Republic of Iraq
Ministry of Higher Education
and Scientific Research
University of Babylon
College of Sciences for Women
Department of Biology

Interactions between some clotting and inflammatory factors in Myocardial infarction patients

A Thesis Submitted to the Council of the College of Sciences for Women/ University of Babylon in Partial Fulfillment of the Requirements for The Degree of Master in Biology

By

Sara Abdul-khaliq Mahdi Al-Fatlawy

Supervised By

Prof. Dr. Dakhel Ghani Omran

2022 A.D. **1444 A.H.**

بِسۡمِ ٱللَّهِ ٱلرَّحۡمَٰنِ ٱلرَّحِيمِ

(وَيَسۡـَٔلُونَكَ عَنِ ٱلرُّوحِۖ قُلِ ٱلرُّوحُ مِنۡ أَمۡرِ رَبِّي وَمَآ أُوتِيتُم مِّنَ ٱلۡعِلۡمِ إِلَّا قَلِيلٗا)

صَدقَ اللهُ العليُ العظيم

سورة الاسراء

(الاية 85)

Supervisor Certification

I certify that this thesis entitled (**Interactions between some clotting and inflammatory factors in Myocardial infarction patients**) was prepared by (**Sara Abdul-khaliq Mahdi Al-Fatlawy**) under our supervision at the College of Science for Women, University of Babylon as a partial requirement for the degree of Master in Biology.

Signature
Name: Dr. Dakhel Ghani Omran
Scientific order: Prof.
Address: College of Sciences for women / University of Babylon
Date: / / 2022

In view of the available recommendation, I forward this thesis for dibate by the examination committee.

Signature
Name: Dr. Hadi Mezail Khudair
Scientific order: Prof.
Address: Head of Biology Department, College of Sciences for women / Babylon University
Date: / / 2022

Certification of Examining Committee

We, the member of examining committee, certify that we have read this thesis entitled (**Interactions between some clotting and inflammatory factors in Myocardial infarction patients**) and after examining the Master student (**Sara Abdul-khaliq Mahdi Al-Fatlawy**) in its contents in / / 2022 and that in our opinion it is adequate as a thesis for the degree of Master in Biology with degree ( ).

Committee Chairman:
Signature:
Name: Dr. Haider Kamil Zaidan
Scientific order: Professor
Address: Al-Mustaqbal College University
Date:

Committee Member
Signature:
Name: Dr.Hassan Ali Farman
Scientific order: Professor
Address: Al-Furat Al-Awsat Technical University
Date:

Committee Member
Signature:
Name: Manar Mohamad Hasan
Scientific order: Lecture Dr.
Address: Collage of Science for women/ University of Babylon
Date:

Committee Member (Supervisor)
Signature:
Name: Dr. Dakhel Ghani Omran
Scientific order: Professor
Address: Collage of Science for women/ University of Babylon
Date:

Date of examination: 9 / 11 / 2022

Deanship authentication of Science College for Women
Approved for the college committee of graduate studies.

Signature:
Name: Abeer Fauzi Murad
Scientific order: Professor
Address: Collage of Science for women/ University of Babylon
Date:

Dedication

To my mother who left us with her body, but her spirit still flutters in the sky of my life

To my father the ideal man who was my support after God, who was the reason i reached this stage

To my brothers, the bond the humerus and the forearm

And to all my family, I dedicate this work

Sara

Acknowledgement

Thanks and gratitude to God, first and foremost, praise be to God for the blessing of access and achievement.

Thanks and appreciation to the dear supervisor, Prof. Dakhel Ghani Omran for his support and assistance me to complete this work.

All thanks; Appreciation and gratitude to the Department of Biological Sciences and the staff of the College of Sciences for Women.

Thanks for the patients and healthy subjects and I am especially grateful to all the staff at Al-Imam Al-Sadiq Hospital, the Resuscitation Department, and Marjan Teaching Hospital, for their great assistance in collecting the study samples. Finally, I thank all my colleagues for their kind and friendly cooperation.

Researcher

Summary:

Myocardial infarction (MI) is one of the most ischemic heart diseases that results damage to cardiac muscle. The present study was employed to investigate some hematological parameters and biomarkers in patients affected with MI of both sexes.To investigate the activity of fibrinolytic system and the incidence of disease.The study was carried out in different locations including Marjan Teaching Hospital (Ischemic heart disease unit), Imam Al-sadiq Hospital, some private laboratories and Babylon university/College of Sciences for Women. The duration of study ranged between November 2021 to April 2022. A total number of subjects who had involved in the present study was eighty (80) individuals. Of those, twenty men and twenty women were affected with MI. The remaining individuals (40) were twenty men and twenty women whose health was normal and recruited as a control groups.

The ages of all individuals (patients and controls) were ranged between 40 to 70 years old. The patients and their control patients had also been classified according to their ages into four groups as follow (40-49, 50-59, 60-69, and 70-79 years old).

In briefly, the finding of this study showed that males affected with MI comprised 60% higher than females that constituted 40%. Moreover, the percentage ratios of patients with MI according to their ages were first group 15%, second group 30%, third group 30%, and fourth group 25% respectively.

Concerning body mass index (BMI), the patients who had BMI 25-33kg/m^2 constituted about 70% higher than those had BMI 29-23 kg/m^2 whose percentage ratio was 30%.

In regard hematological parameters, the results of red blood cells (RBCs), hemoglobin (Hb), total white blood cells (WBCs), granulocytes %, and lymphocytes % were significantly higher ($p<0.05$) in all patients (men and women) than of the control groups. However, values of Hb and RBCs record non-significant differences in all age groups of patients with MI in matching with healthy control.

According to correlation coefficients, the hematological parameters recorded the following data: the granulocytes were recorded significant negative correlation (r=-0.99, sig=0.0001) with lymphocytes. The Hb concentration pointed out a significant positive correlation (r=0.90, sig=0.0001) with RBCs of patients affected with MI. In contrast, Hb levels indicated a significant negative correlation (r=0.36, sig=0.021) with blood platelets of patients with MI.

Concerning biomarkers that involved in this study which included D-dimer, fibrinogen, Troponin, Tissue plasminogen activator -1(tPA-1), interleukin -6, and C-reactive protein (CRP), they showed a significant elevation ($p<0.01$) in all studied groups (men and women) of all ages. Furthermore, these parameters were significantly heightening ($p<0.05$) in patients who have BMI ranged between 25-33 kg/m^2 higher than whose BMI 19-23 kg/m^2.

The most studied biomarkers do not recorded significant correlations with other studied parameters except D-dimer, its results showed a significant negative correlation (r=-0.32, sig=0.042) with lymphocytes of MI patients. Inversely, there was a significant positive correlation (r=0.33, sig=0.035) with granulocytes of patients.

Values of troponin had a significant positive correlation (r=0.71, sig=0.0001) with Hb levels in MI patients, also its results having a significant positive correlation (r=0.63, sig=0.0001) with RBCs of patients subjects. But on the other hand, results of troponin exhibited a significant negative correlation (r=0.66, sig=0.0001) with blood platelets of tested MI patients.

Received operating characteristic curve (ROC) analyses were carried out on biomarkers to explain the sensitivity and specify of those biomarkers in MI disease, the results showed the following: D-dimer the arc under curve (AUC) was 0.740 and cutoff was 298.5, Troponin 0.700, and cutoff was 0.813, tPA-1 was 0.724 and cutoff was 5.175, Fibrinogen AUC was 0.816 and cutoff was 0.816, CRP AUC was 0.724 and cutoff was 6.150, and IL-6 AUC was 0.767 and cutoff was 8.950.

Conclusion of this study was obtained from this study and mentioned above, the resining of hematological parameters especially white blood cells inflammatory and clotting components might return to systemic inflammation, ageing, increased BMI, and harmonic Fluctuations these abnormalities may be worse and progress the development of disease.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

Abbreviations	Meaning
ACS	Acute Coronary Syndrome
ADP	Adenosine Diphosphate
AIS	Acute Ischemic Stroke
AMI	Acute Myocardial Infarction
APTT	Activated partial Thromboplastin Time
APR	Acute Phase Reaction
AUC	Area Under the receiving operating Curve
AV node	Atrioventricular Nodal
BMI	Body Mass Index
BMPs	Bone Morphogenetic Proteins
CAD	Coronary Artery Disease
CAM	Cell Adhesion Molecule
CBC	Complete Blood Count
CHD	Coronary Heart Disease
CRP	C-reactive Protein
CVAD	Central Venous Access Devices
CVD	Cardiovascular Disease
DIC	Disseminated Intravascular Coagulation
DVT	Deep Vein Thrombosis
ECG	Electrocardiograph
ECM	Extracellular Matrix
EDTA	Ethylene-Diamine-Tetra-Acetic Acid
ELISA	Enzyme-Linked Immunosorbent Assay
ERK	Extracellular-Signal-Regulated Kinase
ESR	Erythrocyte Sedimentation Rate
FDA	Food and Drug Administration Has Approved
FI	Fibrinogen
FIIa	Active Thrombin
FIX	Christmas Factor
FIXa	Active Christmas Factor
FV	Labile Factor (Proaccelerin)
FVa	Active Labile Factor (Proaccelerin)
FVII	Stable Factor
FVIIa	Active Stable Factor

FVIII	**Anti-hemophilic Factor**
FVIIIa	**Active Anti-hemophilic Factor**
FX	**Stuart Prower Factor**
FXa	**Active Stuart Prower Factor**
FXI	**Plasma Thromboplastin Antecedent**
FXIa	**Active Plasma Thromboplastin Antecedent**
FXII	**Hageman Factor**
FXIII	**Fibrin Stabilizing Factor**
FXIIIa	**Active Fibrin Stabilizing Factor**
GDFs	**Growth Differentiation Factors**
GP	**Glycoprotein**
Hb	**Hemoglobin**
HDL	**High Density Lipoprotein**
hsCRP	**High-Sensitivity C-reactive Protein**
IHD	**Ischemic Heart Disease**
III	**Tissue Factor (Tissue Thromboplastin)**
IL-1 β	**Interleukin-1 beta**
IL-10	**Interleukin-10**
IL-12	**Interleukin-12**
IL-15	**Interleukin-15**
IL-18	**Interleukin-18**
IL-6	**Interleukin-6**
IV	**Calcium Ions**
KB	**Kappa B**
L,ml,µl	**Liter, Milliliter, Microliter**
LAD	**Left anterior Descending**
LCX	**Left Circum Flex**
LDL	**Low Density Lipoprotein**
LMCA	**Left Main Coronary Artery**
LRRP1	**LDL Receptor-Relater Protein 1**
LSD	**Lowest Significant Differences**
LV	**Left Ventricle**
MCP-1	**Monocyte Chemoattractant Protein-1**
MHC	**Major Histocompatibility Complex**
MI	**Myocardial infarction**
MIC	**Minimum Inhibitory Concentration**

MIF	**Migration Inhibitory Factor**
MPV	**Mean Of Platelets Volume**
NO	**Nitric Oxide**
NSTEMI	**Non-ST-Elevation Myocardial Infarction**
PAI-1	**Plasminogen Activator Inhibitor-1**
PCI	**Pre-Cutaneous Coronary Intervention**
PE	**Pulmonary Embolism**
PLT	**Platelet**
PMN	**Polymorphonuclear**
PV	**Plasma Viscosity**
RBCs	**Red Blood Cells**
RCA	**Right Coronary Artery**
ROC	**Received Operating Characteristic**
rtPA	**Recombinant Tissue Plasminogen Activator**
SA node	**Sinoatrial Nodal**
SE	**Standard Error**
SPSS	**Statistical Package For Social Sciences**
STEMI	**ST-Elevation Myocardial Infarction**
TF	**Tissue Factor**
TGF-β	**Tumor Growth Factor beta**
TNF	**Tumor Necrosis Factor**
TNFα	**Tumor Necrosis Factor alpha**
TPA-1	**Tissue Plasminogen Activator-1**
UDMI	**Universal Definition Of Myocardial Infarction**
VSMCs	**Vascular Smooth Muscle Cells**
VWF	**Von Willebrand Factor**
WBCs	**White Blood Cells**
WHO	**World Health Organisation**

Chapter One
Introduction

1.1. Introduction:

Ischemic heart disease (IHD), also known as ischaemic cardiovascular disease (CVD), cerebrovascular disease, and peripheral arterial disease, is the most common cause of death in the world, CVD is a group of diseases that affect the heart and blood vessels and includes ischaemic heart disease (IHD) and cerebrovascular disease (Severino *et al.*, 2018). Ischemic heart disease (IHD) is a clinical disorder that is characterized by myocardial ischemia, which causes an imbalance between myocardial blood supply and demand, resulting to morbidity and death across the body, this condition is known as ischemic heart disease (IHD) (Smani *et al.*, 2020).

Ischemic heart disease (IHD) is often attributed to coronary artery disease (CAD), which is a condition characterized by the presence of an atherosclerotic plaque that causes a vascular obstruction of more than 50 percent, however there are other potential causes, on the other hand, coronary microvascular dysfunction, which is a condition of impaired vasomotor tone due to several different mechanisms, is able to provoke ischemic heart disease even in the absence of an atherosclerotic plaque, this is because it causes the tone of the vasomotor system to be disrupted, in point of fact, clinical results, angiographic findings, and autopsy findings all point to a diverse pathophysiology of IHD, which should not be connected solely with CAD (Lanza and Crea, 2010).

Angina pectoris is the most typical manifestation of myocardial ischemia (also called angina pectoris), pain in the chest that can also be described as discomfort in the chest, heaviness in the chest, tightness in the chest, pressure, aching, burning, numbness in the chest, fullness in the chest, or squeezing in the chest is angina, indigestion or heartburn-like symptoms are possible, but they don't last as long or are as severe as those associated with an acute myocardial infarction (Ferraro *et al.*, 2020).

Myocardial infarction (MI), more frequently referred to as a heart attack, is a medical condition that causes irreparable damage to the heart muscles and can even result in death, it is essential to make a prompt and correct diagnosis of a heart attack in order to avoid mortality, diagnostic tools for acute myocardial infarction include blood tests and electrocardiogram (ECG) signals (Baloglu *et al.*, 2019).

Under normal conditions, a thrombus is restricted to the immediate location of injury and does not obstruct flow to essential places, however, if the blood vessel lumen is already decreased, as it is in atherosclerosis, a thrombus might spread into otherwise normal vessels under pathologic conditions, a thrombus that has grown in an unneeded location can impede blood flow in vital vessels; it can also demolish valves and other structures necessary for normal hemodynamic function, the most prevalent clinical syndromes include [acute myocardial infarction (AMI), deep vein thrombosis (DVT), pulmonary embolism (PE), acute ischemic stroke (AIS), acute peripheral arterial occlusion, and occlusion of indwelling catheters] (Rivera-Bou *et al.*, 2021).

It is possible that one's life could be in danger if they were to lose their blood, the human body cannot function without blood, hematopoiesis is responsible for the production of blood, which later serves as the transport medium for oxygen to the bodies various tissues and cells, the clotting system in the human body serves to prevent the loss of blood in the event of an injury, platelets, coagulation factors, prostaglandins, enzymes, and proteins are the contributors to the clotting mechanism that act together to form clots and stop a loss of blood, through vasoconstriction, adhesion, activation, and aggregation, the contributors form a transient plug to act as the cork to the leaking blood flow, clots are formed when the clotting mechanism acts together to form clots and stop a loss Shortly afterward, fibrin, which is the functional form of fibrinogen, helps to solidify this fragile platelet plug (Garmo *et al.*, 2021).

Inflammation is caused by variables that increase the risk of cardiovascular disease and can hinder the function of blood vessels, the activation of vascular smooth muscle cells, also known as (VSMCs), that is caused by cardiovascular risk factors results in an increase in the synthesis of the extracellular matrix and enables the migration of VSMCs from the vascular media to the intima (Mozos *et al.*, 2017).

Plasma inflammatory markers are thought to be potential tools for predicting cardiovascular risk (Libby *et al.*,2002 ; Vita *et al.*,2004). Since atherosclerosis is a syndrome that is caused due to the chronic inflammatory interactions of white blood cells (WBCs) in the wall of arteries, plasma inflammatory markers have been studied extensively in recent years (Drechsler *et al.*, 2010).

Endothelial function and the mechanical properties of the arteries are both negatively impacted when the inflammatory cascade is initiated, which is the case in acute and chronic inflammatory disorders as well as in systemic subclinical low-grade inflammation (Aznaouridis and Stefanadis, 2007). Endothelial cells, through a reduction in the bioavailability of nitric oxide (NO) and an increase in endothelin-1 due to inflammation, contribute to arterial stiffening, progressing arterial stiffening, in turn, further impairs endothelial function, thus causing a vicious cycle, endothelial cells contribute to arterial stiffening through a reduction in bioavailability of nitric oxide (NO) (McEniery *et al.*, 2003; Shirwany and Zou , 2010 and Avolio *et al.*, 2011). Reduced levels of NO also contribute to increased leukocyte adhesion (Vita *et al.*, 2004). In addition, endothelial dysfunction is linked to the activation of endothelial cells (ECs), which results in these cells becoming pro-inflammatory, elevating the expression of adhesion molecules, producing monocyte chemoattractant protein-1 (MCP-1), and involving cytokines in both leukocyte transmigration and activation (Vita *et al.*, 2004 ; Lacolley *et al.*, 2015).

In primary care, inflammatory markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and plasma viscosity (PV) are frequently used for the diagnosis and monitoring of inflammatory conditions such as infections, autoimmune conditions, cancers, and other inflammatory conditions include eosinophilic granulomatosis (Watson *et al.*, 2019).

The breakdown of fibrin by the body happens normally, it stops naturally occurring blood clots from becoming larger and causing more complications in the body, primary fibrinolysis describes the natural process through which clots are broken down, secondary fibrinolysis refers to the process by which blood clots are broken down as a result of a medical condition, a medication, or some other factor, the following are the two classifications that can be used to fibrinolytic drugs, which are also known as plasminogen activators in some circles: Agents that do not specifically target fibrin and fibrin-targeting agents (Brummel-Ziedins and Mann, 2018).

1.2.Aims of the study:

1. Highlight the relationship among age, gender, and BMI and incidence of MI.
2. Investigate the relationship between fibrinolytic system and MI.
3. Determine the relationship between MI and pro-inflammatory and inflammatory markers.

