
6	Chloride Kit	Linear Chemical	Spain
7	Sodium Kit	Linear Chemical	Spain
8	Potassium Kit	Linear Chemical	Spain
9	CRP kit	Linear Chemical	Spain

2.7. Biochemical Markers

2.7.1. Determination of Urea Level :

A. Method: Urease-Berthelot Method

B. Principle: Urease existence is crucial to hydrolyze urea to get ammonia in the serum. Berthelot`s reaction is the photometric measurement method for ammonia [138].

$$H_2O + \text{Urea} \xrightarrow{\text{urease}} CO_2 + 2NH_3$$

$$\text{Phenol} + \text{hydrochloride} + NH_3 \longrightarrow \text{the blue compound; indophenol}$$

C. Reagent :

Table(2-4): Reagents kit Urea Composition

Contents	Solutions; principal concentration
R1 EDTA Sodium nitroprusside Urease	**116 mmol/l** **6 mmol/l** **1 g/l**
R2 phenol (diluted)	**120 mmol/l**
R3 Sodium hypochlorite (diluted) Sodium hydroxide	**27 mmol/l** **0.14 N**
CAL. Standard	

D. Procedure:

Table(2-5): Procedure of Urea assay

Wavelength	**546 nm (530-570 nm)**
Cuvette	1cm light path
Temperature	37 ℃
Measurement	Against reagent blank

Table(2-6): Pipetting; into test tubes

Tubes	Blank	Sample	Standard
Distilled water	10 mL	……	……
Standard	……	10 µL	……
Sample	……	……	10 Ml
Reagent 1	100 µL	100 µL	100 Ml

For 10 minutes, incubate at 37°C after mixing.

Tubes	Blank	Sample	Standard
Reagent 2	2.50 ml	2.50 ml	2.50 ml
Reagent 3	2.50 ml	2.50 ml	2.50 ml

For 15 minutes, immediately incubate at 37°C after mixing. Against the blank and reading the absorbance of the sample and the standard. After at least 8 hours, the reaction color would be stable.

E. Calculation:

Urea Concentration = $\frac{A_{sample}}{A_{standard}}$ × Standard conc. (mmol/l)

2.7.2. Determination of Creatinine Level :

A. Method: Colorimetrical

B. Principle: Creatinine in alkaline solution reacts with picric acid to form a colored complex. The amount of the complex formed is directly proportional to the creatinine concentration [139].

C. Reagent :

Table (2-7): Composition of Creatinine kit reagent.

Contents	Initial Concentration of Solutions
CAL. Standard	
R1a. Picric Acid	**35 mmol/l**
R1b. Sodium Hydroxide	**0.32 mmol/l**

D. Procedure:

Table (2-8): Procedure of Creatinine assay.

Wavelength	**492 nm (490-510 nm)**
Cuvette	1cm light path
Temperature	+25/+30/ +37 ℃
Measurement	Against air

Table (2-9): Pipette into Cuvette

Tubes	Sample	Standard
Working reagent	1 ml	1 ml
Standard	0.1 ml	……
Sample	……	0.1 ml

The absorbance of the sample and the standard (A1) must be read after mixing for 30 seconds. The absorbance of the standard and sample (A2) must be read for exactly 2 minutes thereafter.

E. Calculation:

$A_2 - A_1 = \Delta A_{sample}$ or $\Delta A_{standard}$

Creatinine concentration, in plasma or serum.

$\frac{\Delta A_{sample}}{\Delta A_{standard}} \times$ Standard conc. (µmol/l) = µmol/l

2.7.3. Determination of Procalcitonin (PCT) Level.

A. Method: Immunofluorescence Assay

B. Principle: Conjugated with fluorescence latex, PCT anti – human monoclonal anti – body is being used by the test. For PCT product, test line 1 was coated with anti-human PCT polyclonal antibody and test line 2 was coated with another anti-human PCT monoclonal antibody. A complex of antigen – antibody is being formed markedly, when there is a binding between the PCT in sample and the fluorescence anti - human latex – labelled PCT. Test card detection zone is being reached by the complex via capillary property. Thereafter, a marked complex of antigen – antibody is being captured by another monoclonal PCT antibody on the test line, or; the polyclonal antibody. In proportion to the PCT amount in the sample, the test line fluorescence intensity increases [140].

Thereafter, the test card must be inserted into an Immunofluorescence quantitative analyze, 1600 Getein (recently denoted as Getein 1100 and Getein 1600); on the screen, the sample concentration of PCT will be displayed after being measured. In Getein 1100 / 1600, the storage of value is assured and is present for downloading or transmitting to the information system of the hospital or laboratory [141].

C. Procedure:

1. According to user manual, specimens are being collected.

2. Before testing, reagent, sample and test card must be fetched to room temperature.

For Getein1100:

3. In accordance with the lot number of test kit, the SD card lot number must be confirmed.

4. Before using, immediately; the test card must be removed from the well-sealed pouch. With control or patient identification, the test card must be labelled.

5. On a clean table, the test card must be put horizontally.

6. On the sample port of the test card, a 100 µl of sample must be delivered via a sample transfer pipette. After loading the 100 µl sample on the card, one whole blood buffer drop must be added, if a whole blood sample is depended.

7. Time of reaction; 15 minutes. Click on start icon, for android Getein 1100 or press ENT button for Getein 1100 after inserting the test card. The result will be shown on screen and printed automatically after the time of the reaction is being over.

2.7.4. Determination of IL-6 Fast Level :

A. Method: Immunofluorescence Assay

B. Principle: An anti – human I monoclonal IL-6 antibody, fluorescence latex conjugated, conjugated on the o-nitrocellulose membrane junction and sample pad; is used by test, besides other anti – human II monoclonal IL-6 antibody on the test line. Marked antigen – antibody complex, is being formed by binding of the sample IL-6 with the IL-6 anti – human fluorescence latex – labelled antibody. By capillary action, the complex travels to the detection zone of the test. Then, by anti – human II antibody IL-6, a marked complex of antigen-antibody is being seized on the test line. In proportion to the sample amount of IL-6, the test line fluorescence intensity, increases [142].

C. Procedure:

1. According to user manual, collect the specimens.

2. For Getein 1100; before testing, reagent, sample and the test card, should be fetched to room temperature.

3. If necessary, calibration of SD card is performed when confirming the lot number of SD card in accordance with lot number of test kit.

4. Getein 1100 testing interface is being entered.

5. Immediately before use, the test card must be removed from the sealed pouch. With identification of patient or control, the test card must be labelled.

6. Horizontally placed, the test card must be put on a clean table.

7. On the sample port of the test card, a 100 µl of sample must be delivered via a sample transfer pipette. After loading the 100 µl sample on the card, one whole blood buffer drop must be added, if a whole blood sample is depended.

8. Time of reaction; 15 minutes. Click on start icon, for Getein 1100 after inserting the test card. The result will be shown on screen and printed automatically after the time of the reaction is being over.

2.7.5. Determination of C-Reactive Protein (CRP) Level :

A. Method: Slide test; C - reactive protein Determination.

B. Principle: For the semi – quantitation and the direct detection of the C- reactive protein, the rapid procedure of agglutination; the CRP latex kit, is required. In presence of CRP in the serum of a patient, agglutination of specific antihuman C-reactive protein antibodies which coat the suspension latex particles of the reagent; would occur [143].

C. Reagent :

Table (2-10): Composition of C-reactive protein reagent kit

Contents	Initial Concentration of Solutions
CRP latex	**Suspension of polystyrene particles coated with antihuman CRP goat antibodies.**
CRP Positive Control	**Human pooled serum**
CRP Negative Control	**Human pooled serum**
Physiological Saline Buffer Concentrate	**Dilute 1:20 (v/v) with distilled water**
Reaction Slide	
Serum Droppers	
Applicator Sticks	
Rubber teat	

D. Procedure:

After mixing well before use, permit the sample and reagents to catch the room temperature.

1. By the use of disposable serum dropper, pour one drop of sample serum on the slide.

2. With a disposable applicator stick, mix CRP –latex reagent one drop with previously sample drop.

3. For two minutes, gently agitate the slide comes and forth, then examine under adequate source of light immediately for agglutination. Beyond two minutes, examination is denied.

4. By obtaining control serum from the respective vials, the same previously mentioned procedure is being followed for the negative and positive controls.

2.7.6. Determination of Complete blood count:

A. Principle: After being diluted, the blood samples are passed through a delicate tube permitting for one by one cell passage only. Many different channels, to which the blood must be separated because it is impossible to measure everything concerning the cells simultaneously. The signals are conveyed in sequence towards an analog circuit as the cells pass through apertures. Thereafter, towards analysis circuits of particle size distribution permitting transformation to data of aggregative cellular size distribution, the created distribution curves of size data, and the level of discrimination is excluded via a specific microprocessor pertaining to each collection.

B. Procedure:

First of all, checking of the operation reagents was made. Background and power switch are run automatically. After selecting the mode of complete blood analysis, controls of three levels; normal, low and high were accomplished. Sample number keys are pressed to introduce the numbers of sample, then the enter key is pressed. Thereafter, a neat mixing of sample is done. The sample probe is in close contact with the bring tab. Then, by pressing the start key, aspiration of demanded blood amount is done. The LCD screen will do display the analysis and the results are printed [144].

2.7.7 Determination of Albumin Level :

A. Method: Bromocresol Green

B. Principle: The indicator 3,3,5,5-tetrabromo-m cresol sulphonephthalein (bromogresol green, BGG) is quantitative binding target of the serum albumen to make its measurement possible. At 578 nm, complex of albumin-BGG is absorbed maximally. Concentration of albumin in the sample is of linear proportion to the absorbance [145].

Table (2-11): Reagent kit ALB Composition

Contents	Initial Concentration of Solutions
R1. BCG Succinate buffer Bromocresol green Brij 35 Preservative	 **75 mmol/l; PH 4.2S** **1.7 mmol/l**
CAL. Standard	

C. Procedure:

Table (2-12): Procedure of ALB assay

Wavelength	**Hg 578 nm or Hg 623 nm**
Spectrophotometer	630 nm (600-650 nm)
Cuvette	1cm light path
Incubation Temperature	+20 to + 25℃
Measurement	against reagent blank

Table (2-13): Pipette into cuvette:

Tubes	Reagent Blank	Standard	Sample
Distilled $H_{2\,O}$	0.01 ml	……	……
Standard	……	0.01 ml	……
Serum or Plasma	……	……	0.01 ml
R1 (BCG reagent)	3 ml	3 ml	3s ml

Mix, incubate for 5 minutes at +20 to + 25 ℃. Measure the absorbance of the sample (A_{sample}) and the standard (A_{sample}) against the reagent blank.

D. Calculate :

Based on the following formula, the sample albumin concentration is calculated:

$$\text{Albumin Concentration (g/l)} = \frac{A_{sample}}{A_{standard}} \times \text{Concentration of standard}$$

2.7.8. Determination of Chloride Level :

A. Method: Thiocyanate colorimetric method (Endpoint)

B. Principle: From mercuric thiocyanate, the thiocyanate is displaced by chloride ions in the sample. A complex of red ferric – thiocyanate is formed by interaction between the ferric ion and the liberated thiocyanate ion. This complex is proportional to the chloride concentration in sample[146].

$$2Cl^- + Hg(SCN)_2 \longrightarrow HgCl_2 + 2(SCN)^-$$

$$3(SCN)^- + Fe^{+3} \longrightarrow Fe(SCN)_3$$

Table (2-14): Reagent kit Chloride Composition

Contents	Initial Concentration of Solutions
R1 Thiocyanate reagent	Mercuric thiocyanate 2 mmol/L Mercuric nitrate 0.1 mmol/L Iron nitrate 30 mmol/L HNO_3 45 mmol/L.
CAL. Chloride / Phosphorus standard.	Chloride 100 mmol/L / Phosphorus 5 mg/dl

C. Procedure:

Table (2-15): Procedure of Chloride assay

Tubes	Blank	Sample	CAL. Standard
S	1 ml	1 ml	1 ml
Sample	……	10 µL	……
CAL. Standard	……	……	10 ml

Gently mix, by one or two times inversion. Vigorous stir and shake is avoided. At temperature between 25-37 °C, the mixture is incubated for 5 to 10 minutes. Against the reagent blank, read the absorbance of samples and standard at 470±10 nm.

D. Calculation:

$$\frac{\text{A sample}}{\text{A standard}} \times C_{\text{Standard}} = \text{(mmol/L) chloride}$$

2.7.9 Determination of Potassium Level :

A. Method: Fixed time (Enzymatic method)

B. Principle: diagnosis and treatment of diseases pertaining to potassium and electrolyte balance disturbances are done by monitoring and measuring the potassium blood levels. Kinetic coupling assay system is exploited to spectrophotometrically determine the potassium depending upon pyruvate kinase. Accompanying the conversion of NADH to NAD^+, the generated pyruvate is converted to lactate [147].

Table (2-16): Reagent kit Potassium Composition

Contents	Initial Concentration of Solutions
R1	LDH <50 KU/L NADH <10 mmol/L Sodium azide 0.05% Stabilizers
R2	Pyruvate kinase <50 KU/L Sodium azide 0,05% Stabilizers.
CAL. Chloride / Phosphorus standard.	Sodium (Na^+) 160 mmol/L/ Potassium (K^+) 6.0 mmol/L.

C. Procedure:

Table (2-17): Procedure of Potassium assay

Tubes	Blank	Sample	CAL. Standard
R1 Reagent	1 ml	1 ml	1 ml
Sample	……	25 µL	……
CAL. Standard	……	……	25 Ml

Mix, incubate the mixture for 5 minutes at 37 ℃, Add

Tubes	Blank	Sample	CAL. Standard
R2 Reagent	250 µL	250 Ml	250 µL

Mix, incubate for 1 minutes at 37ºC and read (A1) at 405 nm.

D. Calculation:

$$\text{Potassium (mmol/L)} = \frac{(A_2 - A_1)\text{sample}}{(A_2 - A_1)\text{ calibration}} \times \text{C calibrator}$$

2.7.10. Determination of Sodium Level :

A. Method: Fixed Time (Enzymatic method)

B. Principle: diagnosis and treatment of diseases pertaining to sodium and electrolyte balance disturbances are done by monitoring and measuring the sodium blood levels. Activity of sodium – dependent B- galactosidase is exploited with ONPG as a substrate to get enzymatic determination of sodium. Sodium concentration is proportional with the product O-nitrophenyl absorbance at 405 nm [148].

$$\text{ONPG} \xrightarrow[\beta\text{-galactosidase}]{Na^+} \text{O-nitrophenyl} + \text{galactose}$$

Table (2-18): Reagent kit Sodium Composition

Contents	Initial Concentration of Solutions
R1	Good's buffer (pH 8.5) β-D-galactosidase (<8 U/mL) Cryptand (>0.4 mM) Proclin 300 (0.02%).
R2	Good's buffer (pH 6.5) ONPG (>0.5 mM) Proclin 300 (0.02%).
CAL. Sodium / Phosphorus standard.	Sodium (Na+) 160 mmol/L. / Potassium 6.0 mmol/L.

C. Procedure:

Table (2-19): Procedure of Sodium assay

Tubes	Blank	Sample	CAL. Standard
R1 Reagent	1 ml	1 ml	1 ml
Sample	……	40 µL	……
CAL. Standard	……	……	40 Ml
R2 Reagent	0.5 ml	0.5 ml	0.5 ml

Mix, incubate for 1 minute at 37ºC and read (A1) a 405 nm, Incubate for 2 minutes at 37ºC and read (A2) a 405 nm.

D. Calculation:

$$\text{Sodium (mmol/L)} = \frac{(A_2 - A_1)\text{sample}}{(A_2 - A_1)\text{ calibration}} \times \text{C calibrator}$$

2.8. Statistical analysis

All statistical analyses were performed using (SPSS) Statistical Package for the Social Sciences version 26 software .Where the comparison was made between the four groups using ANOVA and also LSD. The (P- value) that less than 0.05 were considered to be statistically significant and the results were expressed as Mean±SD.

Chapter Three

Results &Discussion

3. Results and Discussion

The current study included 120 patients, divided into six groups: 20 patients with chronic kidney disease were undergoing dialysis and had a bacterial infection; 20 patients with chronic kidney disease were undergoing dialysis and had a viral infection; 20 patients with chronic kidney disease were undergoing dialysis with type 2 diabetes and a bacterial infection; 20 patients with chronic kidney disease were undergoing dialysis with type 2 diabetes and a viral infection; 20 patients with type 2 diabetes mellitus; and 20 healthy control participants had no signs or symptoms of any systemic disease. Both males and females aged 40 years and older comprise these patients.

3.1 The demographic characteristics of patients with kidney failure and Diabetes mellitus

3.1.1. Interleukin-6

The mean ± SD of interleukin 6 concentration was 90.40±25.77 for the patients of G1; 42.33±17.32for the patients of G2; 84.95±19.80 for the patients of G3; 36.68±15.10 for the patients of G4; While there were 2.44±0.79 and 2.26±0.59 for the patients of G5 and the control group, respectively. As show in table (3-1).

Table (3-1): Comparison of study parameters (IL6) among study Groups

Parameters	Groups	N	Mean	Std. Deviation	P value
IL-6 pg/ml	G1	20	90.4000	25.77949	a- <0.001*
	G2	20	42.3350	17.32592	b- <0.001*
	G3	20	84.9500	19.80424	c- <0.001*
	G4	20	36.6800	15.10833	d- <0.001*
	G5	20	2.4400	0.79565	e- <0.001*
	Control	20	2.2600	0.59683	f- 0.972

Interleukin-6 (IL-6) is one of the pro-inflammatory cytokines. Infection, inflammation, obesity, and stress all play a role in triggering IL-6 production [149]. Patients on dialysis may have inflammation for several reasons, including those connected to the dialysis procedure itself, the underlying cause of renal failure (such as oxidative stress), or an infection. It appears that exposing blood to bioincompatible dialysis membranes is a significant contributor to chronic inflammation connected to dialysis. White blood cells and complement are triggered by cellulosic membranes and other bioincompatible membranes [150]. Infections caused by bacteria and viruses pose a serious threat to people with CKD. Foreign bodies, hemodialysis catheters, arteriovenous fistulas, and the hemodialysis technique all contribute to inflammation. Chronic stress and negative feelings can also lead to increased cytokine levels [151].

The results of the study showed that patients who have renal failure with DM and bacterial infection showed significantly higher levels of IL-6 compared with the controls ($P<0.0001$). High morbidity and mortality rates have been linked to bacterial infections in hemodialysis (HD) patients [152]. Studies show that the cytokine IL-6 promotes inflammation. As a result of a bacterial infection, it helps kick off the acute phase response in humans. The serum level of interleukin-6 (IL-6) is modest in healthy individuals but rises substantially during the early phase of bacterial infection [153].

Also, the results of the study showed that patients who have renal failure with DM and viral infection showed significantly higher levels of IL-6 compared with the controls ($P<0.0001$). IL-6 is regarded as one of the most critical cytokines during an infection. IL-6 is involved in the development of various virus infections in addition to its involvement in influencing the host immune response [154]. When it comes to the synthesis of cytokines,

the liver is a very necessary organ. The liver plays a crucial role in the clearance of IL-6. Elevated plasma IL-6 levels are the result of a severe liver injury that impairs IL-6 clearance [155], [156].

In viral infections, the cytokines are implicated in establishing an antiviral state as the unspecific first line of defense and virus-specific response. PRRs, which can exist as transmembrane receptors or in other intracellular compartments, are responsible for kicking off this process by recognizing viral molecules. Changes in the receptor's structure initiate a signaling pathway in the cytoplasm that ultimately leads to the translocation of cytoplasmic transcription factors into the nucleus, where they boost the production of several cytokines. Cytokine production might differ in kind depending on the virus and the cell type [157]. They may be able to recognize cells that have been infected by a virus and exert control over inflammatory and immunological responses, the removal of viruses, and processes that cause harm to tissue. It is known that both HBV and HCV infections can alter a wide range of cytokine activities. An imbalance in the production of pro-inflammatory and anti-inflammatory cytokines is what drives the immunopathogenesis of HBV and HCV infections [158].

Results in **Figure (3-1)** show a non-significant difference in the level of IL-6 in type 2 diabetes mellitus compared with the control group (P = 0.912). These results agree with Rona Kartika *et al*., who found that the IL-6 levels showed no significant difference between diabetes patients and the control group [159]. Also, Carey *et al*. discovered that the levels of IL-6 in the plasma of both patients and healthy people were similar. They also found that the higher levels of IL-6 in the plasma of people with type 2 diabetes are strongly linked to their fat mass and not their ability to respond to insulin [160].

The lower level of IL-6 in people with type 2 diabetes compared to a healthy control group, on the other hand, suggests that cell-mediated immunity may be weakened in people who are taking medications to control their blood sugar levels [161]. All previous results agree with this finding. This means that the increase in IL-6 is due to kidney failure and bacterial or viral infection, and there is no effect of diabetes on IL-6.

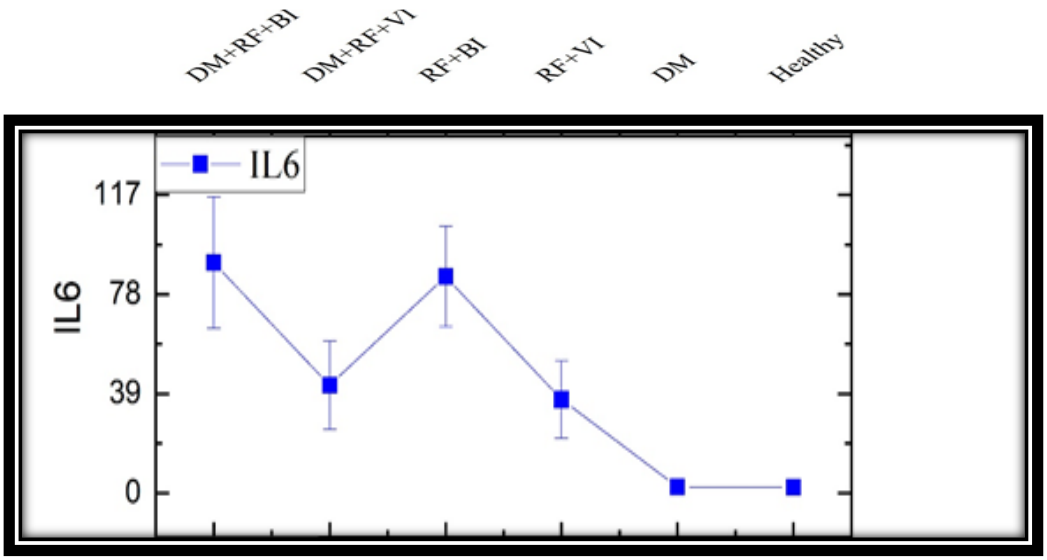


Fig. (3.1): Comparison of study parameters (IL6) among study Group

3.1.2. Procalcitonin (PCT)

The mean ± SD of PCT concentration were 4.77±1.86 for the patients of G1; 0.31±0.09 for the patients of G2; 4.41±1.43 for the patients of G3; 0.28±0.09 for the patients of G4; While there were 0.04±0.01and 0.03±0.01for the patients of G5 and the control group, respectively. As show in table **(3-2).**

Table (3-2): Comparison of study parameter (PCT) among study Groups

Parameters	Groups	N	Mean	Std. Deviation	P value
PCT ng/ml	G1	20	4.7720	1.86547	a- <0.0001*
	G2	20	0.3150	0.09378	b- <0.0001*
	G3	20	4.4160	1.43331	c- 0.826
	G4	20	0.2895	0.09110	d- <0.0001*
	G5	20	0.0430	0.01895	e. 0.873
	Control	20	0.0360	0.01930	f- 0.982

An increasingly popular biomarker for bacterial infections is procalcitonin (PCT). PCT is greatly raised in response to stimulation by pathogens, although its level in otherwise healthy people is below the detection threshold (0.01 ng/mL) [162].

The study found that patients with renal failure and a bacterial infection, with or without DM, had significantly higher levels of PCT than patients with renal failure and a viral infection, with or without DM, and the controls ($P<0.0001$). Patients with severe systemic fungal or parasitic infections also have elevated serum PCT levels, in addition to those with bacterial infections and sepsis, while those with viral infections have lower PCT increases or none at all. This is mainly because cytokines created during viral infections inhibit the generation of tumor necrosis factor-a. As a result, PCT levels in the serum are a reliable and accurate indicator for distinguishing bacterial from viral illnesses. PCT levels in the blood can rise within hours of inflammation and usually reach their highest point within 24 to 48 hours. This makes them more specific than other common lab markers like leukocytosis, increased band cells, and C-reactive protein (CRP) [163].

Steinbach *et al*. explained that there was no correlation between the decline in excretory renal function and the increased concentration of PCT in the blood when comparing patients with varying degrees of renal functional impairment. PCT levels were normal in several HD-treated individuals with end-stage renal failure. Therefore, the slight rise in mean PCT that we've seen in our patients is likely linked to PCT release caused by uremia or extracorporeal treatment, rather than a decline in renal excretion due to impaired renal function. Using high-flux hemodialysis membranes to remove PCT from HD patients may diminish its usefulness as an infection indication. However, similar to what has been observed for certain cytokines, PCT production may be induced by inflammatory activity

caused by a range of metabolic and immunological disorders linked to uremia or dialysis itself. The presence, kind, and severity of an infection are irrelevant to the possibility that HD alone may alter PCT serum levels [164].

Also, results in this study show a non-significant difference in the level of PCT in type 2 diabetes mellitus compared with the control group. Insulin may have anti-inflammatory effects apart from its impact on blood sugar, according to several studies. Increased endothelial nitric oxide release, decreased expression of proinflammatory cytokines, and immune system suppression are some of the ways insulin reduces inflammation. This could be the reason why the PCT levels were low in the diabetic patients. In the study of Al-Shammaree *et al.*, the results showed agreement with those reported by Usman *et al*., which showed that the concentration of PCT decreased in diabetes mellitus patients. and this decrease was observed irrespective of the specific type of diabetes or the presence of any concurrent infection [165].

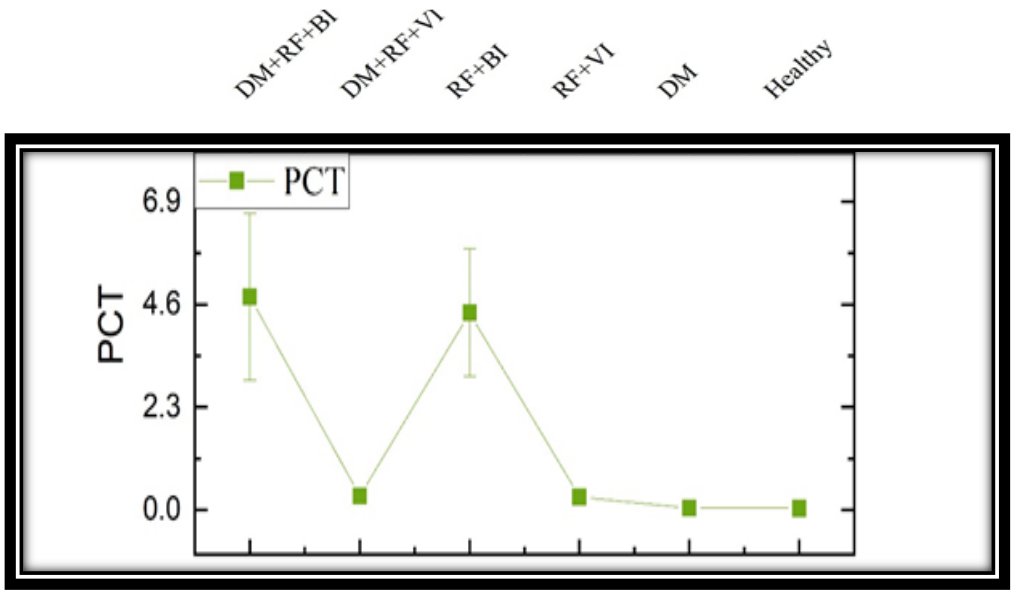


Fig. (3.2): Comparison of study parameter (PCT) among study Groups

3.1.3. C-Reactive Protein

The mean ± SD of CRP concentration were 69.66±16.59 for the patients of G1; 36.32±11.90 for the patients of G2; 62.10±19.94 for the patients of G3; 25.74±11.60 for the patients of G4; While there were 17.02±4.34 and 3.10±1.02for the patients of G5 and the control group, respectively. As show in table **(3-3).**

Table (3-3): Comparison of study parameter (CRP) among study Groups

Parameters	Groups	N	Mean	Std. Deviation	P value
CRP mg/l	G1	20	69.6650	16.59985	a- <0.0001*
	G2	20	36.3250	11.90842	b- <0.0001*
	G3	20	62.1050	19.94926	c- <0.0001*
	G4	20	25.7450	11.60542	d- <0.0001*
	G5	20	17.0280	4.34335	e- <0.0001*
	Control	20	3.1000	1.02598	f- 0.03*

C-reactive protein is a liver-produced protein. It is stable across time and does not vary with gender or age, but quickly rises in cases of infections, autoimmune disorders, or cancer [166]. Patients with chronic kidney disease (CKD) often have inflammation, which becomes even more severe as the disease advances toward end-stage renal disease (ESRD). Increased concentrations of C-reactive protein and other acute-phase proteins in the serum are indicators of chronic inflammation in people with chronic kidney disease (CKD) [167].

The present study states that the level of CRP increased in bacterial and viral infections in CKD patients with and without diabetes mellitus compared with the healthy group, but in bacterial infections, it was higher than in viral infections. Abdel-Messeih *et al*. support this study finding, as they emphasized the levels of serum C-reactive protein were higher in people on hemodialysis than in the control group. This suggests that uremia

and dialysis treatment may make the immune system more active and cause more cytokines and chemokines to be released into the bloodstream. It is known that any change in innate immunity causes inflammatory markers and cytokines to rise. Also, during inflammation, proinflammatory cytokines trigger hepatocytes to produce and synthesize acute-phase proteins like CRP [168]. Also, the study by Dungey *et al*. showed that in chronic kidney disease (CKD), chronic inflammation plays a significant role in the progression of the disease, and it appears that elevated levels of CRP are associated with decreased renal function [169].

Du Clos, on the other hand, found that the C-reactive protein (CRP) plasma levels in bacterial infections tend to be much higher than in viral infections [170].

According to the findings in this study, the level of CRP was significantly higher in people with type 2 diabetes mellitus when compared to the control group, where p value was 0.03*. Increased levels of inflammatory proteins, such as C-reactive protein (CRP), are associated with low-grade inflammation and the development of type 2 diabetes. Several metabolic and inflammatory variables linked to type 2 diabetes, including elevated levels of free fatty acids, adipokines, and blood glucose, may initiate CRP generation. In addition, several human investigations have shown that high blood C-reactive protein levels are associated with obesity and the development of insulin resistance, which in turn leads to type 2 diabetes. Results by Stanimirovic *et al*. provide more evidence that elevated C-reactive protein levels are a key component of the inflammatory state that precedes type 2 diabetes. The C-reactive protein levels in people with type 2 diabetes (4.49–16.48 mg/L) [171].

Kanmani *et al*. explained that there was a strong correlation between CRP concentration and an elevated risk of acquiring type 2 diabetes, particularly among individuals aged 50 and above [172].

In contrast, the study by Pan *et al*. showed that there is no correlation between CRP levels and an elevated risk of developing diabetes in a cohort of Chinese individuals in Singapore [173].

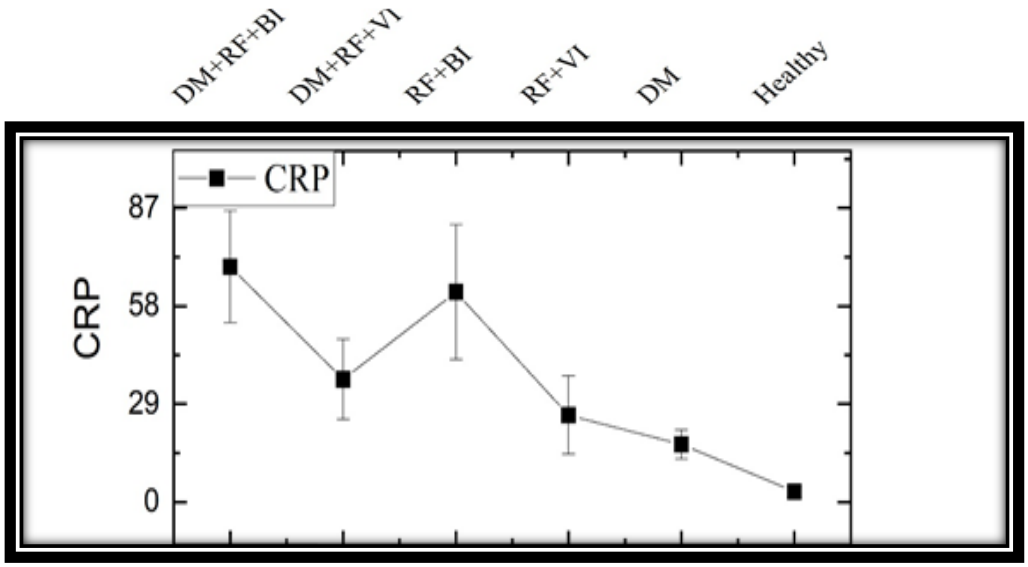


Fig. (3.3): Comparison of study parameter (CRP) among study Groups

3.1.4 Creatinine:

The mean ± SD of Cr concentration were 6.23±1.87 for the patients of G1; 6.99±2.29 for the patients of G2; 8.37±3.12 for the patients of G3; 8.61±2.26 for the patients of G4; While there were 0.69±0.17 and 0.69±0.18 for the patients of G5 and the control group, respectively. As show in **Table (3-4).**

Table (3-4): Comparison of study parameter (Cr) among study Groups

Parameters	Groups	N	Mean	Std. Deviation	P value
Cr mg/dl	G1	20	6.2300	1.87283	a- <0.0001*
	G2	20	6.9950	2.29174	b- <0.0001*
	G3	20	8.3795	3.12715	c- <0.0001*
	G4	20	8.6150	2.26838	d- <0.0001*
	G5	20	0.6900	0.17741	e- <0.0001*
	Control	20	0.6925	0.18934	f- 0.997

The kidney glomerular filtration unit excretes creatinine from the body, which is continuously generated in the body. A decrease in renal function can impact the rate of creatinine filtration by the kidneys. because the kidneys are unable to excrete creatinine through urine, leading to elevated blood serum creatinine levels [174].

The present study shows that the concentration of creatinine was significantly higher in patients among the first four groups than in the diabetes mellitus and control groups ($P<0.0001$). The study by Wafaa H. Ajam showed that CKD patients before hemodialysis have the highest values of creatinine levels compared to healthy controls [175]. A similar study by Mehmood *et al*. reported that serum creatinine rose in all patients with chronic kidney disease [176]. The findings of this study corroborate previous findings of MA *et al*., which found that out of the 164 patients, 26 tested positive for viruses. Serum creatinine in viral-infected CKD patients was higher than in non-viral-infected CKD patients [177].

In addition, Alaa Hussain Hassan discovered that both groups had serum creatinine levels above the recommended level. However, there was a noteworthy distinction between the patients with chronic renal failure who had hepatitis antibodies in their sera compared to those who did not [178]. At the same time, the study by Kosaraju *et al*. found

that no significant difference was observed in the levels of creatinine between the patients with chronic renal failure who had hepatitis antibodies in their sera compared to those who did not [179].

Furthermore, the present study shows that serum creatinine was no more significant in type 2 diabetes mellitus than in the control group, where the p value was 0.943. This agrees with the results of the previous study by Takeuchi *et al*. in Japan, who found that low serum creatinine levels were linked to a higher risk of getting type 2 diabetes mellitus, even when other major risk factors were taken into account, such as age, body mass index (BMI), drinking alcohol, being active in free time, and having a family history of diabetes [180]. Also, Harita *et al*. showed that low serum creatinine increased the risk of type 2 diabetes. Although this study found an association between lower serum creatinine and an increased risk of type 2 diabetes, it did not determine why. They postulated that a smaller amount of skeletal muscle would correlate with a lower serum creatinine level. When skeletal muscle stops responding to insulin, it sets off a cascade of events that culminate in the development of type 2 diabetes [181].

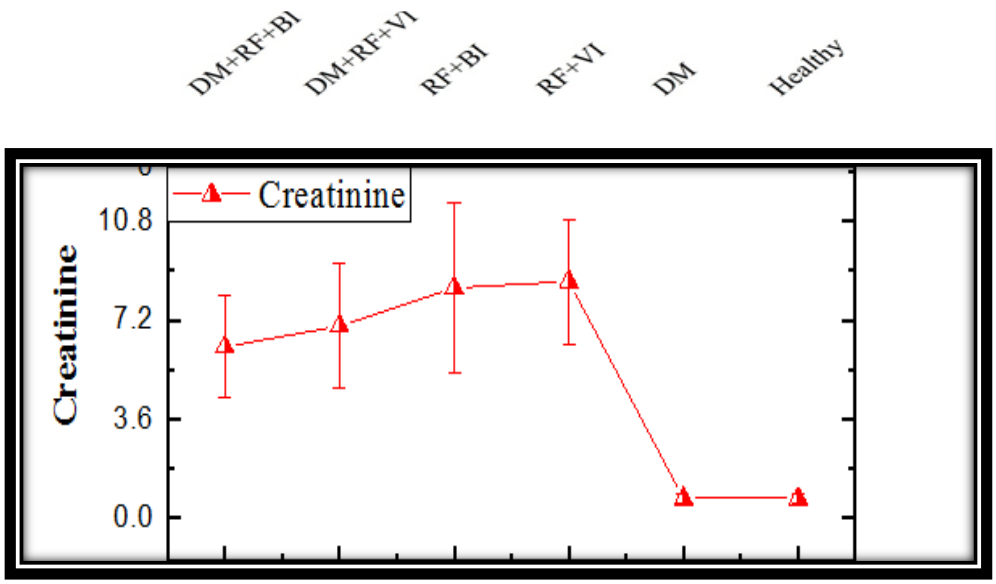


Fig. (3.4): Comparison of study parameter (Cr) among study Groups

3.1.5. Urea

The mean ± SD of serum urea concentrations were 124.0850 ± 19.18674 for the patients of G1; 129.3700 ± 39.84359 for the patients of G2; 120.1950 ± 45.37441 for the patients of G3; 117.4900 ± 27.26289 for the patients of G4; while there were 32.6500 ± 7.57611 and 26.6000 ± 7.87000 for the patients of G5 and the control group, respectively. As shown in **Table (3-5)**.

Table (3-5): Comparison of study parameter (Urea) among study Groups

Parameters	Groups	N	Mean	Std. Deviation	P value
Urea mg/dl	G1	20	124.0850	19.18674	a- <0.0001*
	G2	20	129.3700	39.84359	b- <0.0001*
	G3	20	120.1950	45.37441	c- <0.0001*
	G4	20	117.4900	27.26289	d- <0.0001*
	G5	20	32.6500	7.57611	e- <0.0001*
	Control	20	26.6000	7.87000	f- 0.943

Urea is an organic compound that is produced as a result of protein metabolism in the human body. It is non-toxic and plays a crucial role in eliminating 80–90% of the nitrogen waste. Elevated blood urea levels indicate compromised renal function, while reduced urea levels can be attributed to impaired liver function or not getting enough protein in your diet [182].

In the present study, the level of serum urea concentrations was higher in CKD patients with bacterial infection with and without diabetes mellitus than in the control group ($p< 0.0001$). The kidneys lose their capacity to remove nitrogenous wastes from the bloodstream in patients with chronic kidney failure (CKF). This is because the number of

nephrons has decreased, which leads to the buildup of these substances in the bloodstream and an increase in the levels of urea in the blood [183].

According to the results of this study, the level of serum urea concentrations was higher in CKD patients with viral infection with and without diabetes mellitus than in the control group. This study confirmed previous findings by MA *et al*. that chronic kidney disease and viral infections were linked to higher serum urea concentrations than chronic kidney diseases and non-viral infections. This finding could provide more evidence that viral infections make CKD problems worse [177].

This study outcome showed a non-significant difference in the level of urea in type 2 diabetes mellitus compared with the control group. These results are in agreement with Kurniawan and Kusrini's report that more than 80% of the diabetic participants had normal urea levels (≤40 g/dL). In the group of those aged 45 and up, the average urea level was 34.54 mg/dL, which is still considered normal. Because this finding shows that diabetics still have normal kidney function, it's not out of the question that diabetics manage to keep their blood sugar levels under control [184]. This finding disagreed with the study of Idonije *et al*. who found the level of urea in the serum of patients with type 2 diabetes Mellitus was significantly higher when compared to the control group [185]. Also, the study by Azeez *et al*. showed that Patients with poorly managed blood sugar levels are more likely to develop diabetic nephropathy due to elevated blood urea levels [186].

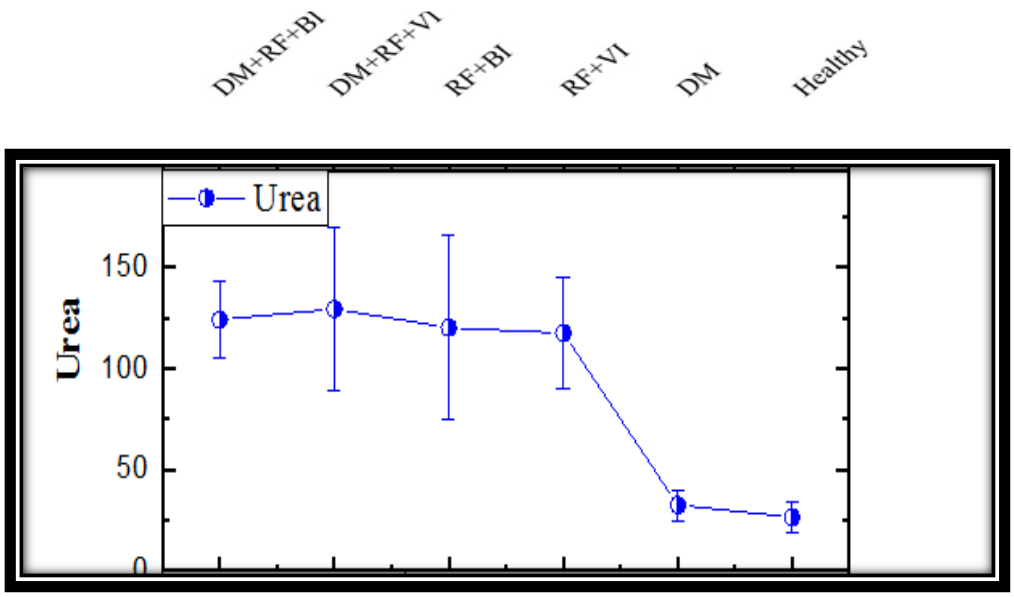


Fig.(3.5): Comparison of study parameter (Urea) among study Groups

3.1.6. Albumin

The mean ± SD of serum Albumin concentrations were 3.40±0.57 for the patients of G1; 3.49±0.43 for the patients of G2; 3.57±0.314 for the patients of G3; 3.65±0.33 for the patients of G4; while there were 4.11±0.65 and 4.28±0.60 for the patients of G5 and the control group, respectively. As shown in **Table (3-6)**.