To carry out these aims the following parameters were conducted:-

1. Complete blood count.
2. BMI, gender, and ages.
3. Determination of some inflammatory mediators (CRP, IL-6, and fibrinolytic).
4. Estimation the activity of fibrinolytic system activity through measurement of tissue plasminogen activator.

Chapter Two
Literatures Review

2. Literatures Review:

2.1. Heart anatomy and physiology:

The heart is a hollow, four-chambered, muscular organ that consists of the upper right and left atria and the lower right and left ventricles, the atria are separated by a thin muscular wall called the interatrial septum; the ventricles are separated by a thick muscular wall called the interventricular septum, the heart actually functions as two separate pumps, the right atrium and ventricle act as one pump to propel unoxygenated blood to the lungs, at the same time, the left atrium and ventricle act as another pump to propel oxygenated blood throughout the systemic circulation, compared with the ventricles, the atria are small, thin-walled chambers, as a rule, they contribute little to the propulsive pumping activity of the heart (Jardins, 2020).

2.2. Blood Supply of the Heart :

2.2.1. Arterial Supply:

The right coronary artery (RCA) and the left main coronary artery (LMCA) extend from the aortic root to supply different regions of the heart. The RCA gives rise to the sinoatrial nodal branch of the right coronary artery, posterior descending artery branch of the RCA, and the marginal branch, the LMCA branches into the circumflex and The left anterior descending artery (LAD), the circumflex artery gives rise to the left marginal artery and posterior descending artery (in a left-dominant heart), the left anterior descending artery gives off the diagonal branches, the RCA supplies blood to the right side of the heart, the sinoatrial nodal branch of the RCA provides blood to the SA node, and the atrioventricular nodal artery delivers blood to the AV node, the marginal branch of the right coronary artery provides blood supply to the lateral portion of the right ventricle. The posterior descending artery branch supplies blood to the inferior aspect of the heart, the LMCA supplies blood to the left side of the

heart, the LAD provides blood to the anterior ventricular septum and the greater portion of the anterior portion of the left ventricle, the left circumflex (LCx) supplies blood to the lateral wall of the left ventricle and sometimes to the posterior inferior aspect of the heart when there is left heart dominance (Huang *et al*., 2017).

2.2.2. Venous Drainage:

The primary physiological function of the coronary veins is to carry deoxygenated blood from the myocardium and empty them into the chambers of the heart, coronary veins can be organized into two groups: the greater and smaller cardiac venous system (Miao and Makaryus, 2021). Greater cardiac venous system the greater cardiac venous system returns three-quarters of the deoxygenated blood from the myocardium to the cardiac chambers, the main venous vasculature of this system includes the coronary sinus and its tributaries, marginal veins, anterior cardiac veins, ventricular veins, and atrial veins (Loukas *et al*., 2009 ; Sirajuddin *et al*., 2020). Coronary sinus is the largest cardiac vein with multiple smaller vessels converging into it, located along the left posterior atrioventricular groove, the coronary sinus empties directly into the right atrium through the coronary sinus orifice, the venous tributaries that merge into the coronary sinus include the great cardiac vein, middle cardiac vein, small cardiac vein, left posterior ventricular, and oblique cardiac vein (Ortale *et al*., 2001; Loukas *et al*., 2009).

Great cardiac vein is starting from the apex of the heart and running parallel with the anterior interventricular artery, the great cardiac vein travels up along the anterior interventricular sulcus towards the base of the left atrium's auricle (Loukas *et al*., 2009). Once the vein reaches the left margin of the heart, it circumvents to the posterior side and eventually converges with the oblique vein

of the left atrium into the coronary sinus, the great cardiac vein empties the blood from both ventricles and the left atrium into the right atrium (Ortale *et al*., 2001; Spencer *et al*., 2013). Middle cardiac vein is originates from the apex of the heart but on the posterior side, the middle cardiac vein travels alongside the posterior interventricular artery in the posterior interventricular sulcus, and empties deoxygenated blood into the coronary sinus (Ortale *et al*., 2001). Small cardiac vein is located in the coronary sulcus between the right atrium and right ventricle, it eventually coalesces with the coronary sinus on the posterior side of the heart and drains to the right atrium (Ortale *et al*., 2001). The small cardiac vein also runs parallel to the right marginal branch of the right coronary artery on the anterior surface of the heart and collects deoxygenated blood from the posterior side of the right chambers (Von-Lüdinghausen, 2003).

Right marginal vein is located on the very inferior margin of the anterior surface of the heart and serves to empty the anterior and diaphragmatic walls of the right ventricle (Ortale *et al*., 2001). This small vein is also known for merging with the small cardiac vein in the coronary sulcus (Von-Lüdinghausen, 2003). Anterior cardiac veins return blood from the anterior right ventricle and drain them directly into the anterior right atrium, the anterior cardiac veins are more superior to the right marginal vein (Spencer *et al*., 2013).

Left Marginal Vein: also known as the obtuse marginal vein, the left marginal vein drains the myocardium of the left ventricle (Loukas *et al*., 2009). This vein travels along the left oblique marginal surface of the heart (Miao and Makaryus, 2021). Left and right ventricular veins vary from person to person, but generally, they function to drain the external walls of the ventricles (Whitmore, 1999). Left and right atrial veins consist of the septal veins, posterolateral veins, and posterosuperior veins that all carry the deoxygenated blood from the left atrium into the right atrium,the right atrial veins drain the right atrial walls (Von-Lüdinghausen *et al*., 1995).

Inferior vein of the left ventricle also known as the posterior vein of the left ventricle, it returns the deoxygenated blood from the inferior and lateral walls of the left ventricle into the coronary sinus, this vein travels between the middle and great cardiac veins (Von-Lüdinghausen, 2003). Oblique vein of the left atrium is a relatively small-sized vein that rounds obliquely and inferiorly towards the posterior left atrium, the vein is also observed to unite with the great cardiac vein to merge with the distal coronary sinus (Spencer *et al*., 2013).

Smaller cardiac venous system returns one-quarter of the deoxygenated blood from the inner layers of the myocardium to the cardiac chambers, this system is mainly composed of Thebesian veins draining deoxygenated blood from all sections of the myocardium chambers, thebesian veins also drain the right side of the heart more than the left side (Boeder *et al*., 2017).

2. 3. Heart Action:

The heart is a muscular pump that normally beats 70 to 90 times per minute in the resting adult and 130 to 150 times per minute in the newborn child, the cardiac cycle is one complete heartbeat composed of two phases: (1) systole (ventricular contraction) and (2) diastole (ventricular relaxation), each phase consists of a series of characteristic changes within the heart as it fins with blood and empties, the atrioventricular valves are closed during ventricular systole (contraction), and the blood is temporarily accommodated in the large veins and atria, the atrioventricular valves open once ventricular diastole (relaxation) occurs, and blood passively nows from the atria to the ventricles, atrial systole occurs when the ventricles are nearly full and forces the remainder of the blood in the atria into the ventricles (Wineski and Snell, 2019).

Each cycle begins with the generation of an action potential in the sinoatrial node, this node is located in the upper lateral wall of the right atrium near the opening of the cava superior vena and the effort flows from here at a speed of 0.3 m/s through both atria and then to the atrioventricular bundle and then into

the ventricles, because of these special arrangements of the transmitter system from the atria to the ventricles, there is a delay of 1.0 second during the passage of the heartbeat from the atria to the ventricles, this allows the atria to contract before the ventricles contract, thus pumping blood into the ventricles before the forceful contraction of the ventricles begins, the atria act as the primary pump for the ventricles, and in turn, the ventricles prepare the main source of energy to move blood through the vascular system of the body (Ganong, 2010).

2.4. Coronary Artery Disease:

Coronary heart disease develops when major blood vessels supplying the heart with blood, oxygen and nutrients become damaged or blocked due to plaque build-up that limits blood flow (Centers for disease control and prevention, 2019). Coronary artery disease (CAD) is the most common cause of angina and acute coronary syndrome and the most common cause of death worldwide, the world health organisation (WHO) has estimated that 3.8 million men and 3.4 million women die from cardiovascular disease (CVD) each year, and since 1990, more people have died from CVD than any other cause, it also has a devastating effect on quality of life, disability-adjusted life years, and a measure of healthy years of life lost (Colledge *et al.*, 2018). Coronary heart disease (CHD) can over time lead to debilitating heart disease, which includes angina pectoris, myocardial infarction, and heart failure (Forbes and Jackson, 2003)

2.5. Atherosclerosis:

Atherosclerosis is a complex inflammatory disease involving aberrant immune and tissue healing responses, which begins with endothelial dysfunction and ends with plaque development, instability and rupture (Hong, *et al.*, 2014).

The complex process of atherosclerosis begins when the endothelium of a normal vessel wall accumulates subendothelial lipid components, eventually forming fatty streaks, the lipid components in plasma, mainly low-density lipoprotein (LDL), are modified by oxygen radicals and enzymes, initiating an

inflammatory cascade within the subendothelial space causing damage and dysfunction, once activated, the endothelium secretes chemokines (e.g., CCL2) and expresses adhesion molecules (e.g., E-selectin and VCAM-1) to promote the adhesion of leukocytes and activated platelets to the endothelial layer, the first types of cells present in the lesions are monocytes, T cells and dendritic cells, monocytes become macrophages in the intima and ingest modified lipids to become foam cells (Hansson, 2005).

Macrophages in the atherosclerotic plaque can release multiple proinflammatory cytokines (IL-1β, IL-6, IL-12, IL-15, IL-18, TNF family members [such as TNF-α] and MIF), as well as anti-inflammatory cytokines, such as IL-10 and TGF-β family members (TGF-β1, BMPs, GDFs) (Shirai *et al.*,2015). Exposure of macrophages to cholesterol crystals and other irritants can trigger the inflammasome, which in turn aggravates local damage and repair pathways that eventually results in the development of vulnerable and unstable plaque (Wong *et al.*, 2012). Unstable plaques typically accumulate T cells and dendritic cells, (Niessner and Weyand, 2010 ; Ait-Oufella *et al.*, 2014), building a microenvironment prone to powerful immune activation events. Stimulated by antigen-presenting dendritic cells, T cells will recruit and activate immune effector cells that interact with vessel wall endothelial cells, smooth muscle cells and myofibroblasts to further promote atherogenesis (Legein *et al.*, 2013).

They cause the intimal smooth muscle cells overlying the plaque to become senescent and the collagen cross-links within the plaque to degrade, this results in thinning of the protective fibrous cap, making the lesion vulnerable to mechanical stress that ultimately causes erosion, fissuring or rupture of the plaque surface, any breach in the integrity of the plaque will expose its contents to blood and will trigger platelet aggregation and thrombosis that extend into the atheromatous plaque and the arterial lumen, this may cause partial or complete obstruction at the site of the lesion or distal embolisation, resulting in infarction or ischaemia of the affected organ. This common mechanism underlies: (1)

Stable angina Ischemia due to fixed atheromatous stenosis of one or more coronary arteries; (2) Unstable angina Ischemia caused by dynamic obstruction of a coronary artery due to plaque rupture or erosion with superimposed thrombosis; (3) Myocardial infarction: Myocardial necrosis caused by acute occlusion of a coronary artery due to plaque rupture or erosion with superimposed thrombosis; (4)Heart failure: Myocardial dysfunction due to infarction or ischemia; (5) Arrhythmia: Altered conduction due to ischaemia or infarction; (6) Sudden death: Ventricular arrhythmia, asystole or massive myocardial infarction; and (7) as well as other manifestations of atherosclerotic disease such as lower limb ischemia and stroke (Hong, *et al.*, 2015).

2.6. Atherosclerosis Risk Factors:

The exact causes and risk factors of atherosclerosis are unknown; however, certain conditions, traits, or habits may raise the chance of developing atherosclerosis, most risk factors including high cholesterol and LDL, low level of high density lipoprotein (HDL) in the blood, hypertension, tobacco smoke, diabetes mellitus, obesity, inactive lifestyle, or age can be controlled and atherosclerosis can be delayed or prevented (Weber and Noels, 2011 and Owen *et al.*,2011).

1-Unhealthy blood cholesterol and lipoproteins levels: Broadly, the ideal levels for cholesterol and various lipoproteins are as follows: Total cholesterol <5mmol/L, Cholesterol: HDL ratio <4, LDL cholesterol <3mmol/L ,HDL cholesterol 2lmmol/L 2;

2-High blood pressure Blood pressure is considered high if it stays at or above 140/90 mmHg over time, if you have diabetes or chronic kidney disease, high blood pressure is defined as 130/80 mmHg or higher;

3-Overweight and obesity refer to body weight that is greater than what is considered healthy for a certain height;

4-Lack of physical activity: A lack of physical activity can worsen other risk factors for atherosclerosis, such as unhealthy blood cholesterol levels, high blood pressure, diabetes and overweight and obesity;

5-Unhealthy diet: Foods that are high in saturated and Tran's fats, cholesterol, sodium and sugar can worsen other atherosclerosis risk factors;

6-Older age: Genetic or lifestyle factors cause plaque to build up in the arteries as with age, in men, the risk increases after the age of 45 and in women, the risk increases after the age of 55;

7-Family history of early heart disease: The one's risk for atherosclerosis increases if his father or a brother was diagnosed with heart disease before 55 years of age, or if your mother or a sister was diagnosed with heart disease before 65 years of age;

8-Inflammation is the body's response to injury or infection, damage to the arteries inner walls seems to trigger inflammation and help plaque grow;

9- High levels of triglycerides in the blood also may raise the risk for atherosclerosis, especially in women;

10- Untreated sleep apnea can raise the risk for high blood diabetes, pressure and even a heart attack or stroke;

11-Stress: The most commonly reported "trigger" for a heart attack is an emotionally upsetting event, especially the one involving anger; and 12-Alcohol: Heavy drinking can damage the heart muscle and worsen other risk factors for atherosclerosis (Rafieian-Kopaei *et al.*,2014).

2.7. Angina:

The term angina pectoris, proposed >2 centuries ago, is commonly considered to be synonymous with obstructive atherosclerotic epicardial coronary artery disease (CAD), the frequently reported association among angina pectoris (central chest pain), myocardial ischemia, and coronary atherosclerosis has

reinforced the concept that anginal pain and myocardial ischemia are almost exclusively caused by obstructive CAD (Ohman, 2016). The primary cause of angina is an imbalance between oxygen supply and oxygen demand in the heart, The most usual cause is coronary artery disease in which atherosclerotic plaque has narrowed the lumen of the vessel that supplies oxygen and nutrients to cardiomyocytes, when there is an increase in oxygen demand, as occurs with exertion, there is an oxygen supply–demand mismatch, such that the oxygen demand is greater than the supply through the narrowed vessel, even vessels that are in an earlier phases of atherosclerosis, before a severely flow-limiting lesion is present, can contribute to ischemia if the plaque is vulnerable and ruptures, some patients experience angina due to a reduced oxygen supply when the coronary arteries undergo vasospasm, Although coronary artery disease is usually thought of as disease of the large epicardial coronary arteries that course along the surface of the heart, there is now evidence that small intramural coronary arteries or microvessels can be diseased and contribute to myocardial ischemia, other causes of angina include hypertrophic cardiomyopathy, valve disease, and especially aortic stenosis; in these cases, again there is a mismatch between supply of oxygen and demand for oxygen by the heart (Kloner and Chaitman, 2017).

2.8. Acute Coronary Syndrome:

Acute coronary syndrome (ACS) refers to a group of conditions that include ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina, it is a type of coronary heart disease (CHD), which is responsible for one-third of total deaths in people older than 35, some forms of CHD can be asymptomatic, but ACS is always symptomatic (Alomari *et al.*, 2019; Kerneis *et al.*, 2019 and Zègre-Hemsey *et al.*, 2019). ACS should be distinguished from stable angina, which develops during physical activity or stress and resolves at rest. In contrast with stable angina, unstable angina occurs suddenly, often at rest or with minimal exertion, or at lesser

degrees of exertion than the individual's previous angina ("crescendo angina"), New-onset angina is also considered unstable angina, since it suggests a new problem in a coronary artery (Kar-mun and Schneider, 2009). ACS is a manifestation of CHD (coronary heart disease) and usually a result of plaque disruption in coronary arteries (atherosclerosis), The common risk factors for the disease are smoking, hypertension, diabetes, hyperlipidemia, male sex, physical inactivity, family obesity, and poor nutritional practices, Cocaine abuse can also lead to vasospasm (Voudris and Kavinsky, 2019; Pop *et al.*, 2019 and Bracey and Meyers, 2021).

A family history of early myocardial infarction (55 years of age) is also a high-risk factor, the underlying pathophysiology in ACS is decreased blood flow to part of heart musculature which is usually secondary to plaque rupture and formation of thrombus, sometimes ACS can be secondary to vasospasm with or without underlying atherosclerosis, the result is decreased blood flow to a part of heart musculature resulting first in ischemia and then infarction of that part of the heart (Singh *et al.*, 2021).

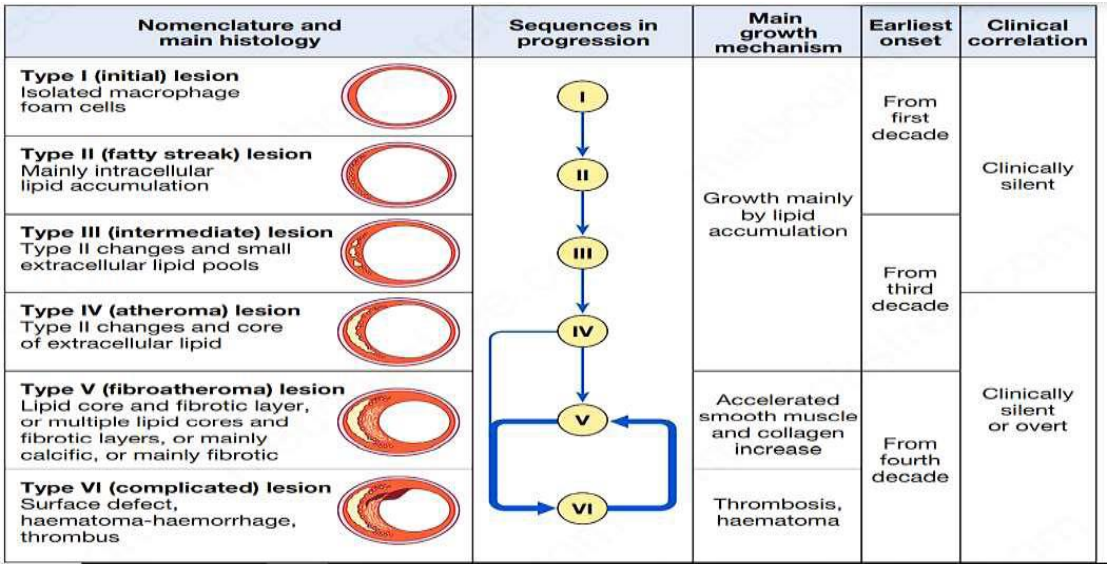

Figure (1) The six Stages of Atherosclerosis (Stary *et al.*, 1995).

2.9. Blood:

Blood is a body fluid in the circulatory system of humans that delivers necessary substances such as nutrients and oxygen to the cells and transports metabolic waste products away from those same cells (Thakare *et al.*, 2021).

Blood consists of a variety of specialized cells, called formed elements, which are suspended in a liquid matrix called plasma, blood makes up about 8 percent of the total body weight, the average total blood volume in the adult male is about 5 to 6 L and about 4 to 5 L in the adult female, the formed elements make up about 45 percent, and the plasma makes up about 55 percent of the total blood volume, the formed elements are composed of the red blood cells, the white blood cells (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and platelets, the plasma is composed of about 91 percent water, 7 percent proteins (albumins, globulins, and fibrinogen), and 2 percent other substances (electrolytes, nutrients, respiratory gases, waste products, and regulatory substances), the functions of blood are to (1) Transport oxygen to the tissue cells and carbon dioxide to the lungs; (2) Transport nutrients and waste products; (3) Transport processed molecules from one part of the body to another—for example, lactic acid is carried by the blood to the liver, where it is converted into glucose; (4) Transport regulatory hormones and enzymes; (5) Regulate the pH and osmosis; (6) Maintain body temperature; (7) Protect against foreign substance; and (8) Form clots (Jardins, 2020).

2.9.1. Red Blood Corpuscles (Erythrocytes):

A typical human red blood cell has a disk diameter of approximately 6.2–8.2 μm (Turgeon, 2004). Adult humans have roughly 20–30 trillion red blood cells at any given time, constituting approximately 70% of all cells by number, women have about 4–5 million red blood cells per microliter (cubic millimeter)

of blood and men about 5–6 million; people living at high altitudes with low oxygen tension will have more (Bianconi *et al*., 2013).

Red blood cells are thus much more common than the other blood particles: there are about 4,000–11,000 white blood cells and about 150,000–400,000 platelets per microliter, human red blood cells take on an average of 60 seconds to complete one cycle of circulation (Hillman *et al.*,2005; Pierigè *et al.*,2008).

The primary function of red blood Corpuscles (RBCs), or erythrocytes, is to transport oxygen from the lungs to the tissues and to transport carbon dioxide from the tissue cells to the lungs, the RBCs are produced in the red bone marrow in the spongy bone of the cranium, bodies of vertebrae, ribs, sternum, and proximal epiphyses of the humerus and femur, it is estimated that the RBCs are produced at the rate of 2 million cells per second, an equal number of worn-out RBCs are destroyed each second by the spleen and liver, the life span of a RBC is about 120 days (Jardins, 2020). The blood's red color is due to the spectral properties of the hemic iron ions in hemoglobin, each hemoglobin molecule carries four heme groups; hemoglobin constitutes about a third of the total cell volume, hemoglobin is responsible for the transport of more than 98% of the oxygen in the body (the remaining oxygen is carried dissolved in the blood plasma), the red blood cells of an average adult human male store collectively about 2.5 grams of iron, representing about 65% of the total iron contained in the body (Bridges, 2007).

2.9.2. Hemoglobin:

Hb has a critical role in oxygen delivery to the tissues, notably, the decrease of hemoglobin, defined as anemia, is common in patients with sepsis and overall in critical illness, it has been estimated that two-thirds of patients admitted to ICU have Hb levels < 120 g/L and that about 40% have Hb < 100 g/L; 97% of patients develops anemia by day 8 and 100% by day 13 of ICU hospitalization(Docherty *et al*., 2018).

The measurement of Hb concentration is pivotal for RBC transfusion decision-making, however, it is always important to evaluate if the benefits of additional oxygen-carrying capacity outweigh the risks, indeed, in the presence of important organ hypoperfusion, an increased Hb concentration leading to increased oxygen delivery could exacerbate organ dysfunction and worsen the patients' outcomes, the Surviving Sepsis Campaign 2016 recommends "RBC transfusion should occur only when hemoglobin concentration decreases to <7.0 g/L in adults in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, or acute hemorrhage" (Li *et al*., 2020).

2.9.3. White Blood Cells (Leukocytes):

White blood cells, also called leukocytes or leucocytes, are the cells of the immune system that are involved in protecting the body against both infectious disease and foreign invaders, all white blood cells are produced and derived from multipotent cells in the bone marrow known as hematopoietic stem cells, leukocytes are found throughout the body, including the blood and lymphatic system (Maton *et al.*, 1997).

The number of leukocytes in the blood is often an indicator of disease, and thus the white blood cell count is an important subset of the complete blood count, the normal white cell count is usually expressed as 4,000 to 11,000 white blood cells per microliter of blood, white blood cells make up approximately 1% of the total blood volume in a healthy adult (Alberts *et al.*, 2002).

All white blood cells are nucleated, which distinguishes them from the anucleated red blood cells and platelets, types of leukocytes can be classified in standard ways, two pairs of broadest categories classify them either by structure (granulocytes or agranulocytes) or by cell lineage (myeloid cells or lymphoid cells), these broadest categories can be further divided into the five main types: neutrophils, eosinophils, basophils, lymphocytes, and monocytes, these types are distinguished by their physical and functional characteristics, monocytes and

neutrophils are phagocytic, further subtypes can be classified (LaFleur-Brooks, 2008).

Granulocytes are distinguished from agranulocytes by their nucleus shape (lobed versus round, that is, polymorphonuclear versus mononuclear) and by their cytoplasm granules (present or absent, or more precisely, visible on light microscopy or not thus visible), the other dichotomy is by lineage: Myeloid cells (neutrophils, monocytes, eosinophils and basophils) are distinguished from lymphoid cells (lymphocytes) by hematopoietic lineage (cellular differentiation lineage) (Orkin and Zon 2008).

Neutrophils are the most abundant white blood cell, constituting 60-70% of the circulating leukocytes (Alberts *et al.*, 2002). They defend against bacterial or fungal infection, they are usually first responders to microbial infection; their activity and death in large numbers form pus, they are commonly referred to as polymorphonuclear (PMN) leukocytes, although, in the technical sense, PMN refers to all granulocytes, they have a multi-lobed nucleus, which consists of three to five lobes connected by slender strands (Saladin, 2012). This gives the neutrophils the appearance of having multiple nuclei, hence the name polymorphonuclear leukocyte, the cytoplasm may look transparent because of fine granules that are pale lilac when stained, neutrophils are active in phagocytosing bacteria and are present in large amount in the pus of wounds, these cells are not able to renew their lysosomes (used in digesting microbes) and die after having phagocytosed a few pathogens (Stevens *et al.*, 2002). Neutrophils are the most common cell type that seen in the early stages of acute inflammation, the average lifespan of inactivated human neutrophils in the circulation has been reported by different approaches to be between 5 and 135 hours (Pillay *et al.*, 2010 and Tak *et al.*, 2013).

Eosinophils compose about 2-4% of white blood cells in circulating blood, this count fluctuates throughout the day, seasonally, and during menstruation, it rises in response to allergies, parasitic infections, collagen diseases, and disease of the spleen and central nervous system, they are rare in the blood, but numerous in the mucous membranes of the respiratory, digestive, and lower urinary tracts, they primarily deal with parasitic infections, eosinophils are also the predominant inflammatory cells in allergic reactions, the most important causes of eosinophilia include allergies such as asthma, hay fever, and hives, and parasitic infections, they secrete chemicals that destroy large parasites, such as hookworms and tapeworms that are too big for any one white blood cell to phagocytize, in general, their nuclei are bi-lobed, The lobes are connected by a thin strand (Saladin, 2012).

Basophils are chiefly responsible for allergic and antigen response by releasing the chemical histamine causing the dilation of blood vessels, because they are the rarest of the white blood cells (less than 0.5% of the total count) and share physicochemical properties with other blood cells, they are difficult to study (Falcone *et al.*, 2000). They can be recognized by several coarse, dark violet granules, giving them a blue hue, the nucleus is bi- or tri-lobed, but it is hard to see because of the number of coarse granules that hide it, they excrete two chemicals that aid in the body's defenses: histamine and heparin, histamine is responsible for widening blood vessels and increasing the flow of blood to injured tissue, it also makes blood vessels more permeable so neutrophils and clotting proteins can get into connective tissue more easily, heparin is an anticoagulant that inhibits blood clotting and promotes the movement of white blood cells into an area, basophils can also release chemical signals that attract eosinophils and neutrophils to an infection site (Pillay *et al.*, 2010 and Saladin, 2012).

Lymphocytes are much more common in the lymphatic system than in blood, lymphocytes are distinguished by having a deeply staining nucleus that may be

eccentric in location, and a relatively small amount of cytoplasm, lymphocytes include: B cells make antibodies that can bind to pathogens, block pathogen invasion, activate the complement system, and enhance pathogen destruction ,T cells and Natural killer cells are able to kill cells of the body that do not display MHC class I molecules, or display stress markers such as MHC class I polypeptide-related sequence A (MIC-A), decreased expression of MHC class I and up-regulation of MIC-A can happen when cells are infected by a virus or become cancerous (Janeway *et al.*, 2001; Cohn *et al.*, 2014 and Omman *et al.*, 2020).

Monocytes, the largest type of white blood cell, share the "vacuum cleaner" (phagocytosis) function of neutrophils, but are much longer lived as they have an extra role: they present pieces of pathogens to T cells so that the pathogens may be recognized again and killed, this causes an antibody response to be mounted, monocytes eventually leave the bloodstream and become tissue macrophages, which remove dead cell debris as well as attack microorganisms, neither dead cell debris nor attacking microorganisms can be dealt with effectively by the neutrophils, unlike neutrophils, monocytes are able to replace their lysosomal contents and are thought to have a much longer active life, they have the kidney-shaped nucleus and are typically not granulated, and they also possess abundant cytoplasm (Pillay *et al.*, 2010).

2.9.4. Platelets:

Platelets, or thrombocytes, are the smallest of the formed elements in the plasma, platelets are roughly disk-shaped and average about 3 μm in diameter, the normal platelet count ranges from 250,000 to 500,000/mm3 of blood, the platelets play an important role in preventing blood loss from a traumatized area by (1) forming platelet plugs that seal holes in small blood vessels and (2) forming blood clots, which work to seal off larger tears in the blood vessels, the

platelets also contain serotonin, which, when released, causes smooth-muscle constriction and reduced blood flow (Jardins, 2020).

2.10. Hemostasis:

Hemostasis is the mechanism that leads to cessation of bleeding from a blood vessel, and it is a process that involves multiple interlinked steps, this cascade culminates into the formation of a “plug” that closes up the damaged site of the blood vessel controlling the bleeding, it begins with trauma to the lining of the blood vessel, the mechanism of hemostasis can divide into four stages, 1) constriction of the blood vessel, 2) formation of a temporary “platelet plug," 3) activation of the coagulation cascade, 4) formation of “fibrin plug” or the final clot, Hemostasis facilitates a series of enzymatic activations that lead to the formation of a clot with platelets and fibrin polymer, this clot seals the injured area, controls and prevents further bleeding while the tissue regeneration process takes place, once the injury starts to heal, the plug slowly remodels, and it dissolves with the restoration of normal tissue at the site of the damage (Smith *et al.*, 2015).

2.10.1. Mechanism :

There are several mechanisms as follow:

1- Vaso Constriction, within about 30 minutes of damage/trauma to the blood vessels, vascular spasm ensues, which leads to vasoconstriction, at the site of the disrupted endothelial lining, the extracellular matrix (ECM)/ collagen becomes exposed to the blood components,2- Platelet Adhesion, this ECM releases cytokines and inflammatory markers that lead to adhesion of the platelets and their aggregation at that site which leads to the formation of a platelet plug and sealing of the defect, the platelet adhesion is a complex process mediated by interactions between various receptors and proteins including tyrosine kinase receptors, glycoprotein receptors, other G-protein receptors as well as the von Willebrand Factor (VWF), the von Willebrand Factor functions via binding to

the Gp 1b-9 within the platelets, 3- Platelet Activation, the platelets that have adhered undergo very specific changes, they release their cytoplasmic granules that include ADP, thromboxane A2, serotonin, and multiple other activation factors, they also undergo a transformation of their shape into a pseudopodal shape which in-turn leads to release reactions of various chemokines, P2Y1 receptors help in the conformational changes in platelets (Periayah *et al.*,2017).

4- Platelet Aggregation, with the mechanisms mentioned above, various platelets are activated, adhered to each other and the damaged endothelial surface leading to the formation of a primary platelet plug (LaPelusa and Dave, 2021).

5- Extrinsic Pathway, the tissue factor binds to factor VII and activates it, the activated factor VII (factor VIIa) further activates factor X and factor IX via proteolysis, activated factor IX (factor IXa) binds with its cofactor – activated factor VIII (factor VIIIa), which leads to the activation of factor X (factor Xa), factor Xa binds to activated factor V (factor Va) and calcium and generates a prothrombinase complex that cleaves the prothrombin into thrombin, 6- Intrinsic Pathway, with thrombin production, there occurs conversion of factor XI to activated factor XI (factor XIa), factor XIa with activated factor VII and tissue factor converts factor IX to activated factor IX (factor IXa), the activated factor IX combines with activated factor VIII (factor VIIIa) and activates factor X, activated factor X (factor Xa) binds with activated factor V (factor Va) and converts prothrombin to thrombin, thrombin acts as a cofactor and catalysis and enhances the bioactivity of many of the aforementioned proteolytic pathways (Palta *et al.*, 2014).

7- Fibrin clot formation, the final steps in the coagulation cascade involve the conversion of fibrinogen to fibrin monomers which polymerizes and forms fibrin polymer mesh and result in a cross-linked fibrin clot, this reaction is catalyzed by activated factor XIII (factor XIIIa) that stimulates the lysine and

the glutamic acid side chains causing cross-linking of the fibrin molecules and formation of a stabilized clot (LaPelusa and Dave, 2021).

8- Clot Resolution (Tertiary Hemostasis), activated platelets contract their internal actin and myosin fibrils in their cytoskeleton, which leads to shrinkage of the clot volume, plasminogen then activates to plasmin, which promotes lysis of the fibrin clot; this restores the flow of blood in the damaged/obstructed blood vessels (Palta *et al*., 2014).

2.11. Blood Coagulation: -

Most if not all clotting factors as proteolytic enzymes called zymogens that are inactive state, to explain the active form of each enzyme, there is an addition of suffix letter "a" following Ruman number of that factor, the major site for synthesis and production of most anticoagulants and coagulants in circulation is liver with exception of clotting factor III, IV, and VIII are synthesized in extrahepatic tissue, Most of proteins are subjected to post-translational modifications in particular vitamin-K dependent clotting factor that is involved carboxylation of glutamic acid of clotting factor to ensure binding of calcium and other cation participating in clotting process (Monroe *et al*., 2010).

The pathways of coagulation is a mechanism of cascade reaction that involve maintain of hemostasis (Chaturved *et al.*, 2019).

There are two essentially pathways necessary for beginning of coagulation that are converged at FX, these pathways are extrinsic and intrinsic pathways, the extrinsic pathway is initiated by exposure of TF which localized in sub endothelium and thein it from complex with FVII which in turns mediates activation inactive FX to FXa (Grover and Mackman, 2018).

Concerning intrinsic pathway which described previously by Davie and Ratnoff (1964), this pathway factors such as FXII, FXI, and FIX and then activation of FVIII (FVIIIa) and FIX (FIXa), these activated factor completely mediate activation of FX to form FXa, following these reaction of both intrinsic

and extrinsic pathway, the FXa with its cofactor FVa produce prothrombinase complex activity which mediates siplit of inactive prothrombin to form active thrombin (FIIa), the FIIa considers the end of coagulation protease that mediates siplit of soluble fibrinogen to form insoluble fibrin threads, at the same time, FIIa activate fibrin stabilizing factor (FXIII) to form fibrin polymere. The intrinsic pathway of coagulation also becomes activated by effects of active forms of extrinsic and common pathway components (Mast, 2016).