Table (3-6): Comparison of study parameter (ALB) among study Groups

Parameters	Groups	N	Mean	Std. Deviation	P value
ALB g/dl	G1	20	3.4000	0.57216	a- <0.0001*
	G2	20	3.4900	0.43274	b- <0.0001*
	G3	20	3.5725	0.31434	c- <0.0001*
	G4	20	3.6500	0.33795	d- <0.0001*
	G5	20	4.1100	0.65446	e- <0.0001*
	Control	20	4.2800	0.60053	f- 0.727

Albumin is the primary component of plasma protein in the body, which plays an essential role in regulating oncotic pressure, microvascular permeability, acid-base

balance, and platelet aggregation prevention. Hypoalbuminemia is linked to morbidity and death in a wide range of populations, including people who have suffered from conditions such as renal illness [187].

According to the results of the present study, the level of albumin in the serum of patients significantly decreased among the first four groups compared to the diabetes mellitus and control groups ($P<0.0001$). This result is also consistent with Haller's, who explained that albumin synthesis is impaired in renal failure patients for several reasons. One of these is protein limitation, which occurs in the latter stages of renal insufficiency and induces anorexia, which in turn promotes malnutrition. People who are on dialysis or who have nephrotic syndrome may lose albumin in their urine, have peritoneal fluid exchanges, or have hemodialysis membranes bind, especially if the membranes are used again and again [188].

Additionally, bacterial and viral infections affect the level of albumin. The study by Wiedermann explained that associating low serum albumin levels with infectious diseases raises the possibility that low albumin mass is to blame for the acquisition and development of infections and their complications. and shown that low serum albumin levels are predictive of not only the onset and progression of acute bacterial, viral, and fungal infections but also of infectious complications in long-term diseases and conditions such as diabetes, hemodialysis, cancer, and chronic inflammatory diseases. In individuals with early bacteremia, C-reactive protein levels fall after a few days of an initial spike, whereas serum albumin levels stay low for a lot longer after a rapid drop from trans-capillary leakage. Low serum albumin levels upon hospital admission increase the

likelihood that patients with community-acquired bacterial or viral illnesses would need treatment in the intensive care unit (ICU) [189].

Furthermore, in the current study, the level of albumin in the serum of diabetes mellitus patients was lower than that of the healthy control group, although there was no significant difference. These results were compatible with a previous study conducted by Chany *et al*. which indicated that decreased albumin levels were linked to various expression markers of inflammation in adipose tissue, regardless of fat percentage. This suggests that albumin could be reflecting an immunological environment that increases the risk of type 2 diabetes. In addition, a larger percentage of fat and plasma glucose concentration were linked to lower albumin levels. further proved that, even after controlling for these variables, lower albumin levels still predict the onset of type 2 diabetes[190].

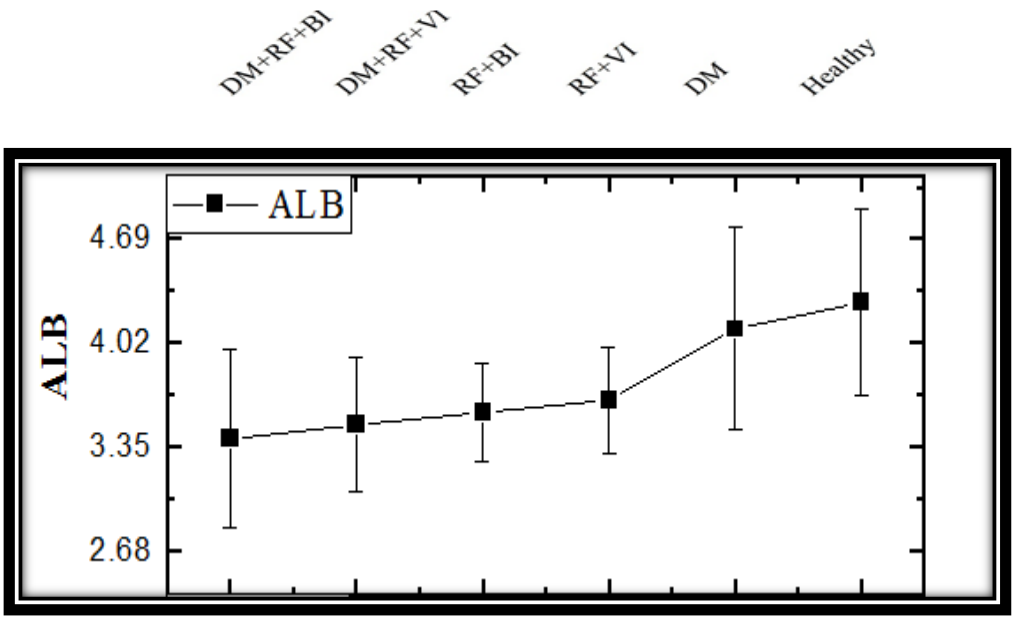


Fig. (3.6): Comparison of study parameter (ALB) among study Group

3.1.7. White blood cells

The mean ± SD of serum WBC concentrations were 6.73±2.04 for the patients of G1; 7.16±2.63 for the patients of G2; 5.16±1.72 for the patients of G3; 5.84±1.34 for the patients of G4; while there were 7.81±1.34 and 7.62±1.80 for the patients of G5 and the control group, respectively. As shown in **Table (3-7)**.

Table (3-7): Comparison of study parameter (WBC) among study Groups

Parameters	Groups	N	Mean	Std. Deviation	P value
WBC	G1	20	6.7300	2.04324	a- <0.0001*
	G2	20	7.1650	2.63504	b- 0.421
	G3	20	5.1600	1.72730	c- 0.904
	G4	20	5.8400	1.34845	d- 0.0001*
	G5	20	7.8150	1.34332	e- 0.014*
	Control	20	7.6200	1.80105	f- 0.997

White blood cells, usually referred to as leukocytes, are an essential component of the immunological response that the body produces. The production of these cells takes place in the bone marrow, and they are an important part of the body's defense mechanism against disease and infection [191].

In the present study, the level of WBC is lower in CKD patients with infections and DM compared with healthy subjects. We did not observe a statistically significant difference in WBC count between the groups except for CKD patients with infection (viral or bacterial infection), which had a significantly lower difference in WBC count. This finding fits with what Arai *et al*. found: people older than 60 with CKD stages G2-G5 before dialysis are more likely to have their CKD get worse if their white blood cell (WBC) count is low. Prior research has failed to demonstrate a causal relationship between

low WBC count and poor renal prognosis in individuals with chronic kidney disease (CKD), making this conclusion all the more remarkable. Even though there was no inflammation, the prognosis was poorer for patients with a low white blood cell count. This study raise the possibility that inflammation and malnutrition are not the only factors that contribute to the link between a low WBC count and the development of CKD. Patients with a low white blood cell count may also be experiencing impaired bone marrow function, which can make them more vulnerable to infections and reduce their ability to repair cells [192].

According to widespread belief, white blood cells (WBCs) tend to rise in cases of bacterial infections, whereas in cases of viral infections, they tend to remain stable or even decrease [193]. In the present study, the findings were the opposite. This agrees with the study by Ishimine *et al*., which found that in the early stages of a bacterial infection, the level of WBC decreased [194]. Also, in the current study, the level of WBC was higher in T2DM patients compared with the individual health group. This agreed with the finding by Adane *et al*. that WBC increased significantly in T2DM patients compared with the control group, and a higher white blood cell count has been described as a sign of chronic inflammation, which is linked to microvascular problems in type 2 diabetes [195].

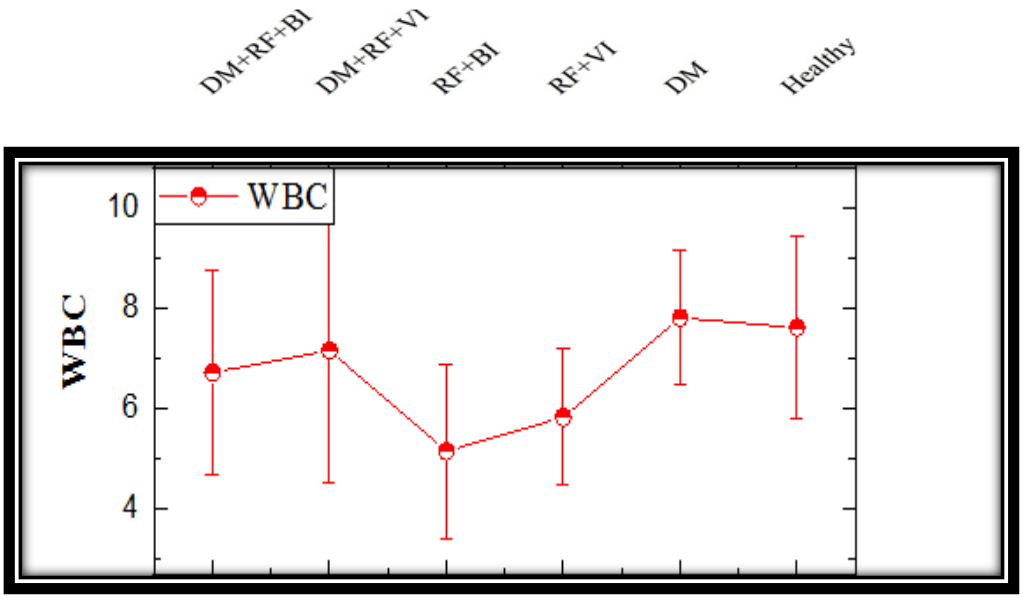


Fig. (3.7): Comparison of study parameter (WBC) among study Groups

3.1.8. Lymphocytes

The mean ± SD of serum lymphocytes concentrations were 1.69±0.60 for the patients of G1; 1.25±0.50 for the patients of G2; 1.52±0.53 for the patients of G3; 1.31±0.56 for the patients of G4; while there were 2.28±0.65 and 2.47±0.70 for the patients of G5 and the control group, respectively. As shown in **Table (3-8)**.

Table (3-8): Comparison of study parameter (LYM) among study Groups

Parameters Groups		N	Mean	Std. Deviation	P value
LYM	G1	20	1.6900	0.60166	a- <0.0001*
	G2	20	1.2550	0.50312	b- <0.0001*
	G3	20	1.5250	0.53888	c- <0.0001*
	G4	20	1.3100	0.56186	d- <0.0001*
	G5	20	2.2850	0.65234	e- <0.0001*
	Control	20	2.4750	0.70403	f. 0.770

Lymphocytes are an essential part of the immune system and are the cells that are responsible for recognizing and reacting to foreign antigens. Based on migration, surface markers, and biological roles, they are classified as T lymphocytes (T cells), B lymphocytes (B cells), or natural killer (NK) cells [196], [197]. Lymphopenia is a disorder characterized by an unusually low amount of lymphocytes in the peripheral blood as compared to normal levels. There is a diagnosis of this condition when the total lymphocyte number is lower than what is considered normal for a certain age group. The presence of viral infections, as well as chemical and physical lymphodepleting agents, can lead to a drop in the number of lymphocytes in the circulation that is immediately noticeable [197].

The present study indicates that LYM concentrations tended to be significantly lower in CKD with infection and DM compared with healthy subjects. The present study indicated that LYM concentrations tended to be significantly lower in CKD with infection and DM compared with healthy subjects. This result matched the findings of Manal and Shaimaa, Kuwae *et al*., who said that people with end-stage renal disease (ESRD) who are on hemodialysis have a lower total peripheral blood lymphocyte count [198], [199].

In a related study, Emmanuel *et al*. discovered that end-stage renal disease (ESRD) patients have lower total lymphocyte counts, which are indicative of lower cellular immunity levels. This lower cellular immunity explains why infections are common in these patients, and infection is the second leading cause of death in ESRD patients. Notably, this lower cellular immunity is more pronounced in ESRD patients receiving hemodialysis [200]. The study by Narjis *et al*. reported an abnormally low number of lymphocytes in the majority of diabetic individuals, whereas only a few patients had

higher lymphocyte levels [201].

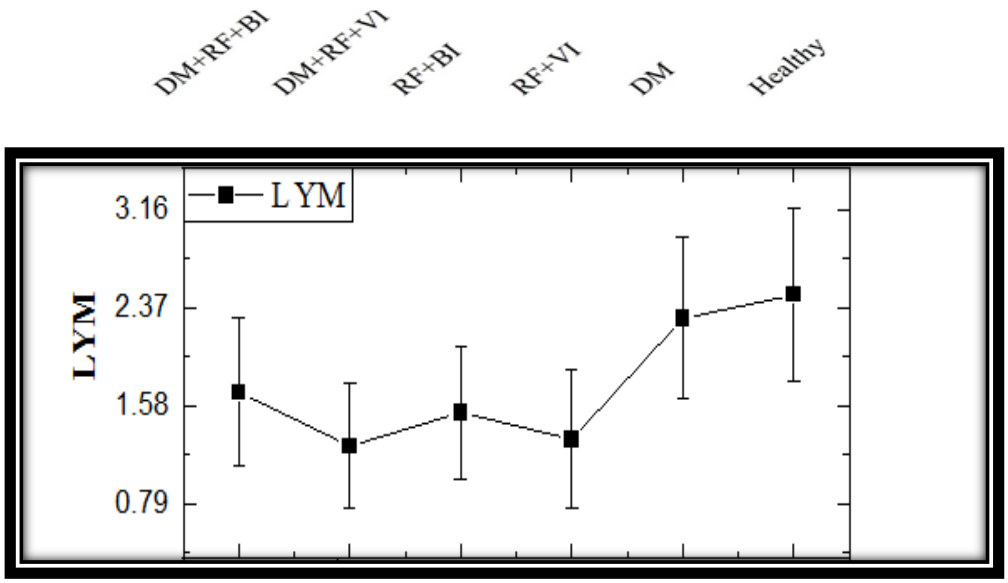


Fig. (3.8): Comparison of study parameter (LYM) among study Groups

3.1.9. Platelets

The mean ± SD of serum platelets concentrations were 188.10±65.50 for the patients of G1; 185.65±51.04 for the patients of G2; 151.25±72.38 for the patients of G3; 165.50±80.41 for the patients of G4; while there were 235.05±79.86 and 242.10±84.52 for the patients of G5 and the control group, respectively. As shown in **Table (3-9)**.

Table (3-9): Comparison of study parameter (PLT) among study Groups

Parameters		N	Mean	Std. Deviation	P value
PLT	G1	20	188.1000	65.50283	a- <0.0001*
	G2	20	185.6500	51.04825	b- 0.084
	G3	20	151.2500	72.38993	c- 0.066
	G4	20	165.5000	80.41897	d- 0.001*
	G5	20	235.0500	79.86665	e- 0.006*
	Control	20	242.1000	84.52275	f- 0.998

Platelet cells are among the first cells to be drawn to areas of inflammation and infection. They play a crucial role in the initiation of intravascular immune responses by working in complicated collaboration with white blood cells and vascular endothelial cells [202].

According to the results of this study, the level of platelets is lower in CKD patients with infections and DM compared with healthy subjects. We did not observe a statistically significant difference in platelet count between the groups except for CKD patients with infection(viral or bacterial infection), which had a significantly lower difference in platelet count. The study by Baaten *et al*. reported that people with chronic kidney disease who are not on dialysis do not see a notable decrease in platelet count. However, platelet counts can drop by as much as 20% in patients with chronic kidney disease at stage 5. One reason could be that megakaryocytes are not making enough platelets or that continuous activation is using up platelets (for example, in hemodialysis, shear stress in the extracorporeal circuit and exposure to the dialysis membrane can cause platelets to clump together, secrete platelets, and form platelet-leukocyte aggregates). In addition to a decrease in platelet count, other abnormalities in platelet function have been shown in CKD patients. Platelets play a crucial role in hemostasis; therefore, any problems with their function, such as hyperactivity or hyporeactivity, can lead to problems with blood clotting or bleeding [203].

Similar to the study by Aashitha Pet *et al*., which found a reduction in platelet count as the stage progressed. There was no evidence from platelet counts that the patients were not in danger of bleeding, but thrombocytopenia was a major risk factor for bleeding in some CKD patients [204].

Furthermore, the study by Assinger found that there is a correlation between viral infections and platelet activation. The host's inflammatory response releases mediators that activate platelets and fosters an environment that is both pro-oxidative and pro-coagulant, which facilitates platelet activation. Through direct contact with these cells, viruses can change the way platelets and megakaryocytes function. leading to thromboytopenia, a condition commonly seen in viral infections, because of the increased consumption and removal of platelets brought about by all these mechanisms that activate them [205]. Also, The study by Orasan *et al*. found that platelets were lower in patients with end-stage renal disease and viral hepatitis[206].

In the present study, the mean platelet count in type 2 diabetic group was lower compared to normal healthy subjects. which was comparable to the research by Hekimsoy *et al*.[207]. Other studies by Zuberi *et al*. observed the opposite findings of a higher platelet count in diabetic subjects as compared to normal healthy subjects[208]. Therefore, the platelet count may be influenced by various factors, such as the average platelet survival rate, the rate of platelet formation, and the turnover rate in diabetic patients[209].

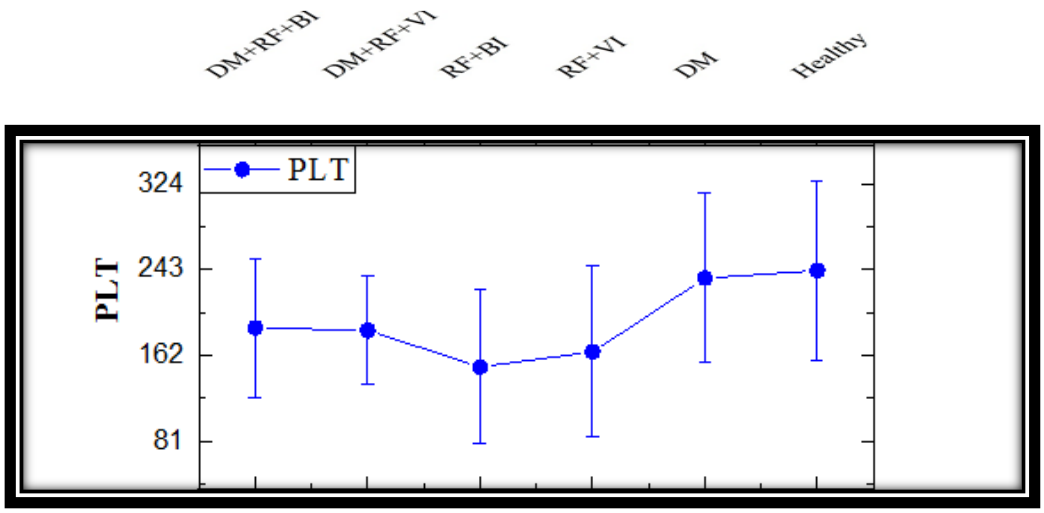


Fig. (3.9): Comparison of study parameter (LYM) among study Group.

3.1.10 Sodium

The mean ± SD of serum sodium concentrations were 4.36±1.43 for the patients of G1; 5.02±1.73 for the patients of G2; 5.54±2.23 for the patients of G3; 5.18±1.60 for the patients of G4; while there were 3.63±0.63 for the patients of the control group. As shown in **Table (3-10)**.

Table (3-10): Comparison of study parameter (Na) among study Groups

Parameters	Groups	N	Mean	Std. Deviation	P value
Na^+	G1	20	136.0500	6.04784	a- 0.015*
	G2	20	138.7950	5.82991	b- 0.102
	G3	20	141.5500	4.65069	c- 0.971
	G4	20	140.1950	5.39615	d- 0.538
	Control	20	139.5500	2.76205	e- 0.984

Kidneys regulate sodium-in-out balance in humans. One well-known symptom of end-stage renal disease is sodium overload. which increases extracellular volume and increases cardiovascular morbidity and mortality. Normal people can maintain their sodium balance on a high-salt diet, according to a 1980s study. Compared to healthy people, renal failure patients who ate a high-sodium diet had higher blood pressure due to the impairment of sodium excretion [210].

In the present study, the level of serum sodium is higher in CKD patients with infections compared with healthy subjects. However, we did not observe a statistically significant difference in serum sodium levels between all groups compared with the healthy control. The findings of this study corroborate previous findings Borrelli *et al*. explain that the prevalent imbalance between sodium intake and loss makes salt restriction more important in end-stage chronic kidney disease, as it increases the risk of hypertension

and CVD. As a result, patients with hypertensive CKD, whether in the early stages or advanced stages, must drastically cut back on salt consumption[211].

In the current study, we note that sodium concentration was lower in patients with chronic kidney disease, infection, and DM. This may be because sodium concentrations are lower in diabetic patients. This agreed with a study by Khan *et al*. that showed a significant lower in serum sodium with increasing fasting blood glucose[212].