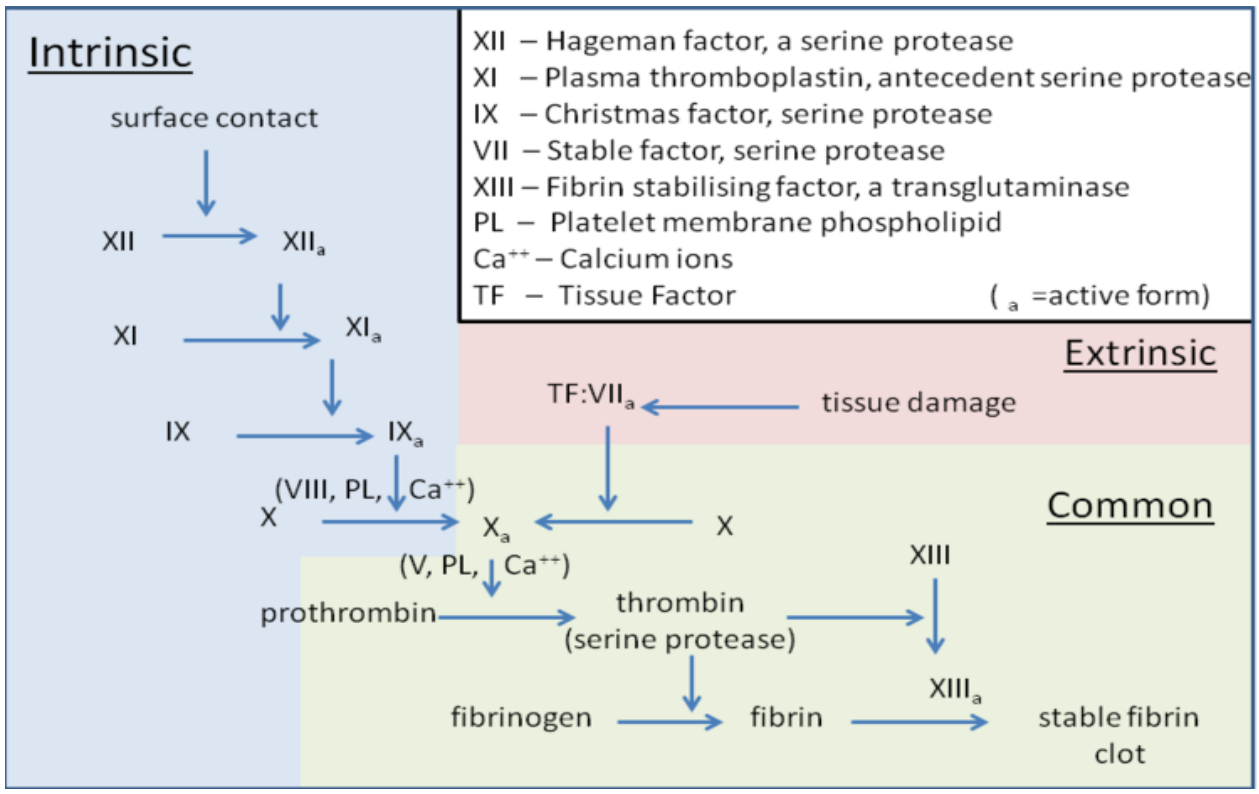

Figure (2): The three pathways that makeup the classical blood coagulation pathway (Pallister and Watson, 2010).

2.12. Fibrinogen:-

FI is produced by three closely related genes including FGA, FGB, and FGG, each of these genes can determine and specifity of the primary polypeptide structure of one of its own three polypeptide chains that are Aα, Bβ, and γ chains respectively (Chung *et al*., 1990).

All genes encoding human fibrinogen are located on chromosome 4 (Kant *et al*., 1985). Hepatocytes are the main synthesis of fibrinogen and then it exported into blood circulation, before FI its serection from hepatocytes, it altered and modified to assembly of its own synthesized polypeptide chains and then translocated into the endoplasmic reticulum in order to interact of polypeptide chains with chaperons (proteins enhance polypeptide chains folding) to help assembly and folding of FI polypeptide chains, this process also helps to distinguish between correctly folding and assembly of FI polypeptides, if there is in proper folding of polypeptide chains they are degraded (Tamura *et al*., 2013).

In normal subjects, FI production is high and its level up to 2-5 mg/ml, and it considers an acute phase protein in response to inflammation and its level can reach to 7mg/ml (Kattula *et al*., 2017).

It is well known that FI (fibrinogen) represents plenty protein in blood stream and has a half-life 3 to 5 days, the stable blood clot and fibrin meshwork is of importance to stop escap and lose of blood and intiates healing process at site of injury (Vilar *et al*., 2020).

In blood circulation, FI initiates hemostasis process and represents a precursor for fibrin as well as enhance assist in aggregation of activated platelets, red blood cells, macrophages, and fibroblasts on site of injury (Shakur and Robert, 2010). Fibrinogen exerts vital and crucial roles to maintain of hemostasis process, thrombin siplits fibrinogen polypeptides to produce fibrin strands

forming network that is required for formation of perfect clot (Levy *et al.*, 2011).

Together, fibrinogen and fibrin exerts major role in maintenance of hemostasis and also the main factor processes of thrombosis , healing of injuries, and other physiological and pathological states, fibrin is resulted when fibrinogen become cleaved by thrombin factor, after complete of perminant clot, fibrinolytic system that is composed from essential components including plasminogen activators which in turn activate further inactive zymogen called plasmin who has proteolytic activity to digest of fibrin (Weisel and Litvinov, 2017).

2.13. Tissue Factor (TF): -

Tissue factor is essential factors of blood clotting, it is expressed by vascular and nonvascular cells of the body and exerts prominent role in hemostasis through its function which involves initiation of blood coagulation (Mackam, 2004).

TF is one of transmembrane proteins as integral protein that expressed by different cells within the human body (Lawson *et al.*, 1992). It is associated primarily and expressed by both endothelial cells and smooth muscles of vessels as well as fibroblast of adventitia and pericytes of vessels, astrocytes in the brain, cardiac cells, epithelial cells of pulmonary alveoli, and endothelial cells of placenta (Fossel *et al*., 1994).

Furthermore, it is well documented that TF can be released and expressed by blood platelets and T lymphocytes and clearly demonstrated that it play a key role in various cellular signaling, gene expression, and surviral of cell (Cimmino and Cirillo, 2018).

According to biochemical point view, TF considers glycosylated protein of plasma membrane that has intracellular and extracellular domains, the mature shape of protein (TF) contains 263 amino acids as a linear polypeptide chain, of these amino acid, 219 amino are located in extracellular N-terminal domain that represents the long portion of TF and arranged as essential situation for binding of VIIa, there are 23 amino acids are embedded within membrane, the remaining amino acids (21) are reside within intracellular C-terminus domain and this short fragment of cytoplasmic domain has two sites of phosphorylation (Dorfleutner and Ruf, 2003and Sharma *et al*., 2004).

Genetically, TF gene are located on chromosome one of human (Guo *et al*., 2001). In regard to function of tissue factor that are related in blood clotting mechanism, the stable factor (FVII), is an enzyme mediates triggering of coagulation cascade, this factor must be initially bound with its specific receptor which named TF, the final complex (TF-FVII) increases the activity of antihemophilic factor (FVIII) (Pendunthi and Rao, 2008).

There are two forms of TF that can be detected as cryptic functional forms, FVII has ability to bind with both forms of TF at different range (Bach, 2006). When FVIIa-bind with TF on surfaces of cells trigger two mechanisms, firstly induce blood coagulation cascade and the second involves induction of intracellular signaling process which depends on the presence of protease-activated receptors which are localized on the cell surface (Rao and pendurthi, 2005).

The interaction occurring between TF and FVII are substantially required for hemostasis and thrombotic diseases, the FVII has trypsinserine protease activity that similar with other clotting factors having proteases activity, the TF can allosterically potentiates FVII through various processes including active site, direct interaction, and spatial stabilization (Gajsiewicz and Morrissey, 2016). The cellular signaling functions of TF include growth of tumor cells,

angiogenesis, and antiapoptotic effects (Hjortoe *et al*., 2004 and Versteeg *et al*., 2008).

2.14. Tissue Plasminogen Activator (tPA):-

Tissue plasminogen activator (tPA) is classified as a serine protease (enzymes that cleave peptide bonds in proteins), it is thus one of the essential components of the dissolution of blood clots, its primary function includes catalyzing the conversion of plasminogen to plasmin, the primary enzyme involved in dissolving blood clots (Jilani and Siddiqui, 2021).

Recombinant biotechnology has allowed tPA to be manufactured in labs, and these synthetic products are called recombinant tissue plasminogen activators (rtPA), examples of these drugs include alteplase, reteplase, and tenecteplase, these drugs have undergone various modifications to amplify their pharmacokinetic and pharmacodynamic properties, especially to prolong their short half-life in the circulation and further increase their fibrin specificity to prevent an unwanted fibrinolytic state, Indications for the use of tPA include the following: (1) Ischemic stroke (most common) in patients presenting to the treating facility within 3 hours (4.5 hours in certain, eligible people) after the onset of symptoms (Gravanis and Tsirka, 2008and Heiferman *et al.*, 2017), (2) Myocardial Infarction would be a delay of more than 1 to 2 hours before percutaneous transluminal coronary angioplasty (Rogers *et al.*, 1987), (3) Pulmonary embolism in massive pulmonary embolisms, causing severe instability due to high pressure on the heart (Niedermeyer *et al.*, 1993), (4) Thrombolysis (e.g., deep vein thrombosis) (Sharifi *et al.*, 2013).

2.14.1. Definitions :

(1) Alteplase is the normal human plasminogen activator and is FDA-approved for managing patients with ischemic stroke, myocardial infarction with ST-elevation (STEMI), acute massive pulmonary embolism, and those with central venous access devices (CVAD) (Demaerschalk *et al.*, 2016; Reed *et al.*, 2021). **(2)Reteplase** is a modified form of human tPA with similar effects but a faster onset and longer duration of action, it is currently FDA-approved for the management of acute myocardial infarction, preferred over alteplase due to its longer half-life, allowing it to be given as a bolus injection rather than through an infusion like alteplase (Zhao *et al.*, 2017; Wang *et al.*, 2018). (3)**Tenecteplase** is another modified version of tPA with a longer half-life, its indication is the management of acute myocardial infarction (Saran *et al.*, 2009).

2.14.2. Mechanism of Action:

tPA is a thrombolytic (i.e., it breaks up blood clots) formed by aggregation of activated platelets into fibrin meshes by activating plasminogen, more specifically, it cleaves the zymogen plasminogen at its Arg561-Val562 peptide bond to form the serine protease, plasmin. Plasmin, an endogenous fibrinolytic enzyme, breaks the cross-links between fibrin molecules, which are the structural support of the blood clot, and its activity is extremely short-lived, this short duration is because alpha 2-antiplasmin, an abundant inhibitor of plasmin, quickly inactivates it and restricts the action of plasmin to the vicinity of the clot, the following sequence summarizes the action of tPA: (1) tPA attaches to the fibrin on the clot surface, (2) It activates the fibrin-bound plasminogen, (3) Plasmin is subsequently cleaved from the plasminogen affiliated with the fibrin, (4) The plasmin breaks up the molecules of fibrin, and the clot dissolves, plasminogen activator inhibitor 1 (PAI 1) eventually terminates the catalytic activity of tPA by binding to it, and this inactive complex (PAI 1-bound tPA) is

removed from the circulation by the liver, more specifically via the scavenger receptor, LDL receptor-related protein 1 (LRRP1), in the nervous system, a neuronal-specific inhibitor of tPA, neuroserpin, acts similarly to PAI 1, and the LRRP1 internalizes the inactive tPA-neuroserpin complexes for removal from circulation (Kramer *et al.,* 2015and Bannish *et al.,* 2017).

2.15. D-dimer:-

D-dimer molecules are generated through the degradation of cross-linked fibrin during fibrinolysis, D-dimer generation requires the activity of three enzymes: thrombin, activated factor XIII (factor XIIIa), and plasmin, the process starts when thrombin generated by the coagulation system converts soluble fibrinogen to fibrin monomers, these monomers then form fibrin polymers through noncovalent interactions based on allosteric changes within the protein as a result of thrombin cleavage of fibrinopeptides from the N-terminal domain, fibrin is strengthened through interactions with factor XIII, which, after activation by thrombin, cross-links the D domains of adjacent fibrin monomers, plasmin digestion of the fibrin clot results in the D-dimer molecule (Johnson *et al*., 2019).

D-dimer measurements are done usually by central laboratory assays as well as by point-of-care assays with various cutoffs designed for both quantitative and qualitative measurements, the presence of D-dimer molecules is suggestive of intravascular coagulation because it can only be generated after thrombin formation and subsequent degradation of cross-linked fibrin, because of this, D-dimer measurements serve as a global marker of activation of the coagulation and fibrinolytic systems, and function as an indirect marker of thrombotic and subsequent thrombolytic activity (Olson, 2015).

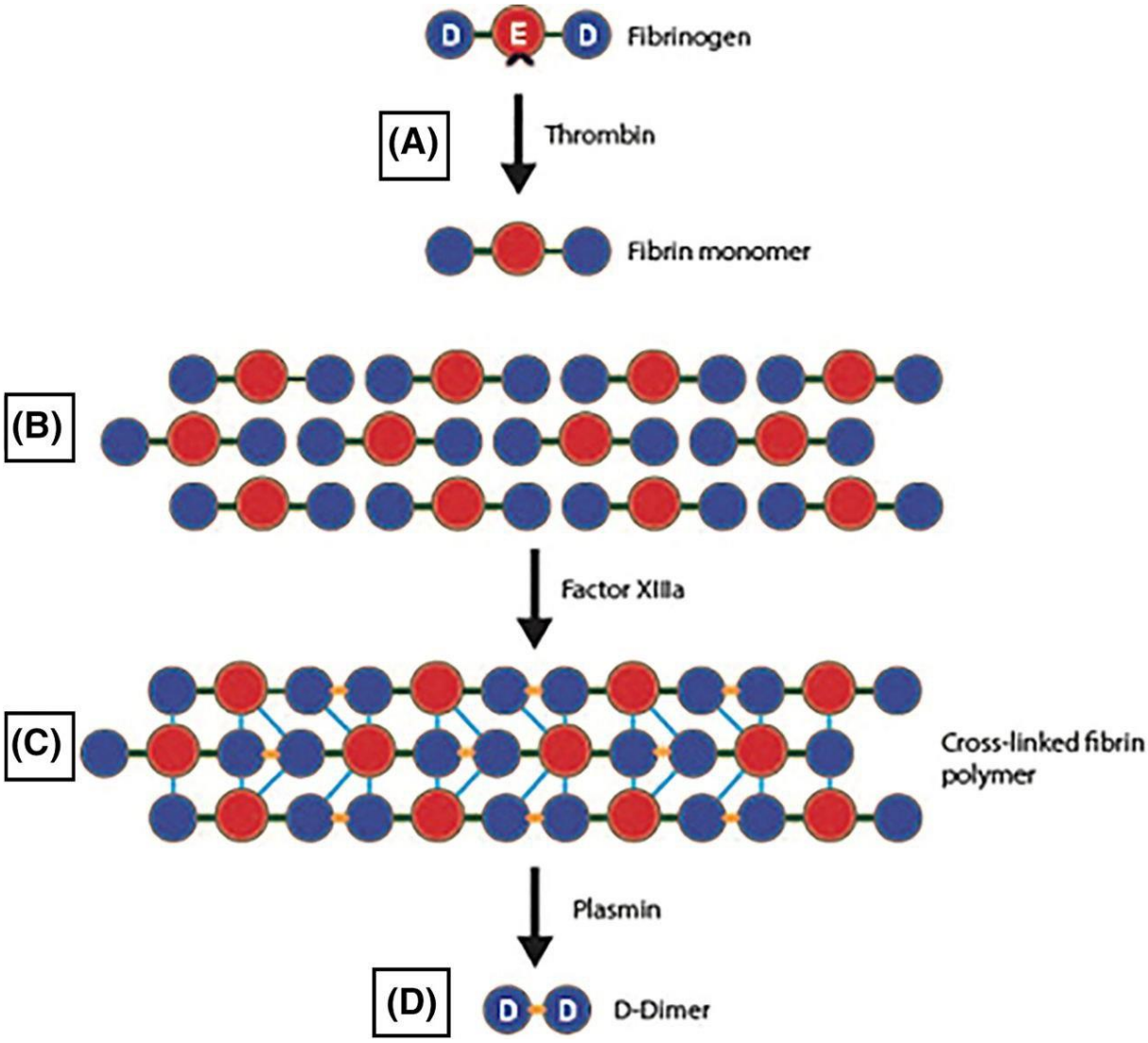

Figure (3): Generation of D-dimer following thrombin generation and fibrinolysis (Johnson *et al.*, 2019).

As a marker of rapid fibrin turnover and high thrombotic activation in both arterial and venous system, interest in D-dimer has grown over time, and its predictive role has been investigated in several acute and chronic cardiovascular care, (Giannitsis *et al.*, 2017). In patients with MI, high circulating D-dimer levels have been correlated with recurrent MI and poor prognosis (Oldgren *et al.*, 2001and Soomro *et al.*, 2016), and early reduction in plasma concentration

of D-dimer by Xime-lagatran administration was associated with decreased risk of new cardiovascular events (Christersson *et al.*, 2007).

In addition, there are some data indicating that D-dimer may be higher in MI patients experiencing no-reflow phenomenon (Erkol *et al.*, 2014). A severe condition in which high thrombotic burden interfere with complete restoration of myocardial blood supply after PCI, which is known to be correlated with adverse outcomes and poor prognosis (Rezkalla *et al.*, 2010).

2.16. Cytokines:-

2.16.1.IL-6:-

IL-6 is a pleiotropic cytokine which bridges the innate and adaptive immune systems (Jones, 2005). Perturbations or dysfunction in the transition from innate to adaptive immunity have long term consequences for inflammation and autoimmunity (Hoebe *et al.*, 2004). The acute response to IL-6, which is largely protective, to chronic, long term signaling leading to pathogenic inflammation and autoimmunity is an example of the varying faces of IL-6 (Kaplanski *et al.*, 2003).

IL-6 has a wide array of biological functions and is produced by many cells of the body, originally identified as a B-cell differentiation factor, IL-6 is now recognized as a cytokine that regulates many processes such as the acute-phase response, inflammation and hematopoiesis, IL-6 can be made by most tissues as well as virtually all cells of the immune system, it can signal either through membrane-bound receptors or, uniquely within the IL-6 family of cytokines, can signal in Trans, with a soluble form of its receptor, IL-6 has been shown to participate in neurogenesis, wound healing and hepatic regeneration (Streetz *et al.*, 2000 and Lin *et al.*, 2003). Acutely, IL-6 responds to almost all perturbations of homeostasis, however, when IL-6 remains elevated chronically, the protective roles IL-6 have maintaining tissue integrity and signaling the

immune response, are no longer required and constant signaling becomes associated with fibrosis and chronic inflammation, this dual role of IL-6, from acute and beneficial to chronic and harmful (Fontes *et al.*, 2015).

2.16.2. IL-6 in the Heart:-

The cellular response to IL-6 in the heart has been well characterized, cardiac tissue provides a revealing example where the duration of signaling, from acute to chronic, demonstrates the protective and pathogenic transition, IL-6 family signaling on cardiac myocytes is cardio protective during the acute response however, when remains elevated chronically, induces maladaptive hypertrophy and decreases contractile function (Terrell *et al.*, 2006).