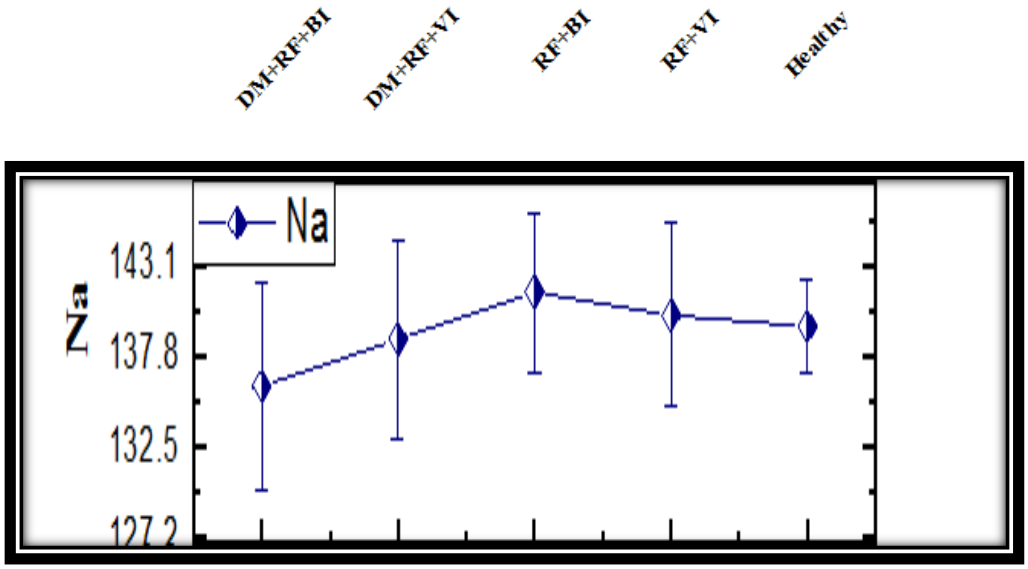


Fig. (3.10): Comparison of study parameter (Na) among study Groups

3.1.11. Potassium

The mean ± SD of serum potassium concentrations were 5.02±0.73for the patients of G1; 4.99±0.73for the patients of G2; 5.33±0.55 for the patients of G3; 5.30±0.87 for the patients of G4; while there were 4.14±0.51 for the patients of the control group. As shown in **Table (3-11)**.

Table (3-11): Comparison of study parameter (K) among study Groups

Parameters	Groups	N	Mean	Std. Deviation	P value
K^+	G1	20	5.0250	0.73045	a- <0.0001*
	G2	20	4.9900	0.73906	b- <0.0001*
	G3	20	5.3350	0.55845	c- 0.001*
	G4	20	5.3000	0.87299	d- <0.0001*
	Control	20	4.1450	0.51450	e- <0.0001*

Potassium is an electrolyte that is extraordinarily important for the health of all human cells and organs. He regulates muscle and heart function, transmits nerve impulses, and keeps cells' osmolarity and acid-base balances in check. K is gaining attention as a key component that helps reduce hypertension caused by sodium overload, and new evidence suggests it has an antihypertensive effect via increasing sodium excretion [213], [214].

The present study indicates that potassium concentrations tended to be significantly higher in all groups compared with healthy subjects. Electrolyte disturbances, including hyperkalemia, are frequent in CKD and ESRD patients[215]. Patients with renal illness often have hyperkalemia as a result of kidney dysfunction affecting potassium (K) homeostasis. This condition has a significant influence on the patient's quality of life and prognosis. Elevated blood K levels are most commonly caused by a low glomerular filtration rate (GFR). In addition to metabolic acidosis and constipation, chronic kidney disease (CKD), diabetic mellitus (DM), or heart failure (HF), and taking RAASIs are the most frequent medications used to protect the heart and kidneys and elevate serum potassium levels. In addition to causing weakness and exhaustion, hyperkalemia greatly raises the risk of lethal arrhythmias, which can lead to rapid death, and it is a key factor in getting ESRD patients started on chronic dialysis[216]. This result agreed with the study

by Sarnowski *et al*., which found that hyperkalemia is a problem in chronic kidney disease [217].

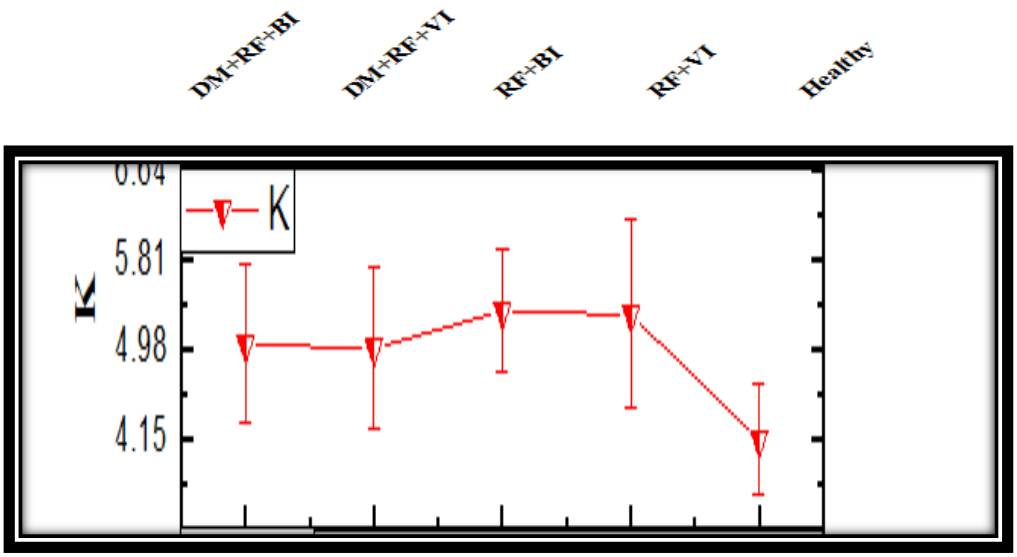


Fig. (3-11): Comparison of study parameters (K) among study 'Groups

3.1.13. Chloride

The mean ± SD of serum chloride concentrations were 103.04±4.35 for the patients of G1; 105.14±5.58 for the patients of G2; 103.95±5.28 for the patients of G3; 105.88±6.56 for the patients of G4; while there were 101.65±2.56 for the patients of the control group. As shown in **Table (3-12)**

Table (3-12): Comparison of study parameter (Cl) among study Groups

Parameters	Groups	N	Mean	Std. Deviation	P value
Cl^-	G1	20	103.0400	4.35411	a- 0.074*
	G2	20	105.1450	5.58093	b- 0.798
	G3	20	103.9500	5.28628	c- 0.101
	G4	20	105.8850	6.56941	d- 0.410
	Control	20	101.6500	2.56032	e- 0.033*

Chloride ions are humans' main extracellular strong anions. Chloride helps maintain the balance of acids and bases, the osmotic pressure in the plasma, the production of hydrochloric acid, the osmotic gradient in the gastrointestinal tract, kidney function, and the activity of electrolytes in cells. Kidney vasoconstriction caused by hyperchloremia lowered renal blood flow and GFR, according to previous investigations. In contrast, hyperchloremia may promote cytokine release and inflammation [218].

According to the findings, the level of sodium in the serum of patients with CKD was higher when compared to the control group. However, we did not observe a statistically significant difference in serum sodium levels between all groups compared with the healthy control except group 4 (RF+VI).

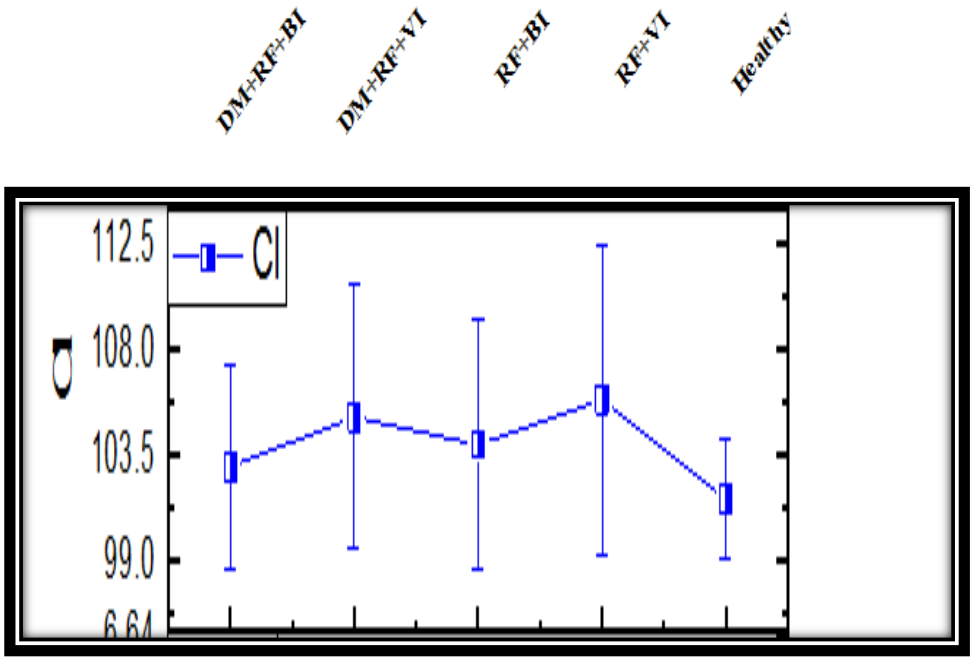


Fig. (3.12): Comparison of study parameter (Cl) among study Groups

3.2. The correlation of IL-6, CRP, PCT in all groups :

3.2.1. The correlation of IL-6, CRP, PCT in group 1

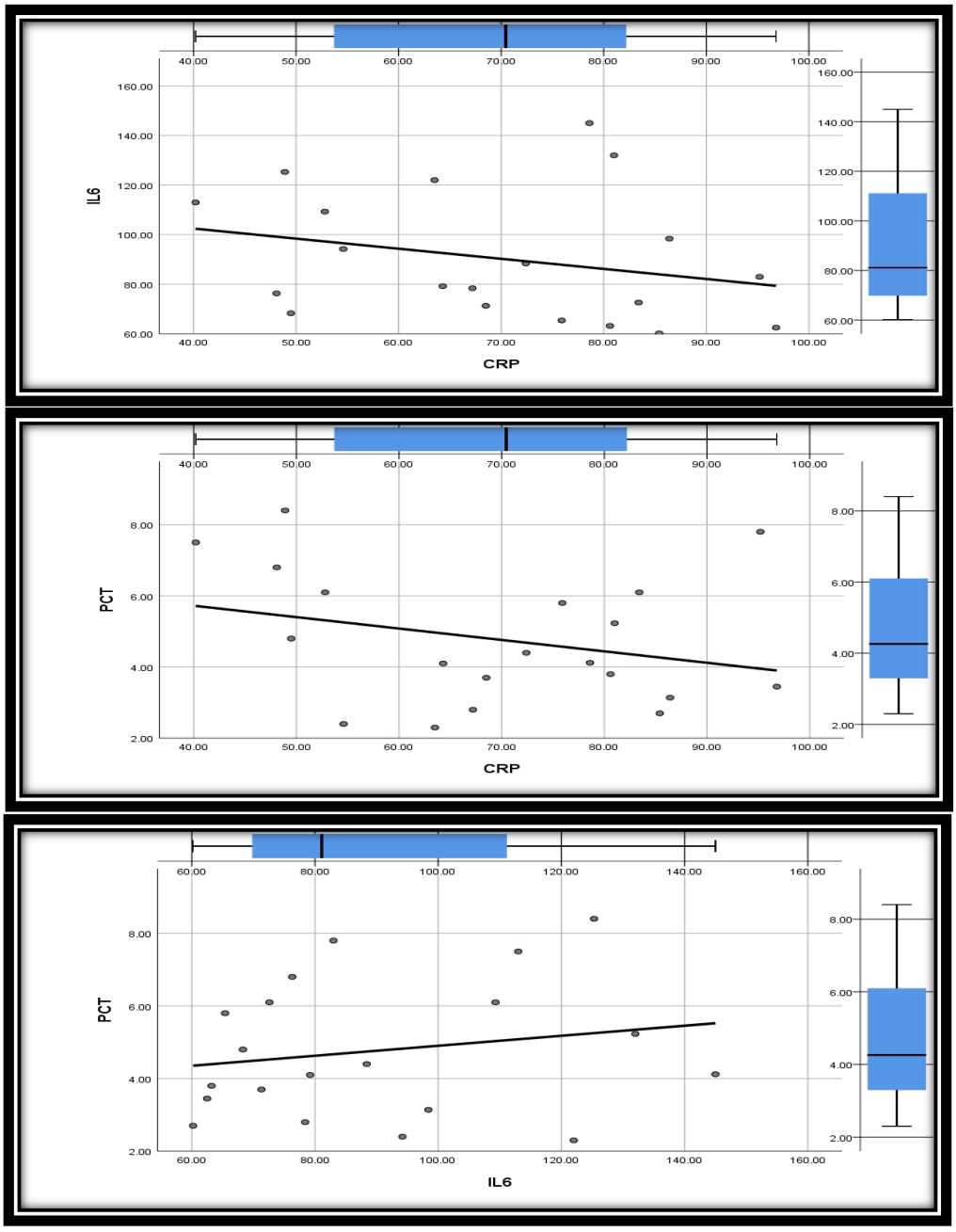


Fig. (3.13): Correlation plots among PCT, IL6 and CRP in G1 group.

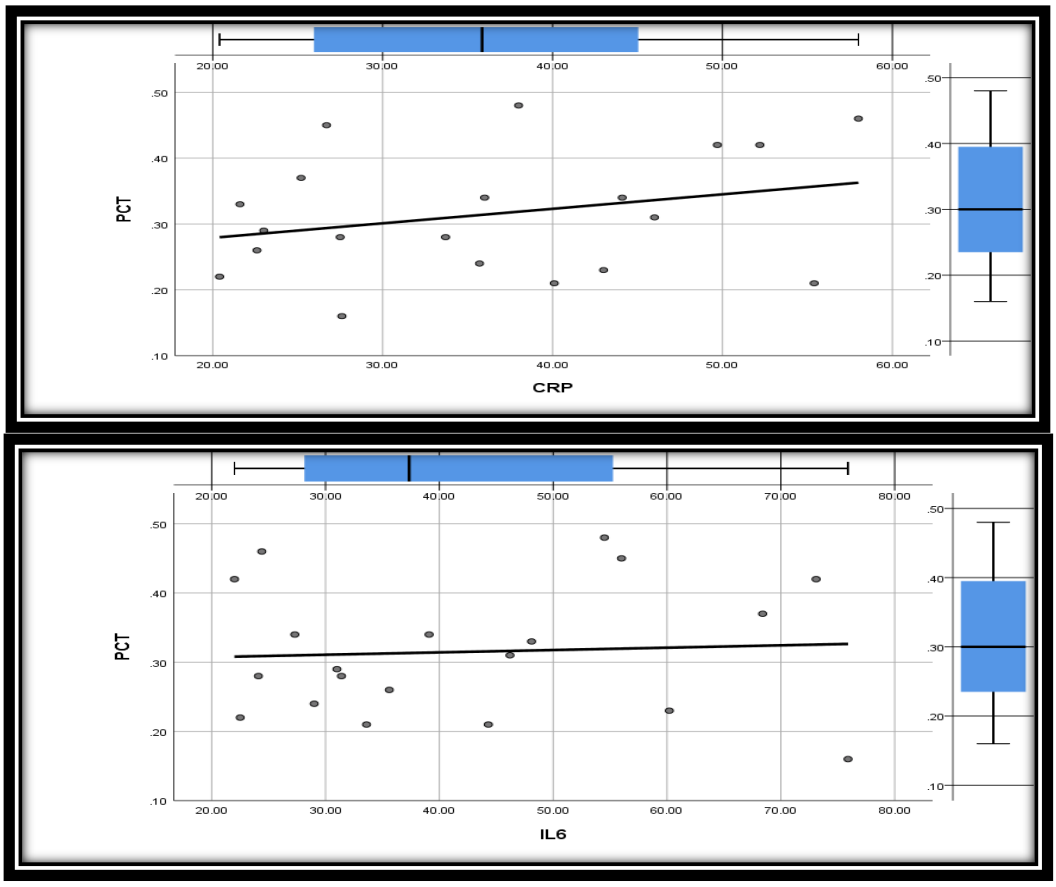
The first scheme, figure (3-13), in the first group showed a weak positive relationship between the PCT and IL-6 (0.190), but there was no significant. Also, the second scheme showed there is a moderately negative relationship between the PCT and

CRP (-0.285), but there is no significant relationship. Finally, in the same figure, the third scheme showed there is a moderate negative relationship between the IL-6 and CRP (-0.262), and there is no significant.

Table (3-13): Correlations among PCT, IL6 and CRP in G1 group.

Parameters		PCT	IL6	CRP
PCT	Pearson Correlation	1	.190	-.285
	P value		.421	.223
IL6	Pearson Correlation	.190	1	-.262
	P value	.421		.264
CRP	Pearson Correlation	-.285	-.262	1
	P value	.223	.264	

3.2.2. The correlation of IL-6, CRP, PCT in group 2



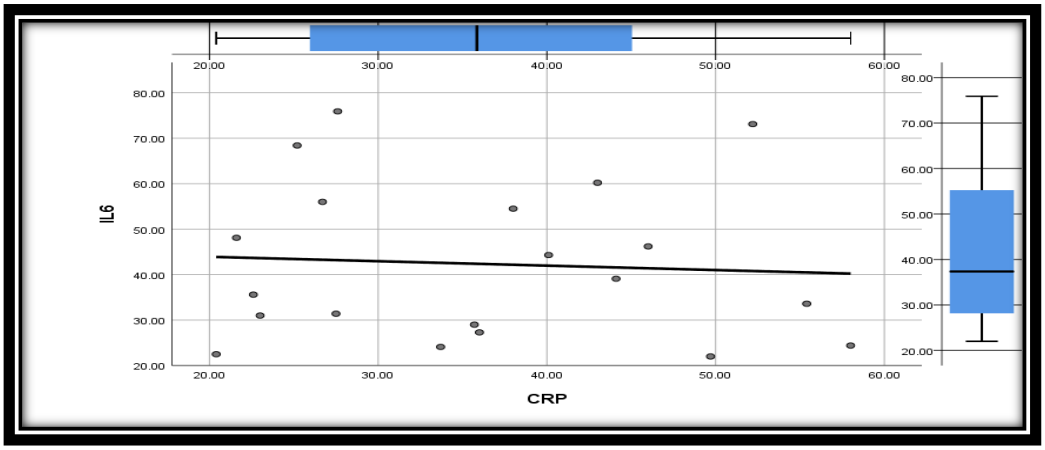


Fig. (3-14): Correlation plots among PCT, IL6 and CRP in G2 group.

The correlation plots between three parameters in the second group figure (3-14) showed that in the first scheme, there is no correlated positive relationship between the PCT and IL-6 and no significant. The second scheme showed a moderately positive relationship between the PCT and CRP with no significant. Finally, the third scheme shows that there is no significant correlation between IL-6 and CRP.

Table (3.14): Correlations among PCT, IL6 and CRP in G2 group.

Parameters		PCT	IL6	CRP
PCT	Pearson Correlation	1	.063	.279
	P value		.792	.233
IL6	Pearson Correlation	.063	1	-.067
	P value	.792		.780
CRP	Pearson Correlation	.279	-.067	1
	P value	.233	.780	

3.2.3 The correlation of IL-6, CRP, PCT in group 3

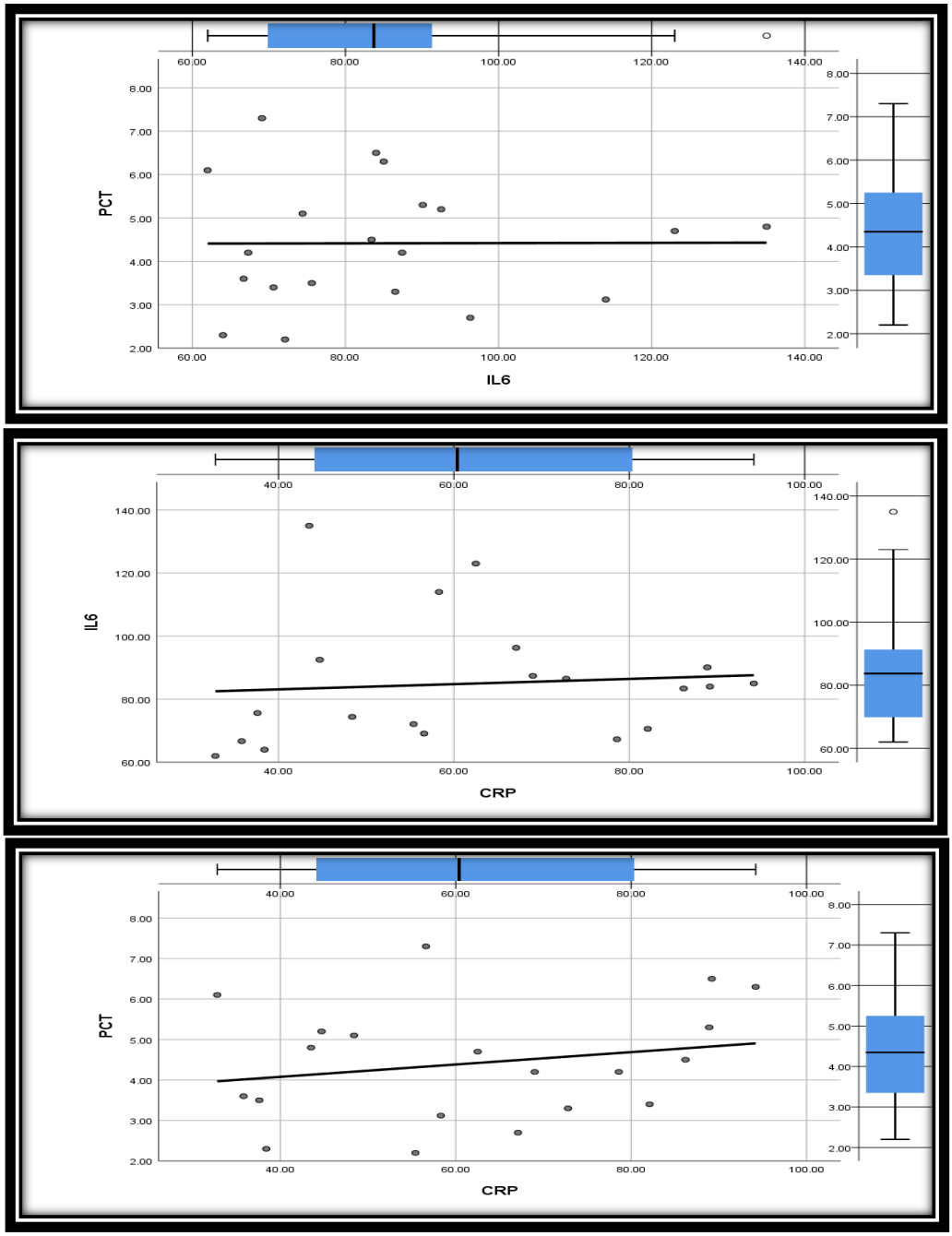


Fig. (3-15): Correlation plots among PCT, IL6 and CRP in G3 group

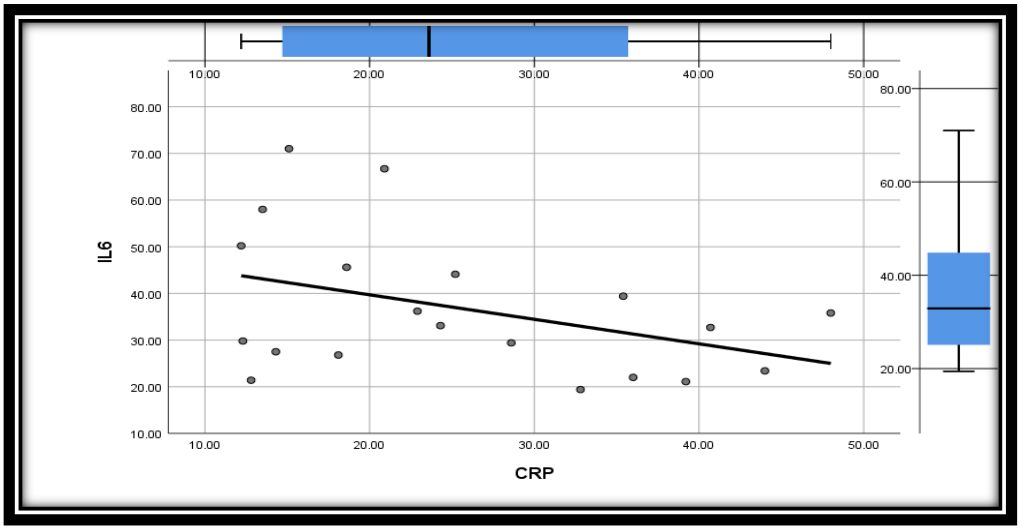
The results of the correlation plots in the third group, figure (3-16), showed that in the first scheme, there is a moderately positive relationship (0.212) between the PCT and CRP and no significant. The second scheme showed no correlated positive relationship

(0.004) between the PCT and IL-6 with no significant. Finally, the third scheme reveals there is no correlated positive relationship (0.084) between the IL-6 and CRP, with no significant.

Table (3-15): Correlations among PCT, IL6 and CRP in G3 group.

Parameters		PCT		IL6	CRP
PCT	Pearson Correlation	1		.004	.212
	P value			.987	.369
IL6	Pearson Correlation	.004		1	.084
	P value	.987			.726
CRP	Pearson Correlation	.212		.084	1
	P value	.369		.726	

3.2.4.The correlation of IL-6, CRP, PCT in group 4



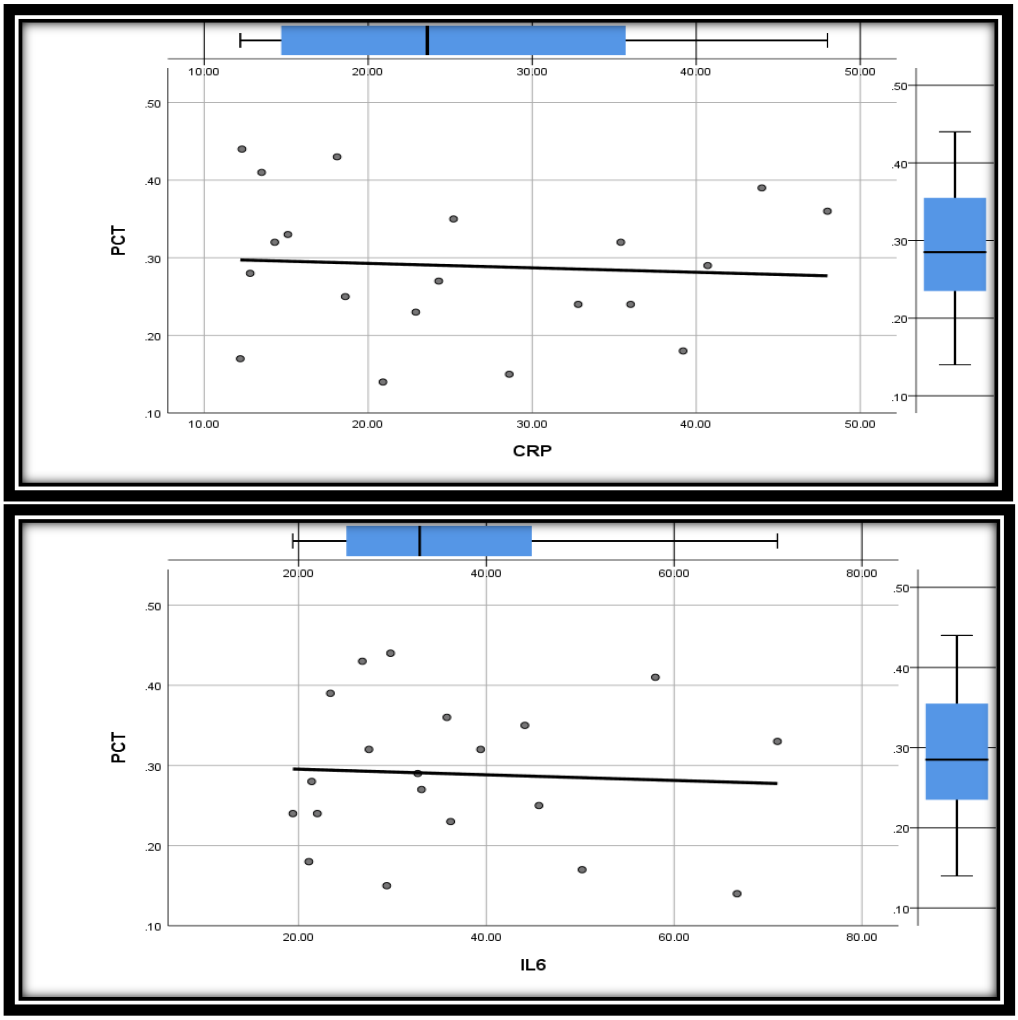


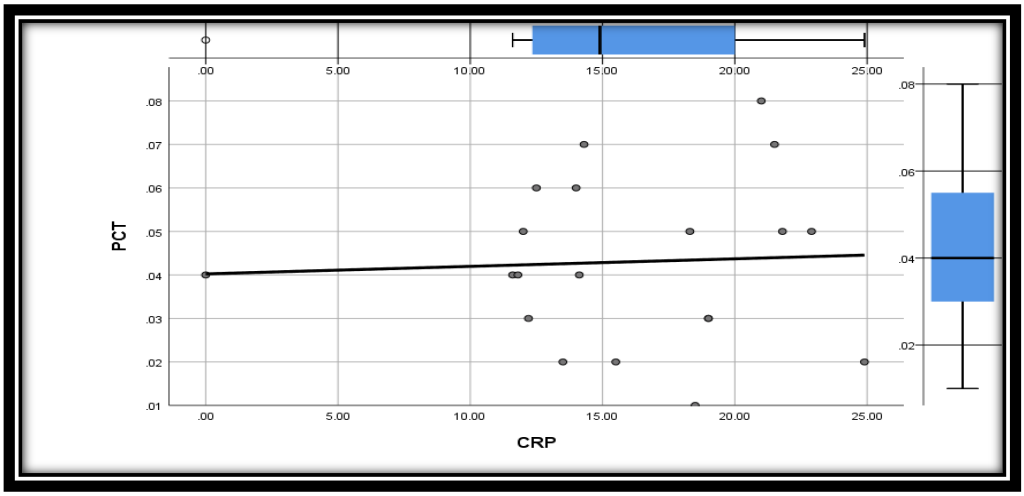
Fig. (3-16): Correlation plots among PCT, IL6 and CRP in G4 group.

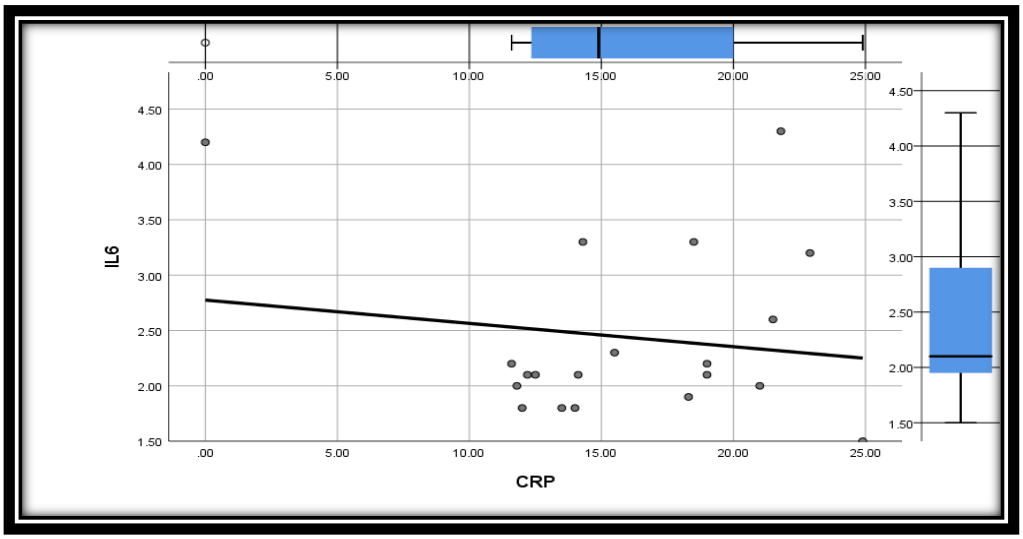
Figure (3-16) (from the fourth group of correlation plots) shows that in the first scheme, the PCT and IL-6 do not have a correlated, negative association (-0.058), and there is no meaningful relationship. In the alternative plan, there was a negative correlation (-0.073) between PCT and CRP, but no statistically significant association. At last, the third scheme shows that IL-6 and CRP have a moderately negative association (-0.403), but there is no significant.

Table (3-16): Correlations among PCT, IL6 and CRP in G4 group.

Parameters		PCT	IL6	CRP
PCT	Pearson Correlation	1	-.058	-.073
	P value		.808	.760
IL6	Pearson Correlation	-.058	1	-.403
	P value	.808		.078
CRP	Pearson Correlation	-.073	-.403	1
	P value	.760	.078	

3.2.5 The correlation of IL-6, CRP, PCT in group 5





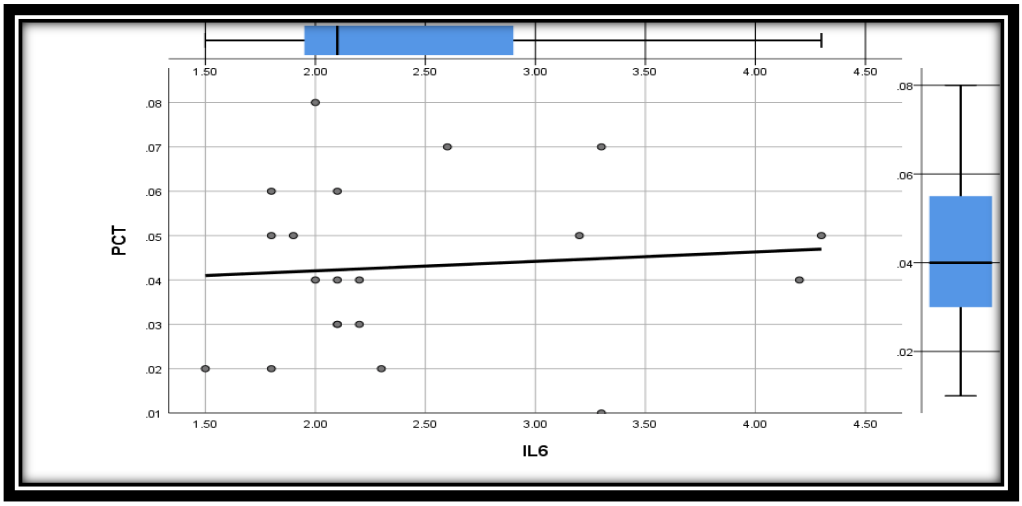


Fig. (3-17): Correlation plots among PCT, IL6 and CRP in G5 group.

Figure (3-17) (from the fifth group of correlation plots) shows that in the first scheme, the PCT and IL-6 do not have a correlated, positive association (0.089), and there is no meaningful relationship. In the alternative plan, there was a negative correlation (-0.148) between IL-6 and CRP but no statistically significant association. At last, the result in table shows that PCT and CRP have a no-correlated positive association (0.051), but there is no significant.

Table (3-17): Correlations among PCT, IL6 and CRP in G5 group.

Parameters		**PCT**	**IL6**	**CRP**
PCT	Pearson Correlation	1	.089	.051
	P value		.708	.830
IL6	Pearson Correlation	.089	1	-.148
	P value	.708		.533
CRP	Pearson Correlation	.051	-.148	1
	P value	.830	.533	

3.2.6 The correlation of IL-6, CRP, PCT in group 6

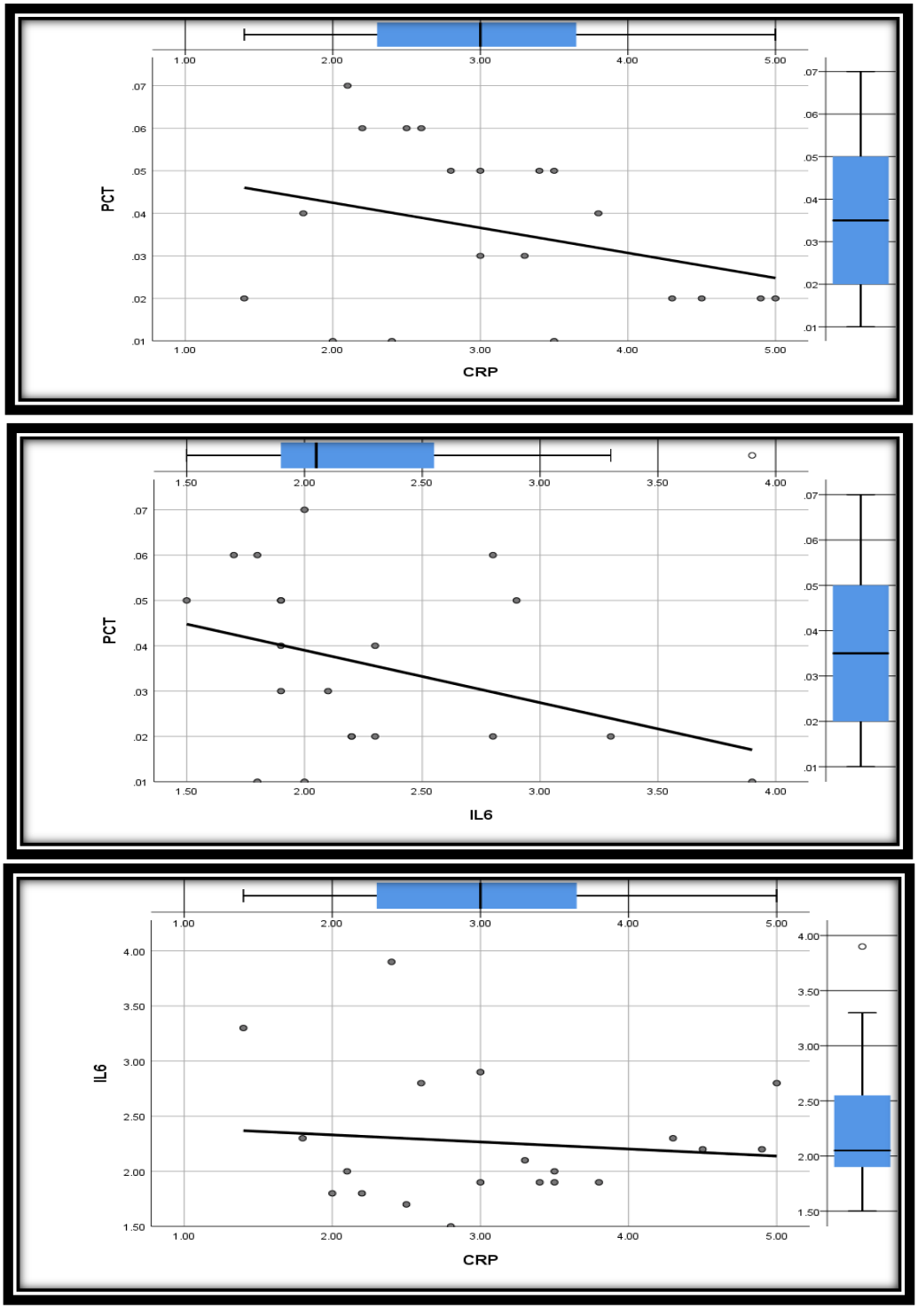


Fig. (3-18): Correlation plots among PCT, IL6 and CRP in healthy group

Figure (3-18) shows that in the three schemes, (PCT and IL-6), (PCT and CRP), and (IL-6 and CRP) all have negative associations (-0.357, -0.314, and -0.11), and there are no significant.

Table (3-18): Correlations among PCT, IL6 and CRP in healthy group.

Parameters		PCT	IL6	CRP
PCT	Pearson Correlation	1	-.357	-.314
	P value		.122	.178
IL6	Pearson Correlation	-.357	1	-.110
	P value	.122		.644
CRP	Pearson Correlation	-.314	-.110	1
	P value	.178	.644	

Chapter Four

Conclusions and Recommendations

4. Conclusions and Recommendations

4.1. Conclusions

1. Patients on dialysis may experience inflammation due to dialysis procedures, underlying causes of renal failure, or infections. Exposure to bioincompatible dialysis membranes contributes to chronic inflammation. Infections caused by bacteria and viruses pose a serious threat to people with kidney disease (CKD). Patients with kidney failure with or without diabetes mellitus who have had bacterial and viral infections show significantly higher levels of IL-6.
2. There is no correlation between the decline in excretory renal function and the increased concentration of PCT in the blood. High-flux hemodialysis membranes may diminish PCT's usefulness as an infection indication. The level of procalcitonin increases in response to a proinflammatory stimulus and is significantly increased in bacterial infections. Viral infections, however, will not lead to elevation.
3. Elevated CRP levels are associated with decreased renal function. It is a key indicator of chronic inflammation in people with chronic kidney disease (CKD), which progresses towards end-stage renal disease (ESRD). CRP levels increase in bacterial and viral infections in CKD patients, with higher levels in bacterial infections.
4. Low serum albumin levels are predictive of the onset and progression of infections and infectious complications in long-term diseases like diabetes, hemodialysis, cancer, and chronic inflammatory diseases. In renal failure patients, albumin synthesis is impaired due to protein limitation, anorexia, and hemodialysis membrane binding.

5. The levels of WBC, LYM, and PLAT concentrations were significantly lower in patients with chronic kidney disease (CKD). One reason could be that megakaryocytes are not making enough platelets or that continuous activation is using up platelets. Low WBC is independently associated with CKD progression
6. The levels of K^+, Na^+ and Cl^- concentrations were significantly higher in patients with chronic kidney disease (CKD). The prevalent imbalance between sodium intake and loss makes salt restriction more important in end-stage chronic kidney disease, as it increases the risk of hypertension and CVD. A low glomerular filtration rate (GFR) most commonly causes elevated blood potassium and chloride levels. In addition to metabolic acidosis and constipation.

4.2. Recommendations

1. A study can be conducted to deal with the role of other cytokines in the diagnosis of renal failure.
2. A study can be conducted to deal with the role of interleukin-6 in renal failure and other chronic diseases, such as myocardial infarction.
3. A study of the causes of viral and bacterial infections in renal failure patients.

References

References

[1] E. H. Choy, F. De Benedetti, T. Takeuchi, M. Hashizume, M. R. John, and T. Kishimoto, "Translating IL-6 biology into effective treatments," Nat Rev Rheumatol, vol. 16, no. 6, pp. 335–345, Jun. 2020, doi: 10.1038/s41584-020-0419-z.

[2] P. Mertowska, S. Mertowski, I. Smarz-Widelska, and E. Grywalska, "Biological Role, Mechanism of Action and the Importance of Interleukins in Kidney Diseases," IJMS, vol. 23, no. 2, p. 647, Jan. 2022, doi: 10.3390/ijms23020647.

[3] A. Abaurrea, A. M. Araujo, and M. M. Caffarel, "The Role of the IL-6 Cytokine Family in Epithelial–Mesenchymal Plasticity in Cancer Progression," IJMS, vol. 22, no. 15, p. 8334, Aug. 2021, doi: 10.3390/ijms22158334.

[4] H. Susilo et al., "The Role of Plasma Interleukin-6 Levels on Atherosclerotic Cardiovascular Disease and Cardiovascular Mortality Risk Scores in Javanese Patients with Chronic Kidney Disease," JPM, vol. 12, no. 7, p. 1122, Jul. 2022, doi: 10.3390/jpm12071122.

[5] Y.-S. Li, H.-C. Ren, and J.-H. Cao, "Roles of Interleukin-6-mediated immunometabolic reprogramming in COVID-19 and other viral infection-associated diseases," International Immunopharmacology, vol. 110, p. 109005, Sep. 2022, doi: 10.1016/j.intimp.2022.109005.