Myocytes themselves make IL-6 in response to injury and in addition to increase IL-6 signaling, increased IL-6 production is associated with depressed cardiac function (Yang *et al.*, 2004). Acutely, IL-6-family cytokines protect myocytes against oxidative stress and its signaling induces an anti-apoptotic program (Yamauchi-Takihara and Kishimoto, 2000; Wollert and Drexler, 2001and Terrell *et al.*, 2006). However, IL-6-family signaling also depresses the basal contractility of the myocytes as well as the beta-adrenergic responsiveness of the cells leading to decreased function (Prabhu, 2004). IL-6 family signaling also induces gene expression in the myocytes that is associated with pathological hypertrophy (Wollert *et al.*, 1996).

The best characterized protective functions of IL-6 family signaling have been studied in ischemia-reperfusion injury and myocardial infarction which both induce IL-6 production by cardiac myocytes (Florholmen *et al.*, 2006). Increased IL-6 plays a role in late phase pre-conditioning that confers cardio protection (Smart *et al.*, 2006). STAT3, the downstream signaling molecule of IL-6, is also required for pre-conditioning (Dawn *et al.*, 2004). However, chronic elevated myocardial production of IL-6-family cytokines, which occurs

post-MI and in HF, have been associated with worse heart outcomes (Frangogiannis *et al.*, 2002 and Terrell *et al.*, 2006). IL-6 is consistently upregulated in the infarct zone after experimental MI and is associated with left ventricle (LV) enlargement (Gwechenberger *et al.*, 1999 and Frangogiannis, 2006). It is thought that the combined effects of IL-6, anti-apoptosis, depressed contractility and hypertrophy, will lead to preserved myocardium in the infarct border zone (Gwechenberger *et al.*, 1999).

2.17.C - Reactive Protein:-

C-reactive protein (CRP) is one of the common test parameters used in clinical practice, to assess, diagnose, and prognose inflammation, however, the role played by CRP in physiological processes is not clearly elucidated, CRP, belonging to pentraxin family of proteins shows a 1000-fold or more increase in concentration during the occurrence of an injury, inflammation or tissue death(Pepys and Hirschfield, 2003). The plasma half-life of CRP is about 19 hours and is constant under all conditions of health and disease, in addition to CRP, the levels of few other proteins termed as acute phase proteins (APR) are also increased during inflammation, CRP, the first acute-phase protein to be described, is a sensitive systemic marker of inflammation and tissue damage(Black *et al*., 2004). Precise response and ease of assay have made CRP an ideal marker of inflammation. CRP was discovered in 1930 by William Tillett and Thomas Francis of Rockefeller University, the researchers have reported that a third serologic fraction or ‘fraction C’ isolated from pneumococcus infected patients, was different from capsular polysaccharide and nucleoprotein fractions detectable by specific antibody response (Tillett and Francis, 1930).

Acute myocardial infarction (MI) results in an inflammatory response involved in myocardial repair (Frangogiannis, 2014). C-reactive protein (CRP), an acute phase reactant as downstream marker of inflammation, has been shown

to correlate with the extent of cardiac injury in the acute phase of MI (Orn *et al.*, 2009 and Reindl *et al.*, 2017). Although the resolution of post-MI inflammation is generally expected after 2 to 4 weeks, a prolonged inflammatory phase can occur (Prabhu and Frangogiannis, 2016). However, it is unknown whether the extent of acute cardiac injury influences residual high-sensitivity (hs) CRP levels at 1 month post-MI, low-grade inflammation measured by hsCRP measured at least 1 month after MI is indeed an established predictor of recurrent cardiovascular events (Ridker *et al.*, 2000; Pai *et al.*, 2004 and Ridker *et al.*, 2008).

2.18. Troponin:-

The measurement of cardiac troponin concentration in systemic venous blood has become a core component of the assessment of patients with acute and chronic cardiovascular disease, this is enshrined in the Universal Definition of Myocardial Infarction (UDMI) (Thygesen *et al.*, 2018). Heart disease remains the most common cause of death in the developed world with 1 in 10 patients still dying of a myocardial infarction (MI) (Rogers *et al*., 2000). With the advent of assays to measure cardiac troponins, the diagnosis and prognostication of acute coronary syndromes (ACS), including myocardial infarction, has greatly improved. A historical perspective of the development of the use of cardiac biomarkers has recently been published (Rosalki *et al*., 2004). Were the first to describe the measurement of cardiac troponin T (cTnT) (Katus *et al*.,1989).

This was followed by (Bodor *et al*., 1992). Who described the development of thecardiac troponin I (cTnI) assay, building on the work of (Cummins *et al*., 1987) both for the diagnosis of MI, after a number of classical studies, the cardiac troponins are now considered the ‘‘gold standard’’ biochemical test for the diagnosis of acute MI (AMI).

The troponin complex was first described in a letter to nature (Bailey, 1946). But it was the work by (Ebashi *et al*., 1968), that showed that the contraction of

striated muscle and not smooth muscle was regulated by a special protein complex, now known as the troponin located on actin filaments, with the development of techniques, such as site-directed mutagenesis, studies have yielded new details about the structure of the troponin complex.

The troponin complex consists of three subunits:

i. Troponin C (TnC): The component that binds calcium and regulates the activation of thin filaments during contraction by removing troponin I inhibition. It has a molecular weight of 18 kDa (Head *et al*., 1977).

ii. Troponin I (TnI): The inhibitory subunit that inhibits ATPAse activity of actinomyosin, its molecular weight is 22 kDa and is encoded for by chromosome 19q13.3 (Perry, 1999).

iii. Troponin T (TnT): The component that plays a structural role and binds the troponin complex to tropomyosin, TnT is also involved in activating actinomyosin ATPAse activity, its molecular weight is 37 kDa and its gene is present on chromosome 1q32 (Perry, 1998).

Chapter Three Materials and Methods

3. Materials and methods:

3.1. Materials:

3.1.1. Subjects of the Study:

The present study was carried out in different locations including Marjan Teaching Hospital (Ischemic heart disease unit) , Imam Al–sadiq Hospital , private laboratories, and Babylon university/College of Sciences for Women. The present study was began at November 2021 to April 2022**.**

A total selective number of subjects was eighty (80) of both men and women. Of those, twenty (20) men were complained from myocardial infarction and twenty (20) men were apparently healthy to serve as a control group. The remaining number (40) women, of them, twenty (20) women were affected with myocardial infarction and twenty (20) women recruited as a control group.

Ages of all subjects of the present study, ranged between 40-79 years old. The subjects (patients and healthy control) of the present study were classified according to their age in to four categories (40-49,50-59, 60-69,70-79 years old).

All patients attended to hospital and health care centers to check up their own myocardial infarction and received therapeutic drugs. In regard control subjects, they were enrolled from public health center, workers in hospitals, and persons who have normal medical history.

3.1.2.Excludid criteria:

The patients who had diabetes mellitus, malignant diseases pulmonary diseases, thyrotoxicosis and hypertension, and auto immune diseases. Furthermore, the women of this study do not intake contractive pills and no hormone replacement therapy.

3.1.3. Design of study: -

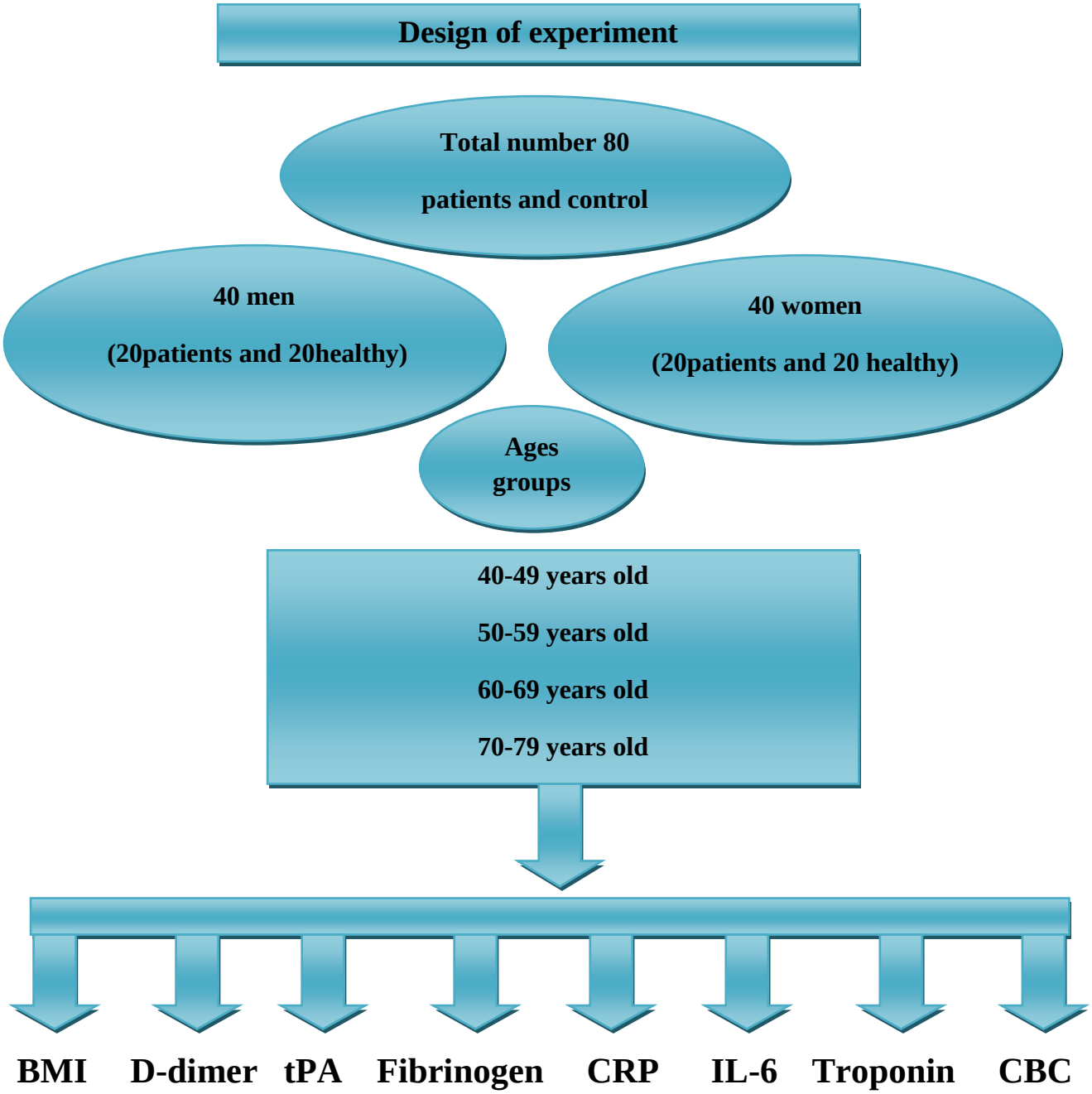

Figure (4): Design of study

3.1.4. Instruments: -

In the following table (3-1), the instruments and their origins that used in the present study: -

Apparatus and materials	Source	Company
Abbott PLUS	USA	Abbott
Centrifuge	Germany	Heattich
Deep Freezer	Germany	Concord
Disposable Syringes	Hungary	Dia Gon
EDTA Tube (3 ml)	USA	Afco
Eppendorf tubes	Jordan	CMA
Gel tube (6 ml)	USA	Afco
Geten1100	USA	Biotech
Gloves	Jordan	CMA
HumaClot Junior	Germany	Human
Micropipette Different sizes	Germany	Slamed
Pipette tips (blue)	USA	Applied Biosysyem
Pipette tips (Yellow)	USA	Applied Biosysyem
Plain tube (10 ml)	Jordan	CMA
Plate Reader for Elisa	USA	Awareness technolog
Refrigerator	Japan	Royal
Slides	China	Sail Brand
Sodium Citrate Tube (2 ml)	USA	Afco

3.1.5. Chemicals: -

Table (3-2) Kits that were used in the present study:

Kits chemical	Source	Company
C- reactive protein Kit	USA	Biotech
D-Dimer Kit	USA	Biotech
Fibrinogen Kit	Germany	Hemostat
Interleukin -6 Kit	USA	Biotech
Tissue plasminogen activator -1 Kit	China	BT LAB
Troponin Kit	Ireland	Abbott

3.2. Methods: -

3.2.1. Collection of Blood Samples: -

Samples of blood were collected from several locations of hospitals and health center cares of Babylon governorate (Marjan Medical City and Imam Al–sadiq Hospital).

Antecubital vein of left arm was selected. The area of collection was firstly warmed by massage to improve blood circulation and protrusion of the vein. Atourniquet was applied around the skin directly about 7 cm above the collectionsite. The skin was exactly sterilized and cleared with ethyl alcohol (70%) and then was permitted the skin to completely dry to avoid hemolysis of blood.

Needles were selected with 23 gauges and blood samples volumes were approximately 5 milliliters from each myocardial infarction patients and healthy control subjects.

Collected about five milliliters of venous blood from each patient and healthy control subjects. The blood was divided into three parts: first part (approximately two milliliters) was collected into EDTA, and the second part of the blood was placed in gel tube for thirty minutes and the third part of the blood was placed in sodium citrate tube for plasma and plasaced in centrifugation at 3000 rpm for 15 min; after that the serum collected and transferred to eppenedrof tube and kept in the freezer (-20c˚) for future analyses and each tube was gave a serial number to refer to each subject (patient and control).

3.2.2. Measurment of body mass index (BMI):

Body mass index is employed to measure weight adjusted for hight, it is a simple test of body to explore how much fat contained within the body and is calculated according to following equation:-

$$BMI = \frac{\text{weight (kg)}}{\text{Hight } (m^2)}$$ (Cole *et al*., 2000).

The limitations of BMI as follow:

BMI kg/m^2	**Weight status**
Below 18.5	Under weight
18.5-24.9	normal
25-29.9	Over weight
30 and above	obese

3.2.3. Hematological Tests:

3.2.3.1. Complete Blood Count (CBC) assay:

Whole blood sample in EDTA tube was used immediately to get complete blood count using automated 3-part hematology autoanalyzer, samples were swirled several times to mix the sample and then processed in the autoanalyzer to get result within 60 seconds, and the result printed out and recorded.

3.2.4. Determination of Tissue Plasminogen Activator-1 (TPA-1):

3.2.4.1. Principles of Method:

This kit is an Enzyme-Linked Immunosorbent Assay (ELISA). The plate has been pre-coated with Human tPA antibody. tPA present in the sample is added and binds to antibodies coated on the wells, and then biotinylated Human tPA Antibody is added and binds to tPA in the sample. Then Streptavidin-HRP is added and binds to the Biotinylated tPA antibody. After incubation unbound Streptavidin-HRP is washed away during a washing step. Substrate solution is then added and color develops in proportion to the amount of Human tPA . The reaction is terminated by addition of acidic stop solution and absorbance is measured at 450 nm.

Components which are supplied with TPA-1 Kit: -

Item	Specification	Storage
Standard solution(96ng/ml)	0.5ml x1	2-8 ℃
Pre-coated ELISA plate	12 * 4 well strips x 1	2-8 ℃
Standard Diluent	3ml x 1	2-8 ℃
Streptavidin-HRP	3ml x 1	2-8 ℃
Stop Solution	3ml x 1	2-8 ℃
Substrate Solution A	3ml x 1	2-8 ℃
Substrate Solution B	3ml x 1	2-8 ℃
Wash Buffer Concentrate(25x)	20ml x 1	2-8 ℃
Biotinylated Human tPA Antibody	1ml x 1	2-8 ℃
User Instruction	1	-
Plate Sealer	2 pics	-
Zipper bag	1 pic	-

3.2.4.2. Procedure of TPA-1 Measurement:

1. Prepare all reagents, standard solutions and samples as instructed. Bring all reagents to room temperature before use. The assay is performed at room temperature.

2. Determine the number of strips required for the assay. Insert the strips in the frames for use. The unused strips should be stored at 2-8°C.

3. Add 50µl standard to standard well. **Note**: Don't add biotinylated antibody to standard well because the standard solution contains biotinylated antibody.

4. Add 40µl sample to sample wells and then add 10µl anti-tPA antibody to sample wells, then add 50µl streptavidin-HRP to sample wells and standard wells (Not blank control well). Mix well. Cover the plate with a sealer. Incubate 60 minutes at 37°C.

5. Remove the sealer and wash the plate 5 times with wash buffer. Soak wells with 300ul wash buffer for 30 seconds to 1 minute for each wash. For automated washing, aspirate or decant each well and wash 5 times with wash buffer. Blot the plate onto paper towels or other absorbent material.

6. Add 50µl substrate solution A to each well and then add 50µl substrate solution B to each well. Incubate plate covered with a new sealer for 10 minutes at 37°C in the dark.

7. Add 50µl Stop Solution to each well, the blue color will change into yellow immediately.

8. Determine the optical density (OD value) of each well immediately using a microplate reader set to 450 nm within 10 minutes after adding the stop solution.

3.2.5. Measurement of C-reactive Protein (CRP):

3.2.5.1. Principle of Method: -

The test uses an anti-human CRP monoclonal antibody conjugated with CRP monoclonal antibody coated on fluorescence latex and another anti-human the test line. After the sample has been applied to the test strip, the fluorescence latex-labelled binds with the CRP in anti-human CP monoclonal antibody sample and antigen-antibody complex. This complex moves to the test forms a marked card antigen-antibody complex is captured on the test line by the detection zone by capillary action. Then marked anti-human CRP monoclonal antibody. The fluorescence intensity of the test line increases in proportion to the amount of CRP in sample.

Then insert test card into Getein1100 Immunofluorescenci Quantitative Analyzer/Getein1600 Immunofluorescenc Quantitative Analyzer (hereinafter referred to as Getein1130 and Getein1600), the concentration of CRP in sample will be measured and displayed on the screen. The value will stored in Getein1100/Getein1600 and available for downloading.

The result can be easily transmitted to the laboratory or hospital information system.

Components which are supplied with CRP kit:-

Item	Storage
hs-CRP+CRP test card in a sealed pouch with desiccant	4-30℃
Capillary pipet	4-30℃
Sample diluent	0-30℃
User manual:1 piece/box	4-30℃
SD card:1 piece/box	4-30℃

3.2.5.2. Procedure of CRP Test:-

1- Collect specimens according to user manual.

2- Test card, sample and reagent should be temperature before testing.