[6] J. Majidpoor and K. Mortezaee, "Interleukin-6 in SARS-CoV-2 induced disease: Interactions and therapeutic applications," Biomedicine & Pharmacotherapy, vol. 145, p. 112419, Jan. 2022, doi: 10.1016/j.biopha.2021.112419.

[7] S. Sahu and G. Dutta, "Emerging evidence for serum procalcitonin estimation at point-of-care and advancement in quantitative sensing strategies over the past decade," Sensors International, vol. 2, p. 100107, 2021, doi: 10.1016/j.sintl.2021.100107.

[8] S. Malinverni et al., "Diagnostic Accuracy of Procalcitonin upon Emergency Department Admission during SARS-CoV-2 Pandemic," Antibiotics, vol. 11, no. 9, p. 1141, Aug. 2022, doi: 10.3390/antibiotics11091141.

[9] A. Piperidou et al., "Serum Procalcitonin Levels in Newly Diagnosed Hodgkin Lymphoma: Correlation with Other Inflammatory Biomarkers," Medicina, vol. 58, no. 10, p. 1331, Sep. 2022, doi: 10.3390/medicina58101331.

[10] T. Levinson and A. Wasserman, "C-Reactive Protein Velocity (CRPv) as a New Biomarker for the Early Detection of Acute Infection/Inflammation," IJMS, vol. 23, no. 15, p. 8100, Jul. 2022, doi: 10.3390/ijms23158100.

[11] D. Tesfe, M. Adugna, Z. M. Nigussie, A. E. Woldeyohanins, and Z. D. Kifle, "The proportion of chronic kidney disease and its associated factors among adult diabetic patients at Tibebe Ghion Specialized Hospital, Bahir Dar, Ethiopia," Metabolism Open, vol. 15, p. 100198, Sep. 2022, doi: 10.1016/j.metop.2022.100198.

[12] E. Gusev, L. Solomatina, Y. Zhuravleva, and A. Sarapultsev, "The Pathogenesis of End-Stage Renal Disease from the Standpoint of the Theory of General Pathological Processes of Inflammation," IJMS, vol. 22, no. 21, p. 11453, Oct. 2021, doi: 10.3390/ijms222111453.

[13] N. F. Imamah and H.-R. Lin, "Palliative Care in Patients with End-Stage Renal Disease: A Meta Synthesis," IJERPH, vol. 18, no. 20, p. 10651, Oct. 2021, doi: 10.3390/ijerph182010651.

[14] J. Rysz, B. Franczyk, J. Ławiński, and A. Gluba-Brzózka, "Oxidative Stress in ESRD Patients on Dialysis and the Risk of Cardiovascular Diseases," Antioxidants, vol. 9, no. 11, p. 1079, Nov. 2020, doi: 10.3390/antiox9111079.

[15] C. Jiang et al., "U-shaped association between serum albumin and development of chronic kidney disease in general hypertensive patients," Clinical Nutrition, vol. 39, no. 1, pp. 258–264, Jan. 2020, doi: 10.1016/j.clnu.2019.02.002.

[16] K. Kene et al., "Prevalence and determinants of Impaired Serum Creatinine and Urea among type 2 diabetic patients of jimma medical center, Jimma, Southwestern Ethiopia, 2019," Endocrine and Metabolic Science, vol. 3, p. 100096, Jun. 2021, doi: 10.1016/j.endmts.2021.100096.

[17] L. Dilworth, A. Facey, and F. Omoruyi, "Diabetes Mellitus and Its Metabolic Complications: The Role of Adipose Tissues," IJMS, vol. 22, no. 14, p. 7644, Jul. 2021, doi: 10.3390/ijms22147644.

[18] S. Alam, Md. K. Hasan, S. Neaz, N. Hussain, Md. F. Hossain, and T. Rahman, "Diabetes Mellitus: Insights from Epidemiology, Biochemistry, Risk Factors, Diagnosis, Complications and Comprehensive Management," Diabetology, vol. 2, no. 2, pp. 36–50, Apr. 2021, doi: 10.3390/diabetology2020004.

[19] R. Hamzé et al., "Type 2 Diabetes Mellitus and Alzheimer's Disease: Shared Molecular Mechanisms and Potential Common Therapeutic Targets," IJMS, vol. 23, no. 23, p. 15287, Dec. 2022, doi: 10.3390/ijms232315287.

[20] I.-S. Jeong and C.-M. Kang, "Time to Diagnosis and Treatment of Diabetes Mellitus among Korean Adults with Hyperglycemia: Using a Community-Based Cohort Study," IJERPH, vol. 19, no. 19, p. 12090, Sep. 2022, doi: 10.3390/ijerph191912090.

[21] E. Feigerlová and S.-F. Battaglia-Hsu, "IL-6 signaling in diabetic nephropathy: From pathophysiology to therapeutic perspectives," Cytokine & Growth Factor Reviews, vol. 37, pp. 57–65, Oct. 2017, doi: 10.1016/j.cytogfr.2017.03.003.

[22] I.-H. Seo and Y.-J. Lee, "Usefulness of Complete Blood Count (CBC) to Assess Cardiovascular and Metabolic Diseases in Clinical Settings: A Comprehensive Literature Review," Biomedicines, vol. 10, no. 11, p. 2697, Oct. 2022, doi: 10.3390/biomedicines10112697.

[23] C. Drucker, J. Gewiese, S. Malchow, J. Scheller, and S. Rose-John, "Impact of interleukin-6 classic- and trans-signaling on liver damage and regeneration," Journal of Autoimmunity, vol. 34, no. 1, pp. 29–37, Feb. 2010, doi: 10.1016/j.jaut.2009.08.003.

[24] H. Su, C.-T. Lei, and C. Zhang, "Interleukin-6 Signaling Pathway and Its Role in Kidney Disease: An Update," Front. Immunol., vol. 8, p. 405, Apr. 2017, doi: 10.3389/fimmu.2017.00405.

[25] K. Zhu, X.-J. Lu, Jian-Fei Lu, and J. Chen, "The interleukin-6 regulates the function of monocytes/macrophages (MO/MΦ) via the interleukin-6 receptor β in ayu (Plecoglossus altivelis)," Fish & Shellfish Immunology, vol. 93, pp. 191–199, Oct. 2019, doi: 10.1016/j.fsi.2019.07.049.

[26] M. Largman-Chalamish et al., "Differentiating between bacterial and viral infections by estimated CRP velocity," PLoS ONE, vol. 17, no. 12, p. e0277401, Dec. 2022, doi: 10.1371/journal.pone.0277401.

[27] F. Pandolfi, L. Franza, V. Carusi, S. Altamura, G. Andriollo, and E. Nucera, “Interleukin-6 in Rheumatoid Arthritis,” IJMS, vol. 21, no. 15, p. 5238, Jul. 2020, doi: 10.3390/ijms21155238.

[28] S. A. Jones and B. J. Jenkins, “Recent insights into targeting the IL-6 cytokine family in inflammatory diseases and cancer,” Nat Rev Immunol, vol. 18, no. 12, pp. 773–789, Dec. 2018, doi: 10.1038/s41577-018-0066-7.

[29] P. C. Heinrich, I. Behrmann, S. Haan, H. M. Hermanns, G. Müller-Newen, and F. Schaper, “Principles of interleukin (IL)-6-type cytokine signalling and its regulation,” Biochemical Journal, vol. 374, no. 1, pp. 1–20, Aug. 2003, doi: 10.1042/bj20030407.

[30] D. A. Harrison, “The JAK/STAT Pathway,” Cold Spring Harbor Perspectives in Biology, vol. 4, no. 3, pp. a011205–a011205, Mar. 2012, doi: 10.1101/cshperspect.a011205.

[31] A. Magno, L. Herat, R. Carnagarin, M. Schlaich, and V. Matthews, “Current Knowledge of IL-6 Cytokine Family Members in Acute and Chronic Kidney Disease,” Biomedicines, vol. 7, no. 1, p. 19, Mar. 2019, doi: 10.3390/biomedicines7010019.

[32] Y. Nechemia-Arbely et al., “IL-6/IL-6R Axis Plays a Critical Role in Acute Kidney Injury,” Journal of the American Society of Nephrology, vol. 19, no. 6, pp. 1106–1115, Jun. 2008, doi: 10.1681/ASN.2007070744.

[33] C. A. Hunter and S. A. Jones, “IL-6 as a keystone cytokine in health and disease,” Nat Immunol, vol. 16, no. 5, pp. 448–457, May 2015, doi: 10.1038/ni.3153.

[34] T. Tanaka, M. Narazaki, and T. Kishimoto, “IL-6 in Inflammation, Immunity, and Disease,” Cold Spring Harbor Perspectives in Biology, vol. 6, no. 10, pp. a016295–a016295, Oct. 2014, doi: 10.1101/cshperspect.a016295.

[35] T. Schumertl, J. Lokau, S. Rose-John, and C. Garbers, “Function and proteolytic generation of the soluble interleukin-6 receptor in health and disease,” Biochimica et Biophysica Acta (BBA) - Molecular Cell Research, vol. 1869, no. 1, p. 119143, Jan. 2022, doi: 10.1016/j.bbamcr.2021.119143.

[36] A. N. Wilkinson et al., “Granulocytes Are Unresponsive to IL-6 Due to an Absence of gp130,” The Journal of Immunology, vol. 200, no. 10, pp. 3547–3555, May 2018, doi: 10.4049/jimmunol.1701191.

[37] T. Taga et al., “Interleukin-6 triggers the association of its receptor with a possible signal transducer, gp130,” Cell, vol. 58, no. 3, pp. 573–581, Aug. 1989, doi: 10.1016/0092-8674(89)90438-8.

[38] M. Hibi, M. Murakami, M. Saito, T. Hirano, T. Taga, and T. Kishimoto, “Molecular cloning and expression of an IL-6 signal transducer, gp130,” Cell, vol. 63, no. 6, pp. 1149–1157, Dec. 1990, doi: 10.1016/0092-8674(90)90411-7.

[39] N. Stahl et al., “Association and activation of Jak-Tyk kinases by CNTF-LIF-OSM-IL-6 beta receptor components,” Science, vol. 263, no. 5143, pp. 92–95, Jan. 1994, doi: 10.1126/science.8272873.

[40] N. Stahl, T. J. Farruggella, T. G. Boulton, Z. Zhong, J. E. Darnell, and G. D. Yancopoulos, “Choice of STATs and other substrates specified by modular tyrosine-based motifs in cytokine receptors,” Science, vol. 267, no. 5202, pp. 1349–1353, Mar. 1995, doi: 10.1126/science.7871433.

[41] R. Starr et al., “A family of cytokine-inducible inhibitors of signalling,” Nature, vol. 387, no. 6636, pp. 917–921, Jun. 1997, doi: 10.1038/43206.

[42] R. Eulenfeld et al., “Interleukin-6 signalling: more than Jaks and STATs,” Eur J Cell Biol, vol. 91, no. 6–7, pp. 486–495, 2012, doi: 10.1016/j.ejcb.2011.09.010.
[43] K. Taniguchi et al., “A gp130-Src-YAP module links inflammation to epithelial regeneration,” Nature, vol. 519, no. 7541, pp. 57–62, Mar. 2015, doi: 10.1038/nature14228.
[44] J. Scheller, A. Chalaris, D. Schmidt-Arras, and S. Rose-John, “The pro- and anti-inflammatory properties of the cytokine interleukin-6,” Biochimica et Biophysica Acta (BBA) - Molecular Cell Research, vol. 1813, no. 5, pp. 878–888, May 2011, doi: 10.1016/j.bbamcr.2011.01.034.
[45] S. Rose-John, G. H. Waetzig, J. Scheller, J. Grötzinger, and D. Seegert, “The IL-6/sIL-6R complex as a novel target for therapeutic approaches,” Expert Opin Ther Targets, vol. 11, no. 5, pp. 613–624, May 2007, doi: 10.1517/14728222.11.5.613.
[46] A. Chalaris, C. Garbers, B. Rabe, S. Rose-John, and J. Scheller, “The soluble Interleukin 6 receptor: Generation and role in inflammation and cancer,” European Journal of Cell Biology, vol. 90, no. 6–7, pp. 484–494, Jun. 2011, doi: 10.1016/j.ejcb.2010.10.007.
[47] J. Scheller, A. Chalaris, D. Schmidt-Arras, and S. Rose-John, “The pro- and anti-inflammatory properties of the cytokine interleukin-6,” Biochimica et Biophysica Acta (BBA) - Molecular Cell Research, vol. 1813, no. 5, pp. 878–888, May 2011, doi: 10.1016/j.bbamcr.2011.01.034.
[48] R. A. Black, “Tumor necrosis factor-alpha converting enzyme,” Int J Biochem Cell Biol, vol. 34, no. 1, pp. 1–5, Jan. 2002, doi: 10.1016/s1357-2725(01)00097-8.
[49] C. P. Blobel, “Remarkable roles of proteolysis on and beyond the cell surface,” Curr Opin Cell Biol, vol. 12, no. 5, pp. 606–612, Oct. 2000, doi: 10.1016/s0955-0674(00)00139-3.
[50] V. Matthews et al., “Cellular cholesterol depletion triggers shedding of the human interleukin-6 receptor by ADAM10 and ADAM17 (TACE),” J Biol Chem, vol. 278, no. 40, pp. 38829–38839, Oct. 2003, doi: 10.1074/jbc.M210584200.
[51] S. Kaur, Y. Bansal, R. Kumar, and G. Bansal, “A panoramic review of IL-6: Structure, pathophysiological roles and inhibitors,” Bioorg Med Chem, vol. 28, no. 5, p. 115327, Mar. 2020, doi: 10.1016/j.bmc.2020.115327.
[52] M. Trovato, S. Sciacchitano, A. Facciolà, A. Valenti, G. Visalli, and A. Di Pietro, “Interleukin‑6 signalling as a valuable cornerstone for molecular medicine (Review),” Int J Mol Med, vol. 47, no. 6, p. 107, Jun. 2021, doi: 10.3892/ijmm.2021.4940.
[53] M. Murakami, D. Kamimura, and T. Hirano, “Pleiotropy and Specificity: Insights from the Interleukin 6 Family of Cytokines,” Immunity, vol. 50, no. 4, pp. 812–831, Apr. 2019, doi: 10.1016/j.immuni.2019.03.027.
[54] J. Van Snick et al., “cDNA cloning of murine interleukin-HP1: homology with human interleukin 6,” Eur J Immunol, vol. 18, no. 2, pp. 193–197, Feb. 1988, doi: 10.1002/eji.1830180202.
[55] P.-C. Tu, C.-T. Li, W.-C. Lin, M.-H. Chen, T.-P. Su, and Y.-M. Bai, “Structural and functional correlates of serum soluble IL-6 receptor level in patients with bipolar disorder,” J Affect Disord, vol. 219, pp. 172–177, Sep. 2017, doi: 10.1016/j.jad.2017.04.036.
[56] Y. Ren, J. Feng, H. Qu, S. Li, and B. Shen, “Three-dimensional structure and function study on the active region in the extracellular ligand-binding domain of

human IL-6 receptor," Sci China C Life Sci, vol. 43, no. 4, pp. 425–432, Aug. 2000, doi: 10.1007/BF02879308.

[57] P. C. Heinrich, J. V. Castell, and T. Andus, "Interleukin-6 and the acute phase response," Biochem J, vol. 265, no. 3, pp. 621–636, Feb. 1990, doi: 10.1042/bj2650621.

[58] S. Black, I. Kushner, and D. Samols, "C-reactive Protein," J Biol Chem, vol. 279, no. 47, pp. 48487–48490, Nov. 2004, doi: 10.1074/jbc.R400025200.

[59] M. Narazaki and T. Kishimoto, "The Two-Faced Cytokine IL-6 in Host Defense and Diseases," IJMS, vol. 19, no. 11, p. 3528, Nov. 2018, doi: 10.3390/ijms19113528.

[60] K. Yasuda, Y. Takeuchi, and K. Hirota, "The pathogenicity of Th17 cells in autoimmune diseases," Semin Immunopathol, vol. 41, no. 3, pp. 283–297, May 2019, doi: 10.1007/s00281-019-00733-8.

[61] A. Camporeale and V. Poli, "IL-6, IL-17 and STAT3: a holy trinity in auto-immunity?," Front Biosci (Landmark Ed), vol. 17, no. 6, pp. 2306–2326, Jun. 2012, doi: 10.2741/4054.

[62] K. Prystaz et al., "Distinct Effects of IL-6 Classic and Trans-Signaling in Bone Fracture Healing," Am J Pathol, vol. 188, no. 2, pp. 474–490, Feb. 2018, doi: 10.1016/j.ajpath.2017.10.011.

[63] M. Hashizume, N. Hayakawa, and M. Mihara, "IL-6 trans-signalling directly induces RANKL on fibroblast-like synovial cells and is involved in RANKL induction by TNF-alpha and IL-17," Rheumatology (Oxford), vol. 47, no. 11, pp. 1635–1640, Nov. 2008, doi: 10.1093/rheumatology/ken363.

[64] C.-W. Lo et al., "IL-6 trans-signaling in formation and progression of malignant ascites in ovarian cancer," Cancer Res, vol. 71, no. 2, pp. 424–434, Jan. 2011, doi: 10.1158/0008-5472.CAN-10-1496.

[65] T. Barkhausen et al., "Selective blockade of interleukin-6 trans-signaling improves survival in a murine polymicrobial sepsis model," Crit Care Med, vol. 39, no. 6, pp. 1407–1413, Jun. 2011, doi: 10.1097/CCM.0b013e318211ff56.

[66] O.-Z. Akácsos-Szász et al., "Pathways of Coagulopathy and Inflammatory Response in SARS-CoV-2 Infection among Type 2 Diabetic Patients," IJMS, vol. 24, no. 5, p. 4319, Feb. 2023, doi: 10.3390/ijms24054319.

[67] J. M. Stouthard et al., "Interleukin-6 stimulates coagulation, not fibrinolysis, in humans," Thromb Haemost, vol. 76, no. 5, pp. 738–742, Nov. 1996.

[68] H. Nara and R. Watanabe, "Anti-Inflammatory Effect of Muscle-Derived Interleukin-6 and Its Involvement in Lipid Metabolism," IJMS, vol. 22, no. 18, p. 9889, Sep. 2021, doi: 10.3390/ijms22189889.

[69] S. Didion, "Cellular and Oxidative Mechanisms Associated with Interleukin-6 Signaling in the Vasculature," IJMS, vol. 18, no. 12, p. 2563, Nov. 2017, doi: 10.3390/ijms18122563.

[70] S. Kang and T. Kishimoto, "Interplay between interleukin-6 signaling and the vascular endothelium in cytokine storms," Exp Mol Med, vol. 53, no. 7, pp. 1116–1123, Jul. 2021, doi: 10.1038/s12276-021-00649-0.

[71] M. Jarlborg and C. Gabay, "Systemic effects of IL-6 blockade in rheumatoid arthritis beyond the joints," Cytokine, vol. 149, p. 155742, Jan. 2022, doi: 10.1016/j.cyto.2021.155742.

[72] S. Rose-John, "IL-6 trans-signaling via the soluble IL-6 receptor: importance for the pro-inflammatory activities of IL-6," Int J Biol Sci, vol. 8, no. 9, pp. 1237–1247, 2012, doi: 10.7150/ijbs.4989.

[73] H. O. Kalkman, "Novel Treatment Targets Based on Insights in the Etiology of Depression: Role of IL-6 Trans-Signaling and Stress-Induced Elevation of Glutamate and ATP," Pharmaceuticals, vol. 12, no. 3, p. 113, Jul. 2019, doi: 10.3390/ph12030113.

[74] A. Cardoneanu, A. M. Burlui, L. A. Macovei, I. Bratoiu, P. Richter, and E. Rezus, "Targeting Systemic Sclerosis from Pathogenic Mechanisms to Clinical Manifestations: Why IL-6?," Biomedicines, vol. 10, no. 2, p. 318, Jan. 2022, doi: 10.3390/biomedicines10020318.

[75] M. Rašková et al., "The Role of IL-6 in Cancer Cell Invasiveness and Metastasis—Overview and Therapeutic Opportunities," Cells, vol. 11, no. 22, p. 3698, Nov. 2022, doi: 10.3390/cells11223698.

[76] T. Korn and M. Hiltensperger, "Role of IL-6 in the commitment of T cell subsets," Cytokine, vol. 146, p. 155654, Oct. 2021, doi: 10.1016/j.cyto.2021.155654.

[77] C. A. Hunter and S. A. Jones, "IL-6 as a keystone cytokine in health and disease," Nat Immunol, vol. 16, no. 5, pp. 448–457, May 2015, doi: 10.1038/ni.3153.

[78] S. Heink et al., "Trans-presentation of IL-6 by dendritic cells is required for the priming of pathogenic TH17 cells," Nat Immunol, vol. 18, no. 1, pp. 74–85, Jan. 2017, doi: 10.1038/ni.3632.

[79] C. Martínez-Pérez, C. Kay, J. Meehan, M. Gray, J. M. Dixon, and A. K. Turnbull, "The IL6-like Cytokine Family: Role and Biomarker Potential in Breast Cancer," JPM, vol. 11, no. 11, p. 1073, Oct. 2021, doi: 10.3390/jpm11111073.

[80] V. K. Venkatesan, M. T. Ramakrishna, I. Izonin, R. Tkachenko, and M. Havryliuk, "Efficient Data Preprocessing with Ensemble Machine Learning Technique for the Early Detection of Chronic Kidney Disease," Applied Sciences, vol. 13, no. 5, p. 2885, Feb. 2023, doi: 10.3390/app13052885.