3- Confirm SD card lot No. in accordance with test kit lot No... Perform "SD card" calibration when necessary.

4- Remove the test card from the sealed pouch immediately before use. Label the test card with patient or control identification.

5- Put the test card on a clean table, horizontally placed.

6- Using sample transfer pipette, deliver 10 µl of sample into one tube of sample diluent, mix gently and thoroughly. Then, drop 100 pl of sample mixture into the sample port on the test card (for disposable capillary pipet using, please refer to the directions in the package).

7- Reaction time: 3 minutes. Insert the test card into Getein1100 and press "ENT" button or click on "Start" icon (for Android Getein 1100) after reaction time is elapsed. The result will be shown on the screen and printed automatically.

3.2.6. Measurement of Fibrinogen Concentration:

3.2.6.1. Principle of Method: -

HEMOSTAT FIBRINOGEN is based on the most commonly used method first described by Clauss[1].

Thrombin in optimised quantity is added to a prediluted plasma sample.

The measured clotting time is inversely proportional to the fibrinogen

concentration in the specimen.

Components which are supplied with Fibrinogen test:-

[RGT] 5 x 2 ml	**Fibrinogen reagent** (lyophilised)	
	Human thrombin	80-100 IU/ml
	Sodium azide	<0.01%
[BUF] 1 x 100 ml	**Imidazole buffered saline** (ready-to-use)	pH 7.4 ± 0.2
	Imidazole	0.05 mol/l
	Buffers and stabilisers	
[CAL] 2 x 1 ml	**Fibrinogen reference plasma** (lyophilised)	
	Human plasma	
	Sodium azide	<0.01%

Material required but not provided

[REF] 35001 HEMOSTAT CONTROL PLASMA NORMAL

[REF] 35002 HEMOSTAT CONTROL PLASMA ABNORMAL

Reagent Preparation, Storage and Stability

Reconstitute [RGT] with 2 ml and [CAL] with 1 ml distilled water (see Note). Store the reagent for 30 min. at 20...25°C, mix gently horizontally several times (5-10) before use, but do not shake, avoid the contact of the reagent with the stopper. Wait until the reagent reaches the working temperature.

Reconstituted [RGT] is stable for 3 days at 20…25°C, 7 days at 15…19°C and 7 days at 2...8°C.

Reconstituted [CAL] is stable for 4 hours when stored at 22°C.

[BUF] is ready-to-use. Store at 2...8°C. Opened vials are stable until the expiration date.

Manual Testing on HumaClot Junior:

Calibration Curve

HumaClot Junior		
Dilution	[CAL] ml	[BUF] ml
1:10	0.1	0.9
1:20	0.1	1.9
1:40	0.1	3.9

3.2.6.2. Procedure of Fibrinogen test:-

Bring [RGT] to room temperature before use and pre-warm test tubes.

Pipette diluted sample/ controls/[CAL] 100 µl

into pre-warmed test tubes

Incubate 3 min. at 37°C

Add [RGT] (room temperature) 50 µl

Start timer with addition of reagent. Record time required for clot

Formation.

3.2.7. Measurement of D-Dimer :

3.2.7.1. Principle of Method: -

The test uses conjugated with an anti-human D-Dimer monoclonal antibody fluorescence D-Dimer monoclonal antibody coated on the test line. After the latex and another anti-human sample has been applied to the test strip, the fluorescence latex-labelled anti-human D-Dimer monoclonal antibody binds complex. This complex moves to the test card detection zone with the D-Dimer in sample and forms a marked antigen-antibody by capillary action. Then marked antigen-antibody complex is captured on the test line by another anti-human D-Dimer monoclonal antibody. The fluorescence intensity of the test line increases in proportion to the amount of D-Dimer in sample.

Then insert test card into Getein1100/Getein1180 Immunofluorescence Quantitative Analyzer/automatically inserted by Getein1600 Immunofluorescence Quantitative Analyzer (hereinafter referred to as Getein1100, Getein1180 and Getein1600), the concentration of D-Dimer in sample will be measured and displayed on the screen. The value will be stored in Getein1100/Getein1180/Getein1600 and available for downloading. The result can be easily transmitted to the laboratory or hospital information system.

Components which are supplied with D-Dimer kit:-

Item	Storage
D-Dimer test card in a sealed pouch with desiccant	4-30℃
Disposable pipet	4-30℃
Sample diluent	0-30℃
User manual:1 piece/box	4-30℃
SD card:1 piece/box	4-30℃

3.2.7.2. Procedure of D-Dimer Test:-

1. Collect specimens according to user manual.

2. Test card, sample and reagent should be brought to room

temperature before testing.

3. Confirm SD card lot No. in accordance with test kit lot No..

Perform "SD card" calibration when necessary.

4. Remove the test card from the sealed pouch immediately before use. Label the test card with patient or control identification.

5. Put the test card on a clean table, horizontally placed.

6. Using sample transfer pipette, deliver 100 µl of sample into one tube of sample diluent, mix gently and thoroughly. Then drop 100 µl of sample mixture into the sample port on the test card.

7. Reaction time: 10 minutes. Insert the test card into Getein1100 and press "ENT" button or click on "Start" icon (for Android Getein 1100) after reaction

time is elapsed. The result will be shown on the screen and printed automatically.

3.2.8. Measurement of IL-6

3.2.8.1. Principle of Method: -

The test uses an anti-human IL-6 monoclonal antibody conjugated with fluorescence latex coated on the junction of nitrocellulose membrane and sample pad,and another anti-human IL-6 monoclonal antibody II coated on the test line. After the sample has been applied to the test strip, the fluorescence latex-labelled anti-human IL-6 antibody I binds with the IL-6 in sample and forms marked antigen-antibody complex. This complex moves to the test card detection zone by capillary action. Then marked antigen-antibody complex is captured on the test line by anti-human IL-6 antibody II. The fluorescence intensity of test line increases in proportion to the amount of IL- 6 in sample.

Then insert test card into Getein1100 Immunofluorescence Quantitative Analyzer/automatically inserted by Getein1600 Immunofluorescence Quantitative Analyzer (hereafter referred to as Getein1100 and Getein1600), the concentration of IL-6 in sample will be measured and displayed on the screen. The value will be stored in Getein1100/Getein1600 and available for downloading. The result can be easily transmitted to the laboratory or hospital information system.

Components which are supplied with IL-6 kit:-

Item	Storage
Getein IL-6 test card in a sealed pouch with desiccant	4-30℃
Disposable pipet	4-30℃
Whole blood buffer: 1 bottle/box	0-30℃
User manual:1 piece/box	4-30℃
SD card:1 piece/box	4-30℃

3.2.8.2. Procedure of IL-6 Test:-

1. Collect specimens according to user manual.

2. Test card, sample and reagent should be brought to room temperature before testing.

3. Confirm SD card lot No. in accordance with test kit lot No..

Perform "SD card" calibration when necessary.

4. Enter testing interface of Getein1100.

5. Remove the test card from the sealed pouch immediately before use. Label the test card with patient or control identification.

6. Put the test card on a clean table, horizontally placed.

7. Using sample transfer pipette, deliver 100 µL of sample into the sample port on the test card (for whole blood sample, one drop of whole blood buffer must be added after loading 100 µL sample on test card).

8. Reaction time: 15 minutes. Insert the test card into Getein1100 and start test after reaction time iS elapsed. The result will be shown on the screen and printed automatically.

3.2.9. Measurement of Troponin:

3.2.9.1. Principle of Method: -

The ARCHITECT STAT High Sensitive Troponin-I assay is a two-step immunoassay to determine the presence of cTnl in human plasma and serum using CMIA technology with flexible assay protocols, referred to as Chemiflex.

1- Sample and anti-troponin I antibody-coated paramagnetic microparticles are combined. The cardiac troponin present in the sample binds to the anti-troponin I coated microparticles.

2- After incubation and washing, anti-troponin I acridinium labeled conjugate is added to create a reaction mixture.

3- Following another incubation and wash cycle, Pre-Trigger and Trigger solutions are added to the reaction mixture.

4- The resulting chemiluminescent reaction is measured as relative light units (RLUs). There is a direct relationship between the amount of cTnl in the sample and the BLUs detected by the ARCHITECT System optics.

The concentration of cTnl iS read relative to a standard curve established with calibrators of known cTnl concentrations.

3.2.9.2. Procedure of Troponin Test:-

Specimen Dilution Procedures

Specimens with a troponin I value exceeding 50,000.0 pg/mL are flagged with the code "> 50,000.0 pg/mL" and may be diluted using the Automated Dilution Protocol or the Manual Dilution Procedure.

Automated Dilution Protocol:

The system performs a 1:10 dilution of the specimen and automatically calculates the concentration of the specimen before dilution and reports the result.

Manual Dilution Procedure:

Suggested dilution: 1:10

1. Add 25 µL of the patient specimen to 225 µL of ARCHITECT Multi-Assay Manual Diluent.

2. The operator must enter the dilution factor in the Patient or Control order screen. The system will use this dilution factor to automatically calculate the concentration of the sample before dilution and report the result. The result should be > 10.0 pg/mL (concentration) before the dilution factor is applied.

3.3. Statistical Analysis

Data was analyzed using SPSS(version 23, SPSS Inc. Chicago, Illinois, USA). Descriptive statistics (mean, standard Error), and differences were compared by two-way ANOVA at $p \leq 0.05$ by using least significant difference (LSD) among studied groups was $p \leq 0.05$. Also, the area analysis under ROC curve was used (Daniel, 1999).

Chapter Four
Results

4. Results:

4.1. Explanation of the relationship of myocardial infarction in relation to gender.

The result which was presented in the Figure 4-1 explained the incidence of myocardial infarction disease in males is greater than of females, since the percentage ratio of men was 56%, while the percentage ratio of females was 44%.

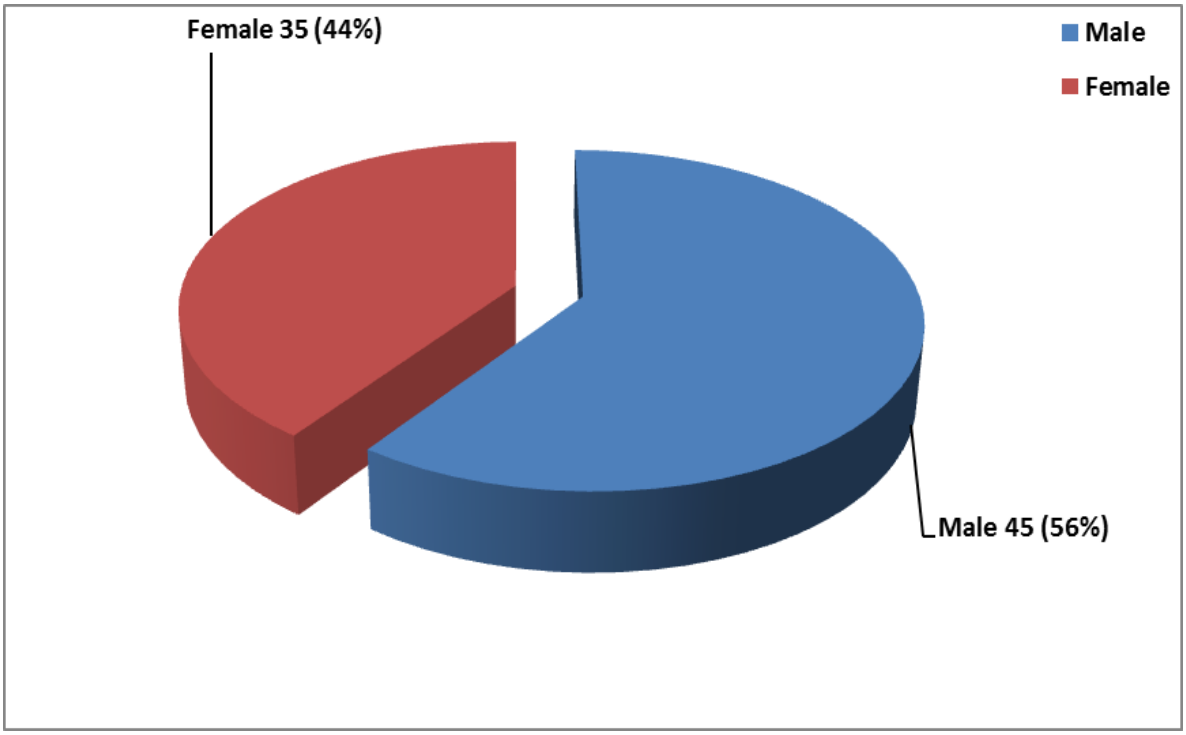

Figure (4.1): Explain the percentage ratio (%) of males and females affected with myocardial infraction.

4.2. Relationship of Age with Myocardial Infarction:

The values which were given in the Figure 4-2 pointed out the age groups with MI most affected were 31%, 38% in (50-59,60-69 years old) compared to the age group (70-79 years old) were 19% and (40-49 years) were 10%.

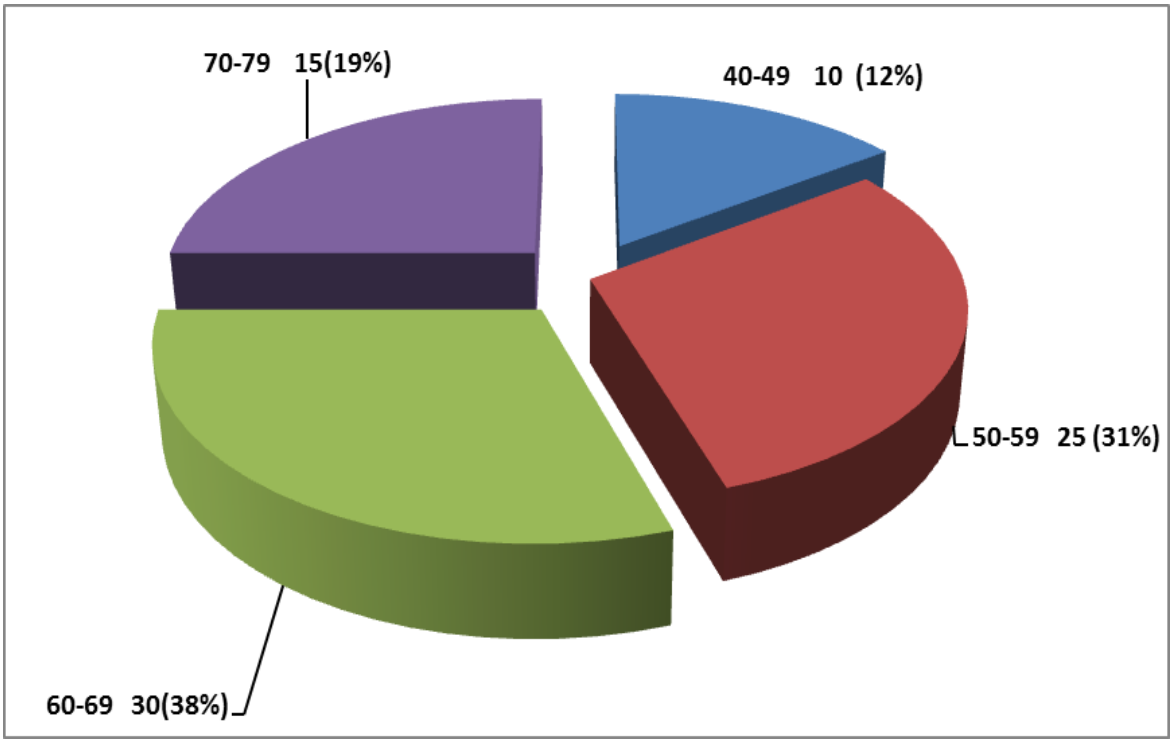

Figure (4.2): Represents the percentage ratio (%) of age groups of patients with myocardial infraction.

4.3. Relation of Body Mass Index and Myocardial Infarction:

Results that explained in the Figure 4-3 explained an increased incidence of MI were 70% in patients who had BMI equal 25-33kg/m² compared those to with BMI equal 19-23kg/m² were lower 30%.

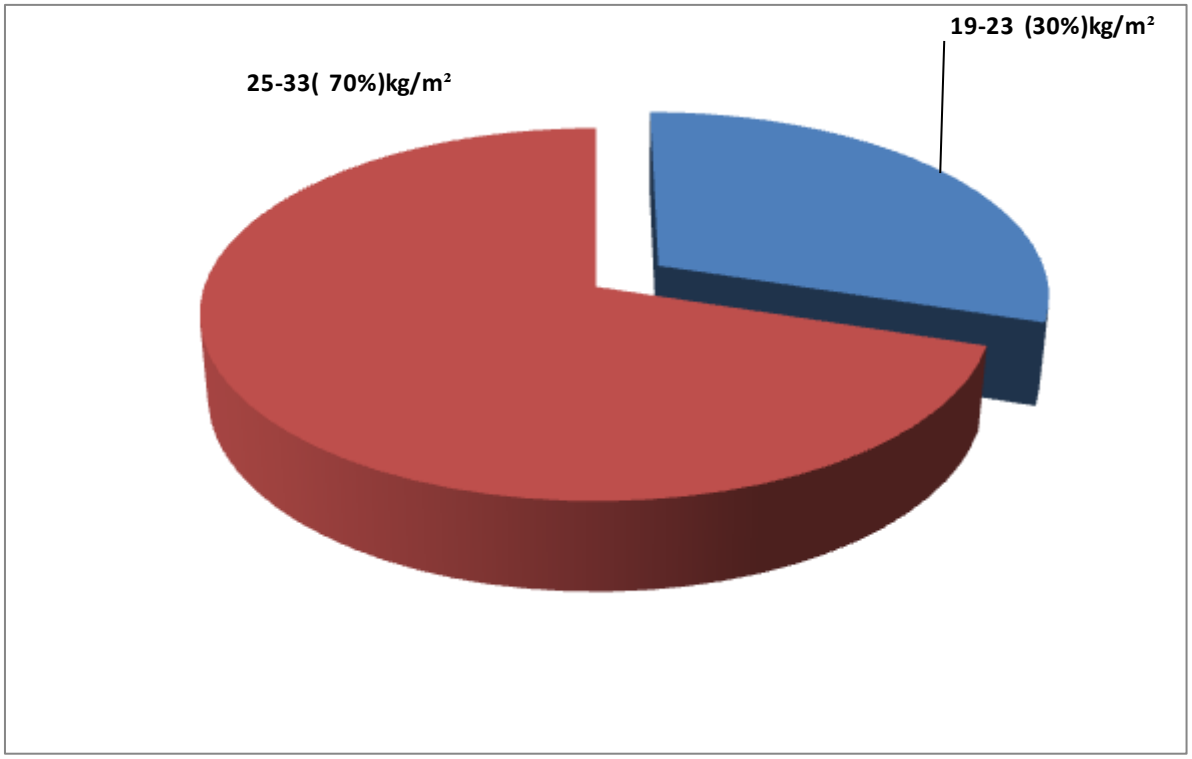

Figure (4.3): The Percentage Ratio (%) of Body Mass Index for Patients Affected with Myocardial Infarction.