[81] T. Petreski, N. Piko, R. Ekart, R. Hojs, and S. Bevc, "Review on Inflammation Markers in Chronic Kidney Disease," Biomedicines, vol. 9, no. 2, p. 182, Feb. 2021, doi: 10.3390/biomedicines9020182.

[82] F. Tinti et al., "Chronic Kidney Disease as a Systemic Inflammatory Syndrome: Update on Mechanisms Involved and Potential Treatment," Life, vol. 11, no. 5, p. 419, May 2021, doi: 10.3390/life11050419.

[83] A. C. Webster, E. V. Nagler, R. L. Morton, and P. Masson, "Chronic Kidney Disease," The Lancet, vol. 389, no. 10075, pp. 1238–1252, Mar. 2017, doi: 10.1016/S0140-6736(16)32064-5.

[84] T. Petreski, N. Piko, R. Ekart, R. Hojs, and S. Bevc, "Review on Inflammation Markers in Chronic Kidney Disease," Biomedicines, vol. 9, no. 2, p. 182, Feb. 2021, doi: 10.3390/biomedicines9020182.

[85] A. S. Levey et al., "The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report," Kidney International, vol. 80, no. 1, pp. 17–28, Jul. 2011, doi: 10.1038/ki.2010.483.

[86] G. Alfano et al., "Rethinking Chronic Kidney Disease in the Aging Population," Life, vol. 12, no. 11, p. 1724, Oct. 2022, doi: 10.3390/life12111724.

[87] S. Giles and S. Fiori, "Glomerular Filtration Rate Estimation by a Novel Numerical Binning-Less Isotonic Statistical Bivariate Numerical Modeling Method," Information, vol. 10, no. 3, p. 100, Mar. 2019, doi: 10.3390/info10030100.

[88] S. G. Jančič, M. Močnik, and N. Marčun Varda, "Glomerular Filtration Rate Assessment in Children," Children, vol. 9, no. 12, p. 1995, Dec. 2022, doi: 10.3390/children9121995.

[89] Y.-C. Lee et al., "All-Cause Standardized Mortality Ratio in Hemodialysis and Peritoneal Dialysis Patients: A Nationwide Population-Based Cohort Study," IJERPH, vol. 20, no. 3, p. 2347, Jan. 2023, doi: 10.3390/ijerph20032347.

[90] S. Vadakedath and V. Kandi, "Dialysis: A Review of the Mechanisms Underlying Complications in the Management of Chronic Renal Failure," Cureus, vol. 9, no. 8, p. e1603, Aug. 2017, doi: 10.7759/cureus.1603.

[91] A. Shukri et al., "Hemodialysis and Peritoneal Dialysis in Germany from a Health Economic View—A Propensity Score Matched Analysis," IJERPH, vol. 19, no. 21, p. 14007, Oct. 2022, doi: 10.3390/ijerph192114007.

[92] Y.-A. Chen, S.-M. Ou, and C.-C. Lin, "Influence of Dialysis Membranes on Clinical Outcomes: From History to Innovation," Membranes, vol. 12, no. 2, p. 152, Jan. 2022, doi: 10.3390/membranes12020152.

[93] I. K. Salim and A. R. Diajil, "Assessment of salivary immunoglobulin A, interleu-kin-6 and C-reactive protein in chronic kidney dis-ease patients on hemodialysis and on conservative treatment," J Bagh Coll Dent, vol. 34, no. 2, pp. 62–73, Jun. 2022, doi: 10.26477/jbcd.v34i2.3146.

[94] P. Branco et al., "Fibrosis of Peritoneal Membrane, Molecular Indicators of Aging and Frailty Unveil Vulnerable Patients in Long-Term Peritoneal Dialysis," IJMS, vol. 24, no. 5, p. 5020, Mar. 2023, doi: 10.3390/ijms24055020.

[95] M. Bonomini et al., "How to Improve the Biocompatibility of Peritoneal Dialysis Solutions (without Jeopardizing the Patient's Health)," IJMS, vol. 22, no. 15, p. 7955, Jul. 2021, doi: 10.3390/ijms22157955.

[96] W.-C. Tsai et al., "Risk Factors for Development and Progression of Chronic Kidney Disease: A Systematic Review and Exploratory Meta-Analysis," Medicine, vol. 95, no. 11, p. e3013, Mar. 2016, doi: 10.1097/MD.0000000000003013.

[97] Z. Nazzal, Z. Hamdan, D. Masri, O. Abu-Kaf, and M. Hamad, "Prevalence and risk factors of chronic kidney disease among Palestinian type 2 diabetic patients: a cross-sectional study," BMC Nephrol, vol. 21, no. 1, p. 484, Dec. 2020, doi: 10.1186/s12882-020-02138-4.

[98] T. A. Berezina, Z. Obradovic, E. Boxhammer, A. A. Berezin, M. Lichtenauer, and A. E. Berezin, "Adropin Predicts Chronic Kidney Disease in Type 2 Diabetes Mellitus Patients with Chronic Heart Failure," JCM, vol. 12, no. 6, p. 2231, Mar. 2023, doi: 10.3390/jcm12062231.

[99] T. Petreski, N. Piko, R. Ekart, R. Hojs, and S. Bevc, "Review on Inflammation Markers in Chronic Kidney Disease," Biomedicines, vol. 9, no. 2, p. 182, Feb. 2021, doi: 10.3390/biomedicines9020182.

[100] F. F. Kreiner, J. M. Kraaijenhof, M. von Herrath, G. K. K. Hovingh, and B. J. von Scholten, "Interleukin 6 in diabetes, chronic kidney disease, and cardiovascular disease: mechanisms and therapeutic perspectives," Expert Review of Clinical Immunology, vol. 18, no. 4, pp. 377–389, Apr. 2022, doi: 10.1080/1744666X.2022.2045952.

[101] E. Feigerlová and S.-F. Battaglia-Hsu, "IL-6 signaling in diabetic nephropathy: From pathophysiology to therapeutic perspectives," Cytokine Growth Factor Rev, vol. 37, pp. 57–65, Oct. 2017, doi: 10.1016/j.cytogfr.2017.03.003.
[102] P. M. Ridker et al., "Inhibition of Interleukin-1β by Canakinumab and Cardiovascular Outcomes in Patients With Chronic Kidney Disease," J Am Coll Cardiol, vol. 71, no. 21, pp. 2405–2414, May 2018, doi: 10.1016/j.jacc.2018.03.490.
[103] A. Poznyak, A. V. Grechko, P. Poggio, V. A. Myasoedova, V. Alfieri, and A. N. Orekhov, "The Diabetes Mellitus–Atherosclerosis Connection: The Role of Lipid and Glucose Metabolism and Chronic Inflammation," IJMS, vol. 21, no. 5, p. 1835, Mar. 2020, doi: 10.3390/ijms21051835.
[104] American Diabetes Association, "Diagnosis and Classification of Diabetes Mellitus," Diabetes Care, vol. 33, no. Supplement_1, pp. S62–S69, Jan. 2010, doi: 10.2337/dc10-S062.
[105] A. Artasensi, A. Pedretti, G. Vistoli, and L. Fumagalli, "Type 2 Diabetes Mellitus: A Review of Multi-Target Drugs," Molecules, vol. 25, no. 8, p. 1987, Apr. 2020, doi: 10.3390/molecules25081987.
[106] F. Del Chierico, N. Rapini, A. Deodati, M. C. Matteoli, S. Cianfarani, and L. Putignani, "Pathophysiology of Type 1 Diabetes and Gut Microbiota Role," IJMS, vol. 23, no. 23, p. 14650, Nov. 2022, doi: 10.3390/ijms232314650.
[107] U. Galicia-Garcia et al., "Pathophysiology of Type 2 Diabetes Mellitus," Int J Mol Sci, vol. 21, no. 17, p. 6275, Aug. 2020, doi: 10.3390/ijms21176275.
[108] Y. Saisho, "Importance of Beta Cell Function for the Treatment of Type 2 Diabetes," J Clin Med, vol. 3, no. 3, pp. 923–943, Aug. 2014, doi: 10.3390/jcm3030923.
[109] R. A. Defronzo, "Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus," Diabetes, vol. 58, no. 4, pp. 773–795, Apr. 2009, doi: 10.2337/db09-9028.
[110] E. U. Alejandro et al., "Gestational Diabetes Mellitus: A Harbinger of the Vicious Cycle of Diabetes," IJMS, vol. 21, no. 14, p. 5003, Jul. 2020, doi: 10.3390/ijms21145003.
[111] American Diabetes Association Professional Practice Committee, "2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2022," Diabetes Care, vol. 45, no. Suppl 1, pp. S17–S38, Jan. 2022, doi: 10.2337/dc22-S002.
[112] S. Vijan, "In the clinic. Type 2 diabetes," Ann Intern Med, vol. 152, no. 5, pp. ITC31-15; quiz ITC316, Mar. 2010, doi: 10.7326/0003-4819-152-5-201003020-01003.
[113] A. L. Siu and on behalf of the U.S. Preventive Services Task Force*, "Screening for Abnormal Blood Glucose and Type 2 Diabetes Mellitus: U.S. Preventive Services Task Force Recommendation Statement," Ann Intern Med, vol. 163, no. 11, pp. 861–868, Dec. 2015, doi: 10.7326/M15-2345.
[114] R. Khan, Z. Chua, J. Tan, Y. Yang, Z. Liao, and Y. Zhao, "From Pre-Diabetes to Diabetes: Diagnosis, Treatments and Translational Research," Medicina, vol. 55, no. 9, p. 546, Aug. 2019, doi: 10.3390/medicina55090546.
[115] P. K. Mandali, A. Prabakaran, K. Annadurai, and U. M. Krishnan, "Trends in Quantification of HbA1c Using Electrochemical and Point-of-Care Analyzers," Sensors, vol. 23, no. 4, p. 1901, Feb. 2023, doi: 10.3390/s23041901.

[116] X.-Y. Shao, C.-R. Wang, C.-M. Xie, X.-G. Wang, R.-L. Liang, and W.-W. Xu, "Rapid and Sensitive Lateral Flow Immunoassay Method for Procalcitonin (PCT) Based on Time-Resolved Immunochromatography," Sensors, vol. 17, no. 3, p. 480, Feb. 2017, doi: 10.3390/s17030480.

[117] H. N. Park et al., "Usefulness of Procalcitonin in the Diagnosis of Bacterial Infection in Immunocompetent Children," Children, vol. 9, no. 8, p. 1263, Aug. 2022, doi: 10.3390/children9081263.

[118] I. Christensen, D. Berild, J. V. Bjørnholt, L.-P. Jelsness-Jørgensen, S. M. Debes, and J. B. Haug, "The Role of Procalcitonin as an Antimicrobial Stewardship Tool in Patients Hospitalized with Seasonal Influenza," Antibiotics, vol. 12, no. 3, p. 573, Mar. 2023, doi: 10.3390/antibiotics12030573.

[119] H. Kim, Y.-H. Roh, and S.-H. Yoon, "Blood Procalcitonin Level as a Diagnostic Marker of Pediatric Bacterial Meningitis: A Systematic Review and Meta-Analysis," Diagnostics, vol. 11, no. 5, p. 846, May 2021, doi: 10.3390/diagnostics11050846.

[120] K. Pesqueda-Cendejas et al., "CRP Serum Levels Are Associated with High Cardiometabolic Risk and Clinical Disease Activity in Systemic Lupus Erythematosus Patients," JCM, vol. 11, no. 7, p. 1849, Mar. 2022, doi: 10.3390/jcm11071849.

[121] S. Shankar et al., "Variations of Serum CRP Levels in Periodontal Health and Diseases: A Clinico-Biochemical Study," Diagnostics (Basel), vol. 13, no. 15, p. 2483, Jul. 2023, doi: 10.3390/diagnostics13152483.

[122] Y. Luan and Y. Yao, "The Clinical Significance and Potential Role of C-Reactive Protein in Chronic Inflammatory and Neurodegenerative Diseases," Front. Immunol., vol. 9, p. 1302, Jun. 2018, doi: 10.3389/fimmu.2018.01302.

[123] I. Melnikov, S. Kozlov, O. Saburova, Y. Avtaeva, K. Guria, and Z. Gabbasov, "Monomeric C-Reactive Protein in Atherosclerotic Cardiovascular Disease: Advances and Perspectives," Int J Mol Sci, vol. 24, no. 3, p. 2079, Jan. 2023, doi: 10.3390/ijms24032079.

[124] U. Smole, B. Kratzer, and W. F. Pickl, "Soluble pattern recognition molecules: Guardians and regulators of homeostasis at airway mucosal surfaces," Eur J Immunol, vol. 50, no. 5, pp. 624–642, May 2020, doi: 10.1002/eji.201847811.

[125] S. Gowda, P. B. Desai, S. S. Kulkarni, V. V. Hull, A. A. K. Math, and S. N. Vernekar, "Markers of renal function tests," N Am J Med Sci, vol. 2, no. 4, pp. 170–173, Apr. 2010.

[126] D. A. Belinskaia, P. A. Voronina, A. A. Batalova, and N. V. Goncharov, "Serum Albumin," Encyclopedia, vol. 1, no. 1, pp. 65–75, Dec. 2020, doi: 10.3390/encyclopedia1010009.

[127] V. Mishra and R. J. Heath, "Structural and Biochemical Features of Human Serum Albumin Essential for Eukaryotic Cell Culture," IJMS, vol. 22, no. 16, p. 8411, Aug. 2021, doi: 10.3390/ijms22168411.

[128] M. P. Brundha, V. P. Pathmashri, and S. Sundari, "Quantitative Changes of Red Blood cells in Cancer Patients under Palliative Radiotherapy-A Retrospective Study," Rese. Jour. of Pharm. and Technol., vol. 12, no. 2, p. 687, 2019, doi: 10.5958/0974-360X.2019.00122.7.

[129] A. A. Sayed, "The Cost-Effectiveness of Requesting a Complete Blood Count (CBC) in the Management of COVID-19 in Saudi Arabia," Healthcare, vol. 10, no. 9, p. 1780, Sep. 2022, doi: 10.3390/healthcare10091780.
[130] L. Agnello et al., "The Value of a Complete Blood Count (CBC) for Sepsis Diagnosis and Prognosis," Diagnostics, vol. 11, no. 10, p. 1881, Oct. 2021, doi: 10.3390/diagnostics11101881.
[131] F. Rustam et al., "White Blood Cell Classification Using Texture and RGB Features of Oversampled Microscopic Images," Healthcare, vol. 10, no. 11, p. 2230, Nov. 2022, doi: 10.3390/healthcare10112230.
[132] S. Ansari, A. H. Navin, A. Babazadeh Sangar, J. Vaez Gharamaleki, and S. Danishvar, "Acute Leukemia Diagnosis Based on Images of Lymphocytes and Monocytes Using Type-II Fuzzy Deep Network," Electronics, vol. 12, no. 5, p. 1116, Feb. 2023, doi: 10.3390/electronics12051116.
[133] Z. Guo, Z. Zhang, M. Prajapati, and Y. Li, "Lymphopenia Caused by Virus Infections and the Mechanisms Beyond," Viruses, vol. 13, no. 9, p. 1876, Sep. 2021, doi: 10.3390/v13091876.
[134] W. Kaewprayoon et al., "Determination of Methemoglobin in Hemoglobin Submicron Particles Using NMR Relaxometry," IJMS, vol. 21, no. 23, p. 8978, Nov. 2020, doi: 10.3390/ijms21238978.
[135] A. I. Alayash, "Hemoglobin Oxidation Reactions in Stored Blood," Antioxidants, vol. 11, no. 4, p. 747, Apr. 2022, doi: 10.3390/antiox11040747.
[136] W. Hermann et al., "Reference Intervals for Platelet Counts in the Elderly: Results from the Prospective SENIORLAB Study," JCM, vol. 9, no. 9, p. 2856, Sep. 2020, doi: 10.3390/jcm9092856.
[137] N. Ludwig, A. Hilger, A. Zarbock, and J. Rossaint, "Platelets at the Crossroads of Pro-Inflammatory and Resolution Pathways during Inflammation," Cells, vol. 11, no. 12, p. 1957, Jun. 2022, doi: 10.3390/cells11121957.
[138] M. W. Weatherburn, "Phenol-hypochlorite reaction for determination of ammonia," Anal. Chem., vol. 39, no. 8, pp. 971–974, Jul. 1967, doi: 10.1021/ac60252a045.
[139] H. Bartels, M. Böhmer, and C. Heierli, "[Serum creatinine determination without protein precipitation]," Clin Chim Acta, vol. 37, pp. 193–197, Mar. 1972, doi: 10.1016/0009-8981(72)90432-9.
[140] C. BalcI, H. Sungurtekin, E. Gürses, U. Sungurtekin, and B. Kaptanoglu, "Usefulness of procalcitonin for diagnosis of sepsis in the intensive care unit," Crit Care, vol. 7, no. 1, pp. 85–90, Feb. 2003, doi: 10.1186/cc1843.
[141] M. Briel et al., "Procalcitonin-guided antibiotic use vs a standard approach for acute respiratory tract infections in primary care," Arch Intern Med, vol. 168, no. 18, pp. 2000–2007; discussion 2007-2008, Oct. 2008, doi: 10.1001/archinte.168.18.2000.
[142] M. Song and J. A. Kellum, "Interleukin-6," Crit Care Med, vol. 33, no. 12 Suppl, pp. S463-465, Dec. 2005, doi: 10.1097/01.ccm.0000186784.62662.a1.
[143] C. Wadsworth and E. Wadsworth, "Efficacy of latex agglutination and quantification methods for determination of C-reactive protein (CRP) in pediatric sera," Clin Chim Acta, vol. 138, no. 3, pp. 309–318, Apr. 1984, doi: 10.1016/0009-8981(84)90138-4.
[144] J. J. M, "A PRACTICAL ATTEMPT FOR INTERPRETATION OF SYSMEX KX-21 BLOOD ANALYZER HISTOGRAMS AND FLAGS RESOLVING," jas, vol. 1, no. 1, pp. 120–135, Dec. 2018, doi: 10.47891/sabujas.v1i1.120-135.

[145] B. T. Doumas, W. A. Watson, and H. G. Biggs, “Albumin standards and the measurement of serum albumin with bromcresol green,” Clin Chim Acta, vol. 31, no. 1, pp. 87–96, Jan. 1971, doi: 10.1016/0009-8981(71)90365-2.
[146] R. G. Schoenfeld and C. J. Lewellen, “A COLORIMETRIC METHOD FOR DETERMINATION OF SERUM CHLORIDE,” Clin Chem, vol. 10, pp. 533–539, Jun. 1964.
[147] M. N. Berry, R. D. Mazzachi, M. Pejakovic, and M. J. Peake, “Enzymatic determination of potassium in serum,” Clin Chem, vol. 35, no. 5, pp. 817–820, May 1989.
[148] M. N. Berry, R. D. Mazzachi, M. Pejakovic, and M. J. Peake, “Enzymatic determination of sodium in serum,” Clin Chem, vol. 34, no. 11, pp. 2295–2298, Nov. 1988.
[149] H. Susilo et al., “The Role of Plasma Interleukin-6 Levels on Atherosclerotic Cardiovascular Disease and Cardiovascular Mortality Risk Scores in Javanese Patients with Chronic Kidney Disease,” JPM, vol. 12, no. 7, p. 1122, Jul. 2022, doi: 10.3390/jpm12071122.
[150] M. Bossola et al., “Circulating bacterial-derived DNA fragments and markers of inflammation in chronic hemodialysis patients,” Clin J Am Soc Nephrol, vol. 4, no. 2, pp. 379–385, Feb. 2009, doi: 10.2215/CJN.03490708.
[151] A. Turon-Skrzypinska et al., “Assessment of Sclerostin and Interleukin 6 Levels and Selected Anthropometric Parameters in Patients Receiving Hemodialysis Replacement Therapy-Pilot Study,” Medicina (Kaunas), vol. 55, no. 12, p. 784, Dec. 2019, doi: 10.3390/medicina55120784.
[152] M. Tao, D. Zheng, X. Liang, Q. He, and W. Zhang, “Diagnostic value of procalcitonin for bacterial infections in patients undergoing hemodialysis: a systematic review and meta-analysis,” Renal Failure, vol. 44, no. 1, pp. 81–93, Dec. 2022, doi: 10.1080/0886022X.2021.2021236.
[153] Y. Wu, M. Wang, Y. Zhu, and S. Lin, “Serum interleukin-6 in the diagnosis of bacterial infection in cirrhotic patients: A meta-analysis,” Medicine (Baltimore), vol. 95, no. 41, p. e5127, Oct. 2016, doi: 10.1097/MD.0000000000005127.
[154] L. Velazquez-Salinas, A. Verdugo-Rodriguez, L. L. Rodriguez, and M. V. Borca, “The Role of Interleukin 6 During Viral Infections,” Front. Microbiol., vol. 10, p. 1057, May 2019, doi: 10.3389/fmicb.2019.01057.
[155] “IL-6 Plays a Crucial Role in HBV Infection,” JCTH, vol. 3, no. 4, pp. 271–276, Dec. 2015, doi: 10.14218/JCTH.2015.00024.
[156] J. R. Larrubia, S. Benito-Martínez, J. Miquel-Plaza, E. Sanz-de-Villalobos, F. González-Mateos, and T. Parra, “Cytokines: their pathogenic and therapeutic role in chronic viral hepatitis,” Rev. esp. enferm. dig., vol. 101, no. 5, May 2009, doi: 10.4321/S1130-01082009000500006.
[157] H. S. Vatansever and E. Becer, “Relationship between IL-6 and COVID-19: to be considered during treatment,” Future Virology, vol. 15, no. 12, pp. 817–822, Dec. 2020, doi: 10.2217/fvl-2020-0168.
[158] S. Khan, A. Bhargava, N. Pathak, Kewal. K. Maudar, S. Varshney, and P. K. Mishra, “Circulating Biomarkers and their Possible Role in Pathogenesis of Chronic Hepatitis B and C Viral Infections,” Ind J Clin Biochem, vol. 26, no. 2, pp. 161–168, Apr. 2011, doi: 10.1007/s12291-010-0098-7.

[159] R. Kartika, D. Purnamasari, S. Pradipta, R. A. Larasati, and H. Wibowo, "Impact of Low Interferon-γ and IL-10 Levels on TNF-α and IL-6 Production by PHA-Induced PBMCs in Type 2 Diabetes Mellitus," J Inflamm Res, vol. 13, pp. 187–193, 2020, doi: 10.2147/JIR.S245064.

[160] A. L. Carey et al., "Interleukin-6 and tumor necrosis factor-? are not increased in patients with Type 2 diabetes: evidence that plasma interleukin-6 is related to fat mass and not insulin responsiveness," Diabetologia, vol. 47, no. 6, Jun. 2004, doi: 10.1007/s00125-004-1403-x.

[161] Ekhlass N Ali, Ashwaq A Khadem, and H. J. Muhammed, "Determination of IL-6 and CRP in Patients with Type Two -Diabetes Mellitus in Baghdad/ Iraq," 2021, doi: 10.13140/RG.2.2.23313.45924.

[162] S.-C. Wu, C.-X. Liang, Y.-L. Zhang, and W.-P. Hu, "Elevated serum procalcitonin level in patients with chronic kidney disease without infection: A case-control study," J Clin Lab Anal, vol. 34, no. 2, p. e23065, Feb. 2020, doi: 10.1002/jcla.23065.

[163] A. Piperidou et al., "Serum Procalcitonin Levels in Newly Diagnosed Hodgkin Lymphoma: Correlation with Other Inflammatory Biomarkers," Medicina, vol. 58, no. 10, p. 1331, Sep. 2022, doi: 10.3390/medicina58101331.

[164] G. Steinbach, E. Bölke, A. Grünert, M. Störck, and K. Orth, "Procalcitonin in patients with acute and chronic renal insufficiency," Wien Klin Wochenschr, vol. 116, no. 24, pp. 849–853, Dec. 2004, doi: 10.1007/s00508-004-0279-6.

[165] A. Usman, "25-OH-Vitamin D and procalcitonin levels after correction of acute hyperglycemia," Med Sci Monit, vol. 19, pp. 264–268, 2013, doi: 10.12659/MSM.883880.

[166] M.-A. Podeanu et al., "C-Reactive Protein as a Marker of Inflammation in Children and Adolescents with Metabolic Syndrome: A Systematic Review and Meta-Analysis," Biomedicines, vol. 11, no. 11, p. 2961, Nov. 2023, doi: 10.3390/biomedicines11112961.

[167] Z. I. Li et al., "C-reactive protein promotes acute renal inflammation and fibrosis in unilateral ureteral obstructive nephropathy in mice," Lab Invest, vol. 91, no. 6, pp. 837–851, Jun. 2011, doi: 10.1038/labinvest.2011.42.

[168] P. L. Abdel-Messeih, M. M. Alkady, N. M. Nosseir, and M. S. Tawfik, "Inflammatory markers in end-stage renal disease patients on haemodialysis," J Med Biochem, vol. 39, no. 4, pp. 481–487, Oct. 2020, doi: 10.5937/jomb0-25120.

[169] M. Dungey, K. L. Hull, A. C. Smith, J. O. Burton, and N. C. Bishop, "Inflammatory Factors and Exercise in Chronic Kidney Disease," International Journal of Endocrinology, vol. 2013, pp. 1–12, 2013, doi: 10.1155/2013/569831.

[170] J. Torzewski et al., "Targeting C-Reactive Protein by Selective Apheresis in Humans: Pros and Cons," J Clin Med, vol. 11, no. 7, p. 1771, Mar. 2022, doi: 10.3390/jcm11071771.

[171] J. Stanimirovic et al., "Role of C-Reactive Protein in Diabetic Inflammation," Mediators Inflamm, vol. 2022, p. 3706508, 2022, doi: 10.1155/2022/3706508.

[172] S. Kanmani, M. Kwon, M.-K. Shin, and M. K. Kim, "Association of C-Reactive Protein with Risk of Developing Type 2 Diabetes Mellitus, and Role of Obesity and Hypertension: A Large Population-Based Korean Cohort Study," Sci Rep, vol. 9, no. 1, p. 4573, Mar. 2019, doi: 10.1038/s41598-019-40987-8.

[173] A. Pan, Y. Wang, J.-M. Yuan, and W.-P. Koh, "High-sensitive C-reactive protein and risk of incident type 2 diabetes: a case-control study nested within the Singapore Chinese Health Study," BMC Endocr Disord, vol. 17, no. 1, p. 8, Feb. 2017, doi: 10.1186/s12902-017-0159-5.

[174] S. Singh and S. Bhatta, "Biochemical and hematological parameters in chronic kidney disease," J. Manmohan Memorial Inst. Health. Sci., vol. 4, no. 1, pp. 4–11, Sep. 2018, doi: 10.3126/jmmihs.v4i1.21132.

[175] W. H. Ajam, "Evaluating of Serum Electrolyte Changes in Chronic Renal Failure Pre and Post Dialysis," MLU, vol. 20, no. 4, pp. 980–983, Nov. 2020, doi: 10.37506/mlu.v20i4.1952.

[176] H. R. Mehmood, Z. Khan, H. M. S. Jahangir, A. Hussain, A. Elahi, and S. M. H. Askari, "Assessment of serum biochemical derangements and associated risk factors of chronic kidney disease," J Taibah Univ Med Sci, vol. 17, no. 3, pp. 376–383, Jun. 2022, doi: 10.1016/j.jtumed.2021.09.009.

[177] E. MA, O. HB, D. T, and E. LA, "Impact of Viral Infaction on Urea and Creatinine Levels in Patients with Chronic Kideny Disease on Haemodialysis ," JMBR, vol. 12, no. 1, pp. 17–23, Jun. 2013.

[178] A. H. Hassan, "Urea and Creatinine in renal failure patients with Viral Hepatitis," HNSJ, vol. 4, no. 8, Aug. 2023, doi: 10.53796/hnsj4811.

[179] K. Kosaraju, S. S. Faujdar, A. Singh, and R. Prabhu, "Hepatitis Viruses in Heamodialysis Patients: An Added Insult to Injury?," Hepatitis Research and Treatment, vol. 2013, pp. 1–4, Mar. 2013, doi: 10.1155/2013/860514.

[180] M. Takeuchi et al., "Serum creatinine levels and risk of incident type 2 diabetes mellitus or dysglycemia in middle-aged Japanese men: a retrospective cohort study," BMJ Open Diab Res Care, vol. 6, no. 1, p. e000492, Feb. 2018, doi: 10.1136/bmjdrc-2017-000492.

[181] N. Harita et al., "Lower serum creatinine is a new risk factor of type 2 diabetes: the Kansai healthcare study," Diabetes Care, vol. 32, no. 3, pp. 424–426, Mar. 2009, doi: 10.2337/dc08-1265.

[182] H. Lin et al., "U-shaped relationship between urea level and hepatic decompensation in chronic liver diseases," Clin Mol Hepatol, vol. 28, no. 1, pp. 77–90, Jan. 2022, doi: 10.3350/cmh.2021.0188.

[183] H. F. Hassen, M. Q. D. Al-Lami, and A. J. H. Al-Saedi, "Evaluation some Biochemical Levels in Patients undergoing Hemodialysis in Baghdad Governorate," Journal of Advanced Laboratory Research in Biology, vol. 9, no. 2, pp. 50–57, 2018.

[184] M. R. Kurniawan and E. Kusrini, "UREUM AND CREATININE HEALTH STUDY IN PATIENTS DIABETES MELLITUS," IJMLST, vol. 2, no. 2, pp. 85–92, Aug. 2020, doi: 10.33086/ijmlst.v2i2.1565.

[185] B. O. Idonije, O. Festus, and O. M. Oluba, "Plasma Glucose, Creatinine and Urea Levels in Type 2 Diabetic Patients Attending A Nigerian Teaching Hospital," Research J. of Medical Sciences, vol. 5, no. 1, pp. 1–3, Jan. 2011, doi: 10.3923/rjmsci.2011.1.3.

[186] F. Azeez, S. Sultan, and L. Othman, "Estimation of Urea and Creatinine in Type 2 Diabetes Mellitus Patients," in Proceedings of the Proceedings of the 1st International Multi-Disciplinary Conference Theme: Sustainable Development and

Smart Planning, IMDC-SDSP 2020, Cyperspace, 28-30 June 2020, Cyberspace: EAI, 2020. doi: 10.4108/eai.28-6-2020.2298519.

[187] P. S. P. Rudy, R. T. Kuswardhani, I. G. P. S. Aryana, N. Astika, I. B. P. Putrawan, and N. K. R. Purnami, "Correlation between albumin serum and frailty in geriatric inpatient and outpatient clinic at Sanglah Hospital Denpasar," Intisari Sains Medis, vol. 12, no. 3, pp. 897–900, Dec. 2021, doi: 10.15562/ism.v12i3.1137.

[188] C. Haller, "Hypoalbuminemia in Renal Failure: Pathogenesis and Therapeutic Considerations," Kidney Blood Press Res, vol. 28, no. 5–6, pp. 307–310, 2005, doi: 10.1159/000090185.

[189] C. J. Wiedermann, "Hypoalbuminemia as Surrogate and Culprit of Infections," IJMS, vol. 22, no. 9, p. 4496, Apr. 2021, doi: 10.3390/ijms22094496.

[190] D. C. Chang, X. Xu, A. W. Ferrante, and J. Krakoff, "Reduced plasma albumin predicts type 2 diabetes and is associated with greater adipose tissue macrophage content and activation," Diabetol Metab Syndr, vol. 11, no. 1, p. 14, Dec. 2019, doi: 10.1186/s13098-019-0409-y.

[191] O. Katar and O. Yildirim, "An Explainable Vision Transformer Model Based White Blood Cells Classification and Localization," Diagnostics, vol. 13, no. 14, p. 2459, Jul. 2023, doi: 10.3390/diagnostics13142459.

[192] Y. Arai et al., "Low white blood cell count is independently associated with chronic kidney disease progression in the elderly: the CKD-ROUTE study," Clin Exp Nephrol, vol. 22, no. 2, pp. 291–298, Apr. 2018, doi: 10.1007/s10157-017-1441-6.

[193] M. Korppi, L. Kröger, and M. Laitinen, "White blood cell and differential counts in acute respiratory viral and bacterial infections in children," Scand J Infect Dis, vol. 25, no. 4, pp. 435–440, 1993, doi: 10.3109/00365549309008524.

[194] N. Ishimine et al., "Combination of white blood cell count and left shift level real-timely reflects a course of bacterial infection," J Clin Lab Anal, vol. 27, no. 5, pp. 407–411, Sep. 2013, doi: 10.1002/jcla.21619.

[195] T. Adane, F. Asrie, Z. Getaneh, and S. Getawa, "White blood cells and platelet profiles of diabetic patients at University of Gondar specialized referral hospital: A comparative cross-sectional study," J Clin Lab Anal, vol. 35, no. 6, p. e23808, Jun. 2021, doi: 10.1002/jcla.23808.

[196] P. C. Calder, P. Yaqoob, F. Thies, F. A. Wallace, and E. A. Miles, "Fatty acids and lymphocyte functions," Br J Nutr, vol. 87, no. S1, pp. S31–S48, Jan. 2002, doi: 10.1079/BJN2001455.

[197] Z. Guo, Z. Zhang, M. Prajapati, and Y. Li, "Lymphopenia Caused by Virus Infections and the Mechanisms Beyond," Viruses, vol. 13, no. 9, p. 1876, Sep. 2021, doi: 10.3390/v13091876.

[198] N. Kuwae, J. D. Kopple, and K. Kalantar-Zadeh, "A low lymphocyte percentage is a predictor of mortality and hospitalization in hemodialysis patients," CN, vol. 63, no. 01, pp. 22–34, Jan. 2005, doi: 10.5414/CNP63022.

[199] M. A. El-Salam, "Peripheral Blood Lymphocyte Subsets Counts in Children on Regular Hemodialysis," IJI, vol. 3, no. 1, p. 1, 2015, doi: 10.11648/j.iji.20150301.11.

[200] A. E. Emmanuel, A. E. Mathias, T. M. Jessy, and F. M. Isaac, "Correlation of lymphocyte count with serum calcium level and neutrophil-to-lymphocyte ratio in end stage renal disease patients undergoing hemodialysis in Adamawa State,

Nigeria," Int. J. Med. Med. Sci., vol. 9, no. 5, pp. 47–50, May 2017, doi: 10.5897/IJMMS2016.1275.

[201] M. Narjis, M. Noreen, S. Z. Safi, N. E. Ilahi, S. Y. Alomar, and A. F. Alkhuriji, "Cross talk between complete blood count and progression of type II diabetes mellitus," Journal of King Saud University - Science, vol. 33, no. 6, p. 101492, Sep. 2021, doi: 10.1016/j.jksus.2021.101492.

[202] S. M. G. Trivigno, G. F. Guidetti, S. S. Barbieri, and M. Zarà, "Blood Platelets in Infection: The Multiple Roles of the Platelet Signalling Machinery," IJMS, vol. 24, no. 8, p. 7462, Apr. 2023, doi: 10.3390/ijms24087462.

[203] C. C. F. M. J. Baaten et al., "Platelet Abnormalities in CKD and Their Implications for Antiplatelet Therapy," CJASN, vol. 17, no. 1, pp. 155–170, Jan. 2022, doi: 10.2215/CJN.04100321.

[204] Dr. M. A. Aashitha P, Dr. S. K. Chander U2, and Dr. M. E, "A Correlative Study of Platelet Indices in Different Stages of Chronic Kidney Disease Patients in A Tertiary Care Centre," Saudi Journal of Pathology and Microbiology, doi: 10.36348/sjpm.2021.v06i10.009.

[205] A. Assinger, "Platelets and infection - an emerging role of platelets in viral infection," Front Immunol, vol. 5, p. 649, 2014, doi: 10.3389/fimmu.2014.00649.

[206] O. Orasan et al., "Thrombocytopenia in end-stage renal disease and chronic viral hepatitis B or C," JMMS, vol. 5, no. 2, pp. 236–243, Oct. 2018, doi: 10.22543/7674.52.P236243.

[207] Z. Hekimsoy, B. Payzin, T. Ornek, and G. Kandoğan, "Mean platelet volume in Type 2 diabetic patients," J Diabetes Complications, vol. 18, no. 3, pp. 173–176, 2004, doi: 10.1016/S1056-8727(02)00282-9.

[208] B. F. Zuberi, N. Akhtar, and S. Afsar, "Comparison of mean platelet volume in patients with diabetes mellitus, impaired fasting glucose and non-diabetic subjects," Singapore Med J, vol. 49, no. 2, pp. 114–116, Feb. 2008.

[209] K. H. A. Naeem, M. A. H. Hazari, F. Khatoon, F. Bahmed, and F. Mohammedi, "Influence of glycaemic control on platelet count in type II diabetics in absence of vascular complications," MIJOPHY, vol. 5, no. 2, pp. 22–24, 2017, doi: 10.26611/103524.

[210] Y. Ito et al., "Tissue Sodium Accumulation Induces Organ Inflammation and Injury in Chronic Kidney Disease," IJMS, vol. 24, no. 9, p. 8329, May 2023, doi: 10.3390/ijms24098329.

[211] S. Borrelli et al., "Sodium Intake and Chronic Kidney Disease," Int J Mol Sci, vol. 21, no. 13, p. 4744, Jul. 2020, doi: 10.3390/ijms21134744.

[212] R. N. Khan, F. Saba, S. F. Kausar, and M. H. Siddiqui, "Pattern of electrolyte imbalance in Type 2 diabetes patients: Experience from a tertiary care hospital," Pak J Med Sci, vol. 35, no. 3, pp. 797–801, 2019, doi: 10.12669/pjms.35.3.844.

[213] S. Yamada and M. Inaba, "Potassium Metabolism and Management in Patients with CKD," Nutrients, vol. 13, no. 6, p. 1751, May 2021, doi: 10.3390/nu13061751.

[214] H. Nagasu et al., "The Impact of Potassium Binders on Mortality in Patients with Hyperkalemia: A Single-Center Study," Kidney and Dialysis, vol. 3, no. 3, pp. 244–254, Jun. 2023, doi: 10.3390/kidneydial3030022.

[215] Z. Rafique et al., "Hyperkalemia and Electrocardiogram Manifestations in End-Stage Renal Disease," IJERPH, vol. 19, no. 23, p. 16140, Dec. 2022, doi: 10.3390/ijerph192316140.

[216] S. Bianchi, F. Aucella, L. De Nicola, S. Genovesi, E. Paoletti, and G. Regolisti, "Management of hyperkalemia in patients with kidney disease: a position paper endorsed by the Italian Society of Nephrology," J Nephrol, vol. 32, no. 4, pp. 499–516, Aug. 2019, doi: 10.1007/s40620-019-00617-y.

[217] A. Sarnowski, R. M. Gama, A. Dawson, H. Mason, and D. Banerjee, "Hyperkalemia in Chronic Kidney Disease: Links, Risks and Management," Int J Nephrol Renovasc Dis, vol. 15, pp. 215–228, 2022, doi: 10.2147/IJNRD.S326464.

[218] T. Petnak et al., "Serum Chloride Levels at Hospital Discharge and One-Year Mortality among Hospitalized Patients," Medical Sciences, vol. 8, no. 2, p. 22, May 2020, doi: 10.3390/medsci8020022.

Appendix

Normal Value for Laboratory Tests	
Test	**Values**
Interleukin-6 (IL-6)	≥7 pg/ml
Procalcitonin (PCT)	> 0.1 ng/ml
C-Reactive Protein (CRP)	0 - 6 mg/L
Serum Urea	10 - 50 mg/dL
Serum Creatinine	0.6 - 1.1 mg/dL
Serum Albumin	3.8 - 4.4 g/dL
Chloride	98 - 111 mmol/L
Potassium	13.7 – 19.9 mg/dL
Sodium	136 -146 mmol/L
White blood cells	$5.0 – 11.6 \times 10^9$/L
Lymphocytes	$1.3 – 4.0 \times 10^9$/L
Platelets	$150 – 450 \times 10^9$/L

الخلاصــة

يعد الانترلوكين-٦، الذي تم اكتشافه في عام ١٩٨٦، واحدًا من أكثر السيتوكينات التي تمت دراستها في أمراض مزمنة. فهو يزيد الالتهاب سوءًا عن طريق تنشيط الخلايا البائية التي تؤثر على إنتاج بروتينات الطور الحاد الكبدية. تتناول هذه الدراسة تأثير بعض العوامل الديموغرافية على مرضى الكلى المصابين أو غير المصابين بداء السكري والذين أصيبوا بعدوى بكتيرية أو فيروسية. العينات تم جمعها ل ١٢٠ مريضا، مقسمة إلى ست مجموعات.

تضم المجموعات الأربع الأولى ٨٠ مريضاً يعانون من الفشل الكلوي المزمن مع وجود عدوى بكتيرية أو فيروسية بناءً على التقارير الطبية السابقة والفحوصات المخبرية والفحوصات السريرية من قبل استشاريين أمراض الكلى. ان عمر المرضى ٤٠ سنة فما فوق وتم ادخالهم الى مستشفى الحسين التعليمي في محافظة المثنى خلال الفترة من كانون الثاني ٢٠٢٣ الى نهاية آب ٢٠٢٣. وتمت مقارنة النتائج مع ٤٠ شخصا (٢٠ شخصا يعانون من مرض السكري) و (٢٠ شخصا أصحاء بفئة عمرية ٤٠ سنة وما فوق) كمجموعة ضابطة. تم سحب عينات الدم لتحليل الانترلوكين-٦ البروكالسيتونين و CRP واختبار وظائف الكلى والألبومين وكريات الدم البيضاء والخلايا الليمفاوية والصفائح الدموية و الكلور و البوتاسيوم والصوديوم .

وجد في هذه الدراسة أن مستوى الانترلوكين-٦ كان مرتفعا في المرضى الذين يعانون من الفشل الكلوي المزمن مع أو بدون داء السكري مع عدوى بكتيرية أو فيروسية، لكنه كان أعلى في المرضى الذين يعانون من عدوى بكتيرية مع أو بدون مرض السكري. ويظهر الشيء نفسه بالنسبة لـ CRP . كانت هناك زيادة في مستوى البروكالسيتونين في المرضى الذين يعانون من الفشل الكلوي المزمن مع أو بدون داء السكري مع عدوى بكتيرية. كانت هناك زيادة في مستويات اليوريا والكرياتينين و البوتاسيوم و الكلور ولكن انخفاض في مستويات الألبومين وكريات الدم البيضاء والخلايا الليمفاوية والصفائح الدموية لدى المرضى.

جمهورية العراق
وزارة التعليم العالي والبحث العلمي
جامعة المثنى
كلية العلوم
قسم الكيمياء

دور الانترلوكين-٦ مع بعض المعايير الكيموحيوية في شدة الإصابات الميكروبية لمرضى الكلى في محافظة المثنى

رسالة مقدمة الى

كلية العلوم / جامعة المثنى

كجزء من متطلبات نيل درجة الماجستير في الكيمياء

من قبل الطالب

أنوار اياد جابر

بكالوريوس علوم كيمياء ٢٠١٩

بأشراف

أ.د. جواد كاظم مريح

١٤٤٦ هـ ٢٠٢٤ م