4.5. Results of White Blood Count (WBC cell/mm^3), Granulocytes(%) , Lymphocyte(%), Hemoglobin (Hb g/dL) , Red Blood Count (RBC cell/mm^3), Platelet (PLT cell/mm^3) in Patient affected with myocardial infarction and those healthy control groups.

Value which were depicted in Table 4-1 indicated a significant different in the level of WBCs , granulocytes , lymphocytes, Hb and RBCs at level $p<0.05$ (8.04±0.2 cell/mm^3, 84.59±5.0 %, 14.01±1.5 %,12.67±2.2 g/dL, 4.67±0.2 cell/mm^3 respectively) in patient compared to control(5.04±0.1 cell/mm^3 , 70.46±6.0 %, 28.30±1.7 %, 12.14±1.1 g/dL and 4.95±0.1 cell/mm^3 respectivly). whereas platelets were non-significantly different ($p>0.05$) in patient (192.13±2.9 cell/mm^3) affected with MI in a comparison with those healthy subjects (186.00±5.2 cell/mm^3).

Table (4.1): Showed the results of hematological parameters WBC x10^3 cell/mm^3, Granulocytes%, Lymphocytes%, Hb g/dL, RBCs x10^9 cell/mm^3 and platelets x10^3 cell/mm^3 of patients affected with myocardial infarction.

Groups / Parameters	Patient (n=40)	Control (n=40)	Pvalue
	Mean ±S.E		
WBCs x10^3 (cell/mm^3)	8.04±0.2	5.04±0.1	≤0.0001**
Granulocytes (%)	84.59±5.0	70.46±6.0	≤0.0001**
Lymphocyte(%)	14.01±1.5	28.30±1.7	≤0.0001**
Hb (g/dL)	12.67±2.2	12.14±1.1	0.016*
RBCs x10^9 (cell/mm^3)	4.67±0.2	4.95±0.1	0.027*
PLT x10^3 (cell/mm^3)	192.13±2.9	186.00±5.2	0.158

-All values are mean ±SE
-Results with two asterisks were significantly different at p≤0.0001.
-Results with one asterisks were significantly different at p≤0.05.
-Results with no asterisks were non-significantly different at p>0.05.

4.6. Levels of the Biochemical Markers D-Dimer, Fibrinogen, Troponin, Tissue Plasminogen Activator-1, Interleukin-6 and C-reactive protein in Patient Affected with myocardial infarction and Those Healthy Control Groups.

Means that were depicted in Table 4-2 they were significantly increased ($p<0.01$) in the level of d-dimer (ng/ml), fibrinogen (mg/dl), troponin (pg/ml), tPA-1 (ng/ml), IL-6 (pg/ml) and CRP (mg/dl) (926.93±32.1, 478.89±15.8 mg/dl, 24.29±1.3 ng/ml, 10.36±0.2 ng/ml, 13.83±1.2 pg/ml and 11.82±1.3 mg/dl) in patient compared to control (266.40±7.6 ng/ml, 222.60±4.5 mg/dl, 0.98±0.17 pg/ml, 4.93±0.1 ng/ml, 5.27±1.1 pg/ml and 4.98±1.6 mg/dl) .

Table (4.2): The biochemical markers (D-dimer, fibrinogen, troponin, tissue plasminogen activator-1 (TPA-1), interleukin-6 (IL-6) and c-reactive protein(CRP)) of patients affected with myocardial infarction and healthy control group.

Groups / Parameters	Patient (n=40)	Control (n=40)	Pvalue
	Mean ±S.E		
D-dimer (ng/ml)	926.93±32.1	266.40±7.6	≤0.0001**
Fibrinogen(mg/dl)	478.89±15.8	222.60±4.5	≤0.0001**
Troponin (pg/ml)	24.29±1.3	0.98±0.17	≤0.0001**
tPA-1 (ng/ml)	10.36±0.2	4.93±0.1	≤0.0001**
IL-6 (pg/ml)	13.83±1.2	5.27±1.1	≤0.0001**
CRP (mg/dl)	11.82±1.3	4.98±1.6	≤0.0001**

-All values are mean ±SE

-Results with two asterisks were significantly different at $p\leq0.0001$.

4.7. The Hematological Parameters White Blood Count (WBC cell/mm^3), Granulocytes(%) , Lymphocyte(%), Hemoglobin (Hb g/dL) , Red Blood Count (RBC cell/mm^3), Platelet (PLT cell/mm^3) in Patient affected with myocardial infarction and Those Healthy Control Groups According to Gender.

The levels which were illustrated in following Table 4-3 explained the means ±SE of all mentioned above parameters of both patient and control, the results of WBCs a significantly different at $p<0.05$ were achieved for people with MI of both sexes, males patient (8.01±2.1 cell/mm^3) and females patient (8.06±1.6 cell/mm^3) when compared with healthy persons of both sexes, males healthy (5.07±0.6 cell/mm^3) and females healthy (5.01±1.4 cell/mm^3), granulocyte value a significantly different at $p<0.05$ were achieved for people with MI of both sexes, males patient (85.12±9.7 %) and females patient (84.06±11.7%) when compared with healthy persons of both sexes, males healthy (71.45±9.1%) and females healthy (69.48±4.7 %), lymphocyte value a significant decrease at $p<0.05$ were achieved for people with MI of both sexes, males patient (13.28±2.6 %) and females patient (14.74±3.1 %) when compared with healthy persons of both sexes, males healthy (27.07±7.2%) and females healthy (29.53±8.1%), Hb and RBC value a significantly different at $p<0.05$ were achieved for people with MI of both sexes, males patient (12.91±3.3 g/dL, 5.05±1.2 cell/mm^3 respectivly) and females patient (11.37±1.2 g/dL, 4.28±0.7 cell/mm^3 respectivly) compared with healthy persons of both sexes, males healthy (13.42±2.3 g/dL, 5.41±1.2 cell/mm^3 respectivly) and females healthy (11.91±2.2 g/dL, 4.49±0.9 cell/mm^3 respectivly) and PLT males patient (181.30±12.8 cell/mm^3) was non-significant difference at $p>0.05$ compared with males healthy (186.40±22.1 cell/mm^3) ,when PLT females healthy value a significantly different at $p<0.05$ were achieved for people with MI (202.95±14.4 cell/mm^3) compared with females healthy (185.60±13.4 cell/mm^3).

Table (4.3): The Results of Hematological Parameters White Blood Count (WBC cell/mm^3), Granulocytes(%) , Lymphocyte(%), Hemoglobin (Hb g/dL) , Red Blood Count (RBC cell/mm^3), Platelet (PLT cell/mm^3) in Patient affected with myocardial infarction and Those Healthy Control Groups According to Gender.

Groups / Parameters	Males		Females		$LSD_{(0.05)}$ (gender*group)
	Patient	Control	Patient	Control	
	Mean ±S.E				
WBCs x10^3 (cell/mm^3)	8.01±2.1	5.07±0.6	8.06±1.6	5.01±1.4	**0.345**
Granulocyte (%)	85.12±9.7	71.45±9.1	84.06±11.7	69.48±4.7	**1.878**
Lymphocyte (%)	13.28±2.6	27.07±7.2	14.74±3.1	29.53±8.1	**1.945**
Hb (g/dL)	12.91±3.3	13.42±2.3	11.37±1.2	11.91±2.2	**0.303**
RBCs x10^9 (cell/mm^3)	5.05±1.2	5.41±1.2	4.28±0.7	4.49±0.9	**0.192**
PLT x10^3 (cell/mm^3)	181.30±12.8	186.40±22.1	202.95±14.4	185.60±13.4	**9.412**

-All values were mean ±SE

-Means were significantly different (LSD) at $p<0.05$.

-Means were non- significantly different (LSD) at $p>0.05$.

4.8. Levels of Biochemical Markers D-dimer, Fibrinogen , Troponin, Tissue Plasminogen Activator-1 (tPA-1), Interleukin-6 (IL-6) and C-reactive Protein(CRP) of Patients Affected with Myocardial Infarction According to Gender.

Means which were illustrated in following table 4-4 explained the means ±SE of all mentioned above parameters of both patients and controls, showed a significant increase d-dimer, fibrinogen, troponin, TPA-1, IL-6 and CRP (860.55±16.9 ng/ml, 488.40±30.2 mg/dl, 31.90±4.6 pg/ml, 10.28±1.1 ng/ml, 13.46±2.4 pg/ml and 11.65±1.6 mg/dl) in males and females (993.30±35.4 ng/ml, 469.35±22.6 mg/dl, 16.69±2.4 pg/ml, 10.44±1.6 ng/ml, 14.20±1.1 pg/ml and 11.99±1.9 mg/dl) at $p<0.05$ value was obtained for all parameters in patients compared with control healthy.

Table (4.4): The Biochemical Markers D-dimer, Fibrinogen , Troponin, Tissue Plasminogen Activator-1 (TPA-1), Interleukin-6 (IL-6) and C-reactive Protein(CRP) of Patients Affected with Myocardial Infarction According to Gender.

Groups / Parameters	Males		Females		$LSD_{(0.05)}$ (gender*group)
	Patient	Control	Patient	Control	
	Mean ±S.E				
D-dimer (ng/ml)	860.55±16.9	259.90±25.4	993.30±35.4	272.90±20.9	**76.840**
Fibrinogen (mg/dl)	488.40±30.2	219.85±28.1	469.35±22.6	225.35±17.8	**17.397**
Troponin (pg/ml)	31.90±4.6	0.80±0.03	16.69±2.4	1.16±0.6	**1.476**
TPA-1 (ng/ml)	10.28±1.1	4.88±0.9	10.44±1.6	4.99±1.2	**0.511**
IL-6 (pg/ml)	13.46±2.4	5.33±1.3	14.20±1.1	5.21±0.9	**0.614**
CRP (mg/dl)	11.65±1.6	5.01±0.6	11.99±1.9	4.95±0.2	**0.740**

-All values were mean ±SE

-Means were significantly different (LSD) at $p<0.05$.

-Means were non- significantly different (LSD) at $p>0.05$.

4.9. Results of Hematological Parameters White Blood Count (WBC cell/mm^3), Granulocytes(%) , Lymphocyte(%), Hemoglobin (Hb g/dL) , Red Blood Count (RBC cell/mm^3), Platelet (PLT cell/mm^3) of Patients Affected with MI According to Gender and Age.

Data that were illustrated in Table 4-5 explained the means ±SE of all mentioned above parameters of both patients and controls, showed the statistical differences among studied age groups all (40-49, 50-59, 60-69,70-79 years old) and high significant difference (LSD) values were obtained for (WBCs ,granulocyte and lymphocyte) all groups compared to Hb and RBCs was non-significantly different and PLT males in age groups (40-49, 50-59 and 70-79 years old) was low significant difference (LSD) while in age groups (60-69 years) was high significant difference (LSD), while PLT females in age groups (40-49 and 60-69 years) was high significant difference (LSD), while in age groups (50-59 and 70-79 years old) was low significant difference (LSD).

Table (4.5): The Results of Hematological Parameters White Blood Count (WBC cell/mm^3), Granulocytes(%) , Lymphocyte(%), Hemoglobin (Hb g/dL) , Red Blood Count (RBC cell/mm^3), Platelet (PLT cell/mm^3) of Patients Affected with Myocardial Infarction and Control Group According to Gender and Age.

Groups / Parameters	Age (year)	Males		Females		$LSD_{(0.05)}$
		Patient	Control	Patient	Control	
		Mean ±S.E				
WBC (cell/mm^3)	40-49	7.77±1.2	4.79±0.3	8.00±0.1	5.37±0.9	0.156
	50-59	8.56±1.3	5.77±0.1	8.07±0.2	4.63±0.4	
	60-69	7.66±0.6	4.79±0.1	8.30±0.2	5.02±0.1	
	70-79	8.06±0.2	4.94±0.2	7.88±0.2	5.01±0.2	
Granulocytes (%)	40-49	83.54±12.4	70.84±11.4	83.14±14.3	70.10±10.1	4.936
	50-59	86.86±6.9	70.84±10.3	84.50±10.7	72.00±7.8	
	60-69	83.66±11.2	71.72±13.4	84.82±9.4	70.08±9.9	
	70-79	86.42±7.9	72.40±10.6	83.78±8.8	65.72±5.4	
Lymphocytes (%)	40-49	14.46±2.4	27.42±2.2	15.66±0.9	28.90±3.6	5.426
	50-59	11.34±2.1	27.56±1.6	13.90±1.1	27.00±4.2	
	60-69	14.74±1.9	27.08±1.4	14.18±1.5	28.92±2.7	
	70-79	12.58±1.7	26.20±1.7	15.22±1.6	33.28±2.9	
Hb (g/dL)	40-49	13.58±1.2	14.16±2.2	11.50±1.1	12.24±1.1	N.S
	50-59	12.92±2.1	13.92±2.4	11.42±0.6	11.92±1.2	
	60-69	13.04±1.3	13.20±2.3	11.42±0.4	11.84±0.9	
	70-79	12.10±2.6	12.40±2.0	11.12±0.3	11.64±0.5	
RBC (cell/mm^3)	40-49	5.46±0.2	5.72±0.1	4.19±0.7	4.69±0.6	N.S
	50-59	5.06±0.3	5.79±0.2	4.35±0.7	4.42±0.5	
	60-69	4.99±0.1	5.26±0.1	4.33±0.5	4.58±0.4	
	70-79	4.69±0.2	4.89±0.3	4.25±0.4	4.25±0.4	
PLT (cell/mm^3)	40-49	200.40±20.5	197.60±20.6	204.20±22.3	166.80±11.6	12.464
	50-59	180.80±22.7	186.00±13.4	202.40±16.4	193.00±13.4	
	60-69	174.40±16.7	190.00±22.4	202.80±17.4	182.00±20.4	
	70-79	169.60±17.7	172.00±13.3	202.40±25.6	200.60±9.8	

-All values were mean ±SE

-Means were significantly different (LSD) at $p<0.05$.

-Means were non- significantly different (LSD) at $p>0.05$.

4.10. Results of Biochemical Markers D-dimer, Fibrinogen , Troponin, Tissue Plasminogen Activator-1 (TPA-1), Interleukin-6 (IL-6) and C-reactive Protein(CRP) of Patients Affected with Myocardial Infarction and Control Group According to Gender and Age.

The levels which were illustrated in Table 4-6 explained the means ±SE of all mentioned above parameters of both patients and controls, They were a statistical differences among all studied age groups (40-49, 50-59, 60-69,70-79 years old) and significant difference (LSD) value was obtained for all groups.

Table (4.6): Illustrate the Biochemical Markers D-dimer, Fibrinogen, Troponin, Tissue Plasminogen Activator-1 (TPA-1), Interleukin-6 (IL-6) and C-reactive Protein(CRP) of Patients Affected with Myocardial Infarction Healthy Groups According to Gender and Age.

Groups / Parameters	Age (year)	Males		Females		$LSD_{(0.05)}$
		Patient	Control	Patient	Control	
		Mean ±S.E				
D-dimer (ng/ml)	40-49	872.20±45.1	283.00±12.5	849.00±20.3	238.00±16.4	296.031
	50-59	864.60±36.2	249.20±10.4	1091.6±45.1	255.20±17.2	
	60-69	858.40±27.8	238.80±13.7	1078.80±50.6	335.00±13.9	
	70-79	847.00±19.8	268.60±17.8	953.80±37.4	263.40±12.7	
Fibrinogen (mg/dl)	40-49	480.40±10.6	202.40±17.7	454.40±23.4	238.00±22.6	110.762
	50-59	487.40±24.1	242.80±19.6	475.60±26.7	226.80±30.4	
	60-69	481.20±34.2	221.80±18.5	497.40±18.7	232.00±37.2	
	70-79	504.60±41.2	212.40±22.1	450.00±13.9	204.60±17.6	
Troponin (pg/ml)	40-49	25.70±4.5	0.98±0.01	16.96±2.4	0.50±0.03	1.677
	50-59	34.96±7.9	0.38±0.02	16.52±0.6	0.84±0.01	
	60-69	35.76±6.7	1.06±0.07	16.40±2.7	1.36±0.2	
	70-79	31.16±4.5	0.76±0.03	16.88±3.7	1.92±0.1	
TPA-1 ((ng/ml)	40-49	10.32±1.6	4.74±0.9	10.83±1.7	5.12±0.9	0.332
	50-59	10.09±1.7	4.88±0.5	9.94±1.2	4.60±0.2	
	60-69	9.90±0.9	5.12±0.5	11.54±1.2	5.42±0.3	
	70-79	10.81±1.3	4.79±0.3	9.43±1.2	4.80±0.1	
IL-6 (pg/ml)	40-49	12.56±1.1	5.96±1.6	12.18±1.1	9.52±2.1	1.264
	50-59	12.70±1.3	5.30±0.9	14.84±1.2	4.64±1.7	
	60-69	15.14±2.1	5.30±0.7	14.82±1.3	6.08±0.9	
	70-79	13.44±1.9	4.76±0.6	14.96±2.3	5.58±1.1	
CRP (mg/dl)	40-49	12.54±2.1	5.70±0.9	12.58±1.2	4.88±0.9	1.522
	50-59	10.82±0.9	4.74±0.9	9.60±1.1	4.98±0.6	
	60-69	10.44±0.7	4.76±0.5	13.06±1.3	5.08±0.5	
	70-79	12.80±1.3	4.82±0.6	12.74±1.3	4.86±0.5	

-All values were mean ±SE

-Means were significantly different (LSD) at $p<0.05$.

4.11. levels of biochemical markers D-dimer , Fibrinogen , Troponin, Tissue Plasminogen Activator-1 (TPA-1), Interleukin-6 (IL-6) and C-reactive Protein(CRP) of Patients Affected with Myocardial Infarction According to Body Mass Index (BMI Kg/m^2).

Means which were depicted in Table 4-7 indicated a significant increase in the level of IL-6, CRP, fibrinogen, TPA-1, d-dimer and troponin (14.56±0.7 pg/ml, 12.92±0.7 mg/dl, 493.00±14.4 mg/dl, 11.01±0.5 ng/ml, 918.60±46.2 ng/ml and 25.98±3.9 pg/ml respectivly) in patient at level p<0.01 compared to control (5.46±0.5 pg/ml, 4.32±0.3 mg/dl, 203.20±7.8 mg/dl**,** 4.91±0.3 ng/ml**,** 255.00±22.2 ng/ml and 1.20±0.3 pg/ml respectivly)**.**

Table (4.7): The Biochemical Markers D-dimer , Fibrinogen , Troponin, Tissue Plasminogen Activator-1 (tPA-1), Interleukin-6 (IL-6) and C-reactive Protein(CRP) of Patients Affected with Myocardial Infarction According to Body Mass Index (BMI Kg/m^2).

BMI groups / Parameters	BMI (Kg/m^2)		p-value
	Patient (25-33)	Control (19-23)	
	Mean±S.E		
D-dimer (ng/ml)	918.60±46.2	255.00±22.2	≤0.0001**
Fibrinogen(mg/dl)	493.00±14.4	203.20±7.8	≤0.0001**
Troponin (pg/ml)	25.98±3.9	1.20±0.3	≤0.0001**
tPA-1 (ng/ml)	11.01±0.5	4.91±0.3	≤0.0001**
IL-6 (pg/ml)	14.56±0.7	5.46±0.5	≤0.0001**
CRP (mg/dl)	12.92±0.7	4.32±0.3	≤0.0001**

-All values were mean ±SE

-Results with two asterisk were significantly different at p≤0.0001.

4.12. Correlations Among Studied Parameters

Table (4.8): Pearson correlation coefficient among different hematological parameters of patients affected with myocardial infarction.

		GRA	LYM	HB	RBC	PLT	D-dimer	Fibro	Tropo	TPA	IL-6	CRP
WBC	**r**	.256	-.225	-.193	-.231	.043	.202	-.018	.063	.133	-.041	-.041
	Sig.	.110	.163	.233	.152	.792	.212	.912	.697	.415	.801	.804
GRA	**r**	1	-.990**	-.055	.099	-.030-	.335*	.189	.239	.165	-.162-	-.049-
	Sig.		.000	.735	.543	.857	.035	.242	.138	.309	.318	.762
LYM	**r**		1	-.029-	-.180-	.013	-.324-*	-.190-	-.272-	-.153-	.183	.105
	Sig.			.857	.265	.935	.042	.241	.089	.345	.258	.519
HB	**r**			1	.901**	-.363-*	-.275-	.214	.710**	-.045	-.246-	-.144
	Sig.				.000	.021	.086	.186	.000	.784	.127	.375
RBC	**r**				1	-.303-	-.185-	.234	.635**	.019	-.243-	-.273-
	Sig.					.057	.253	.146	.000	.906	.131	.088
PLT	**r**					1	.259	-.045-	-.662-**	.193	-.105-	-.072
	Sig.						.106	.781	.000	.232	.517	.660
Ddimer	**r**						1	-.104-	-.286	.261	.272	-.084-
	Sig.							.523	.073	.104	.090	.608
Fibro	**r**							1	.271	.253	-.074-	.046
	Sig.								.091	.115	.650	.776
Tropo	**r**								1	-.130-	-.150-	-.196-
	Sig.									.423	.354	.226
TPA	**r**									1	-.116-	-.058-
	Sig.										.475	.724
IL-6	**r**										1	-.006-
	Sig.											.971

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Showed that there was a significant negative correlation (R^2=0.9803 , sig = 0.0001) between granulocytes% and lymphocytes% in patients affected with myocardial infarction.

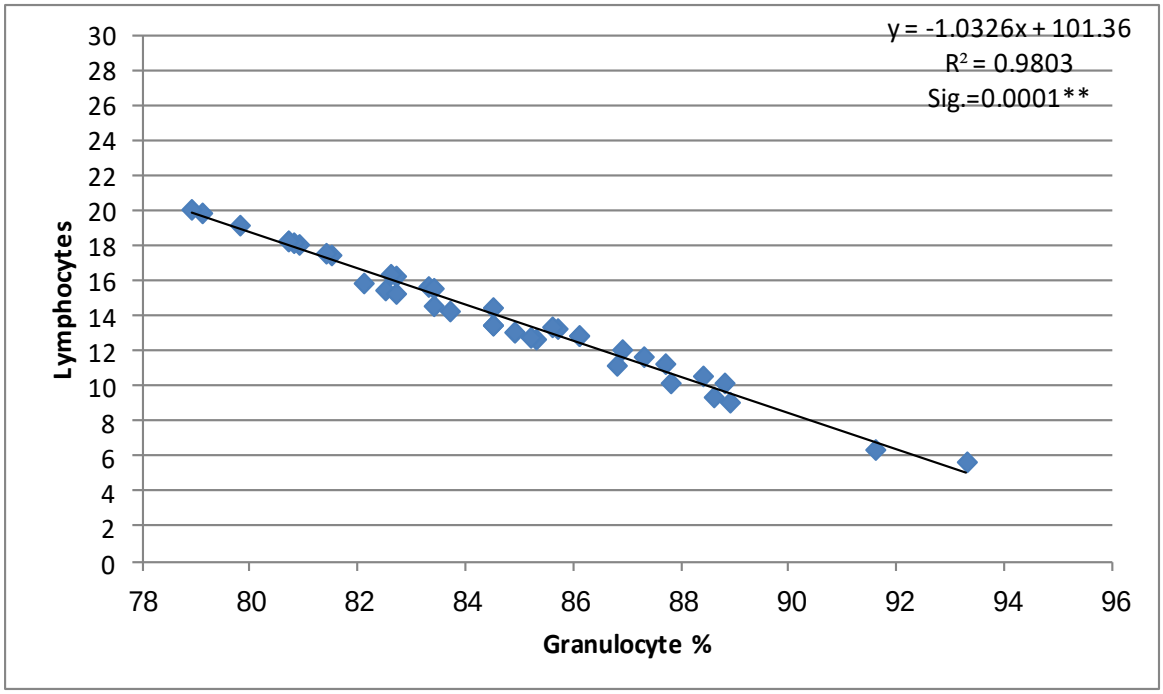

Figure (4.5): Correlation coefficient between granulocytes and lymphocytes in patients affected with myocardial infarction.

Documented that there was a significant negative correlation (R^2=0.1048 , sig = 0.042) recorded between lymphocytes and D-dimer of patients with myocardial infarction.

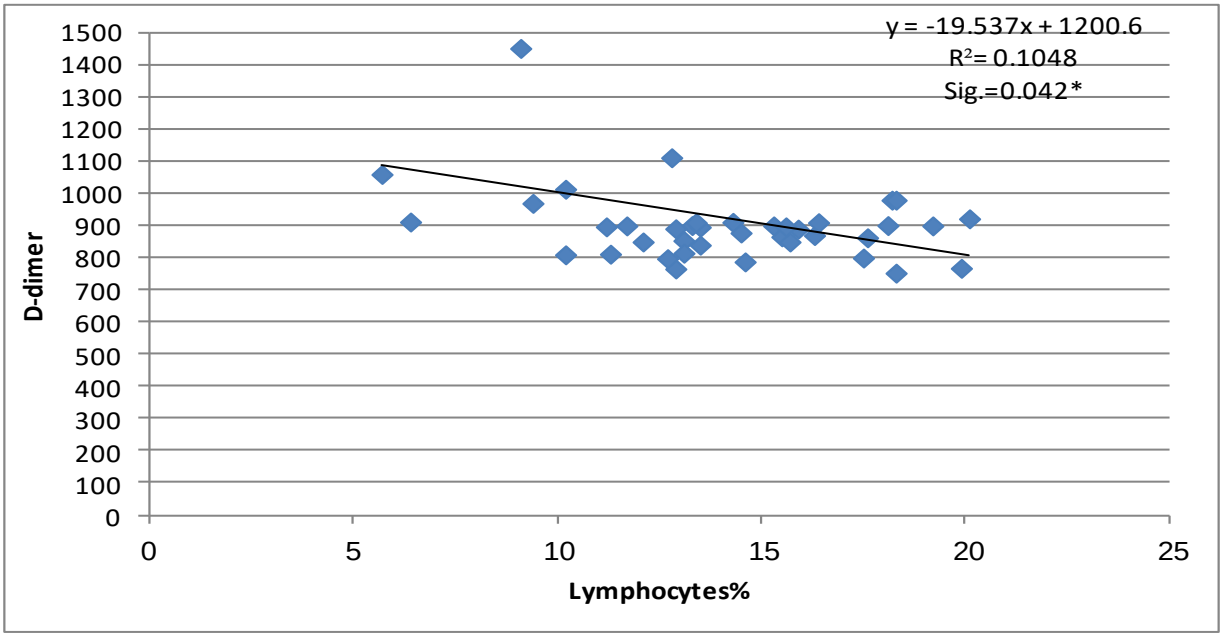

Figure (4.6): Correlation coefficient between lymphocytes and D-dimer of patients with myocardial infarction.

The significant positive correlation (R^2=0.1119, sig= 0.035) between granulocytes and d-dimer levels of patients with myocardial infarction.

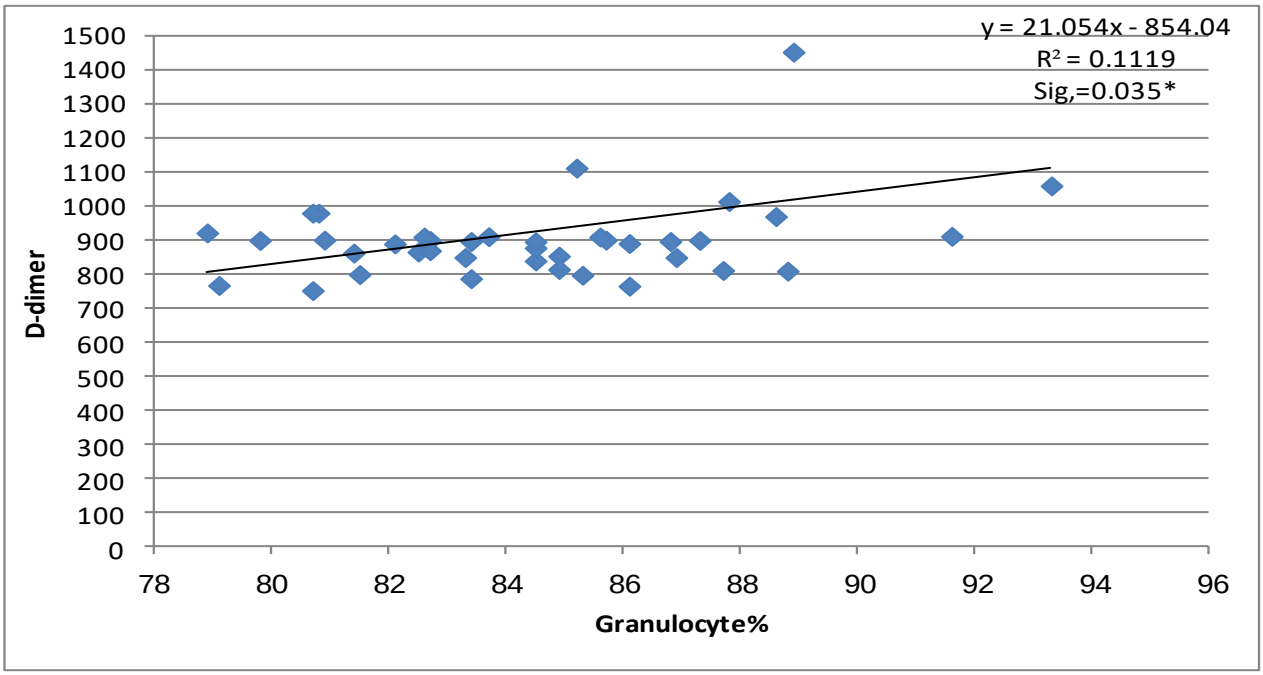

Figure (4.7): Correlation Coefficient Between Granulocytes and D-dimer of patients with myocardial infarction.

Showed that there was a significant positive correlation (R^2=0.812, sig= 0.0001) occurring between Hb and RBCs of patients with myocardial infarction.

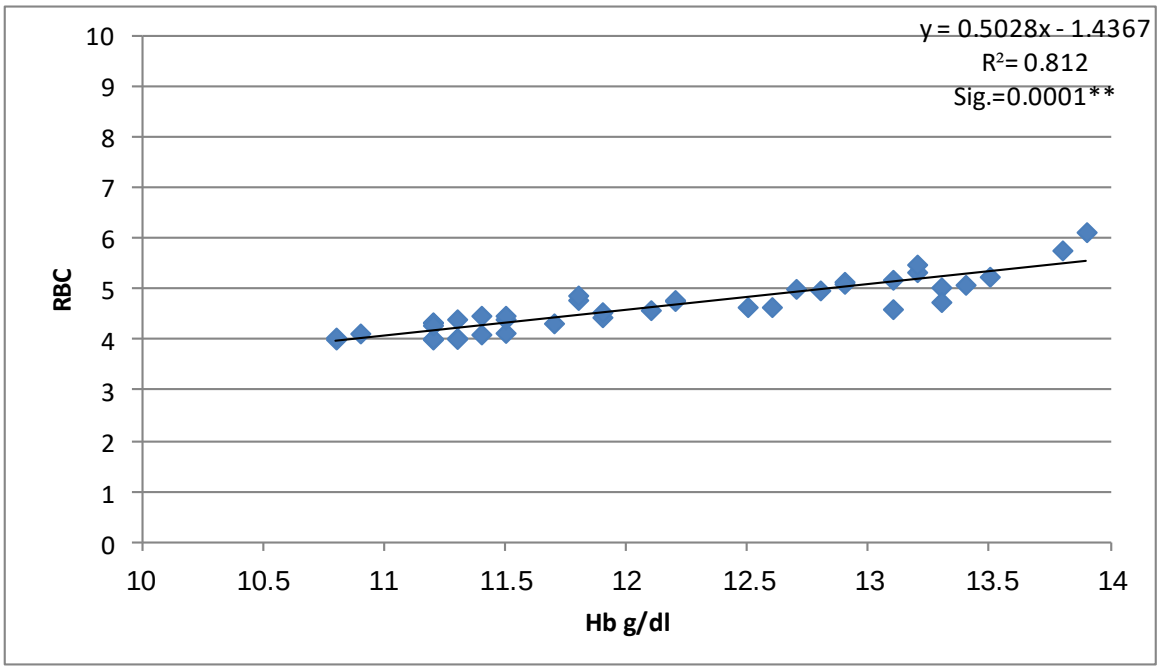

Figure (4.8): Correlation coefficient between Hb and RBCs of patients with myocardial infarction.

Documented that there was a significant positive correlation (R^2=0.5042 , sig = 0.0001) recorded between Hb and troponin of patients with myocardial infarction.

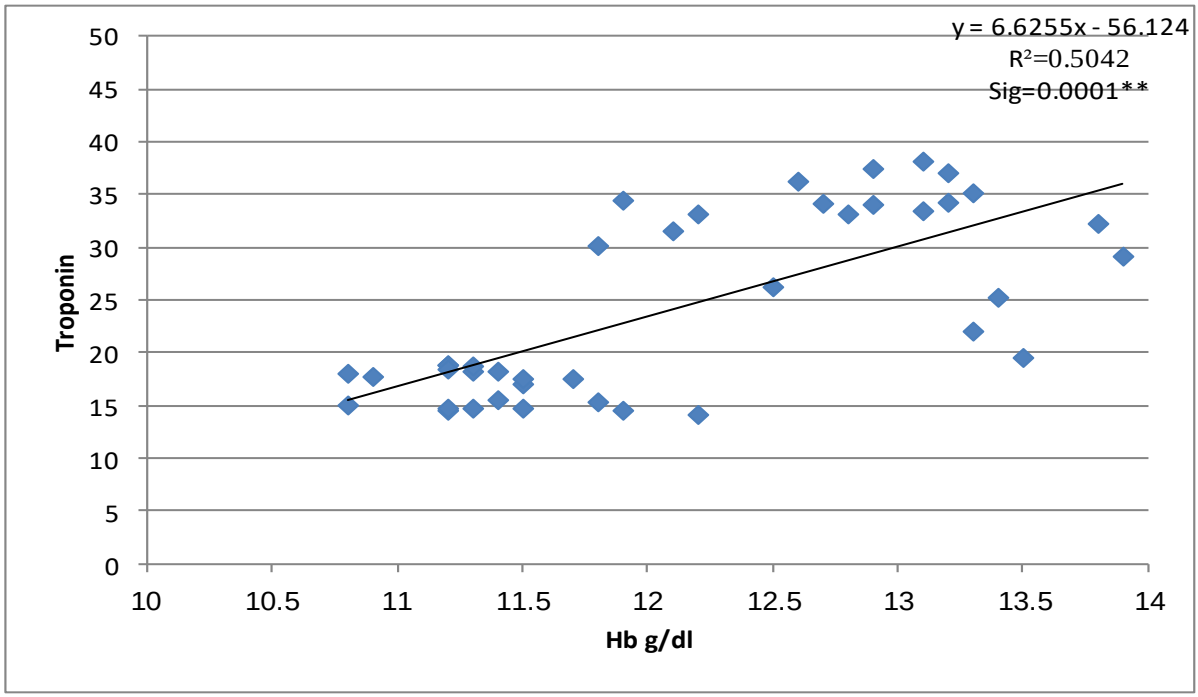

Figure (4.9): Correlation Coefficient Between Hb and Troponin of patients with myocardial infarction.

Showed there was a significant positive correlation (R^2=0.4036 , sig = 0.0001) between RBCs and troponin-I of patients with myocardial infarction.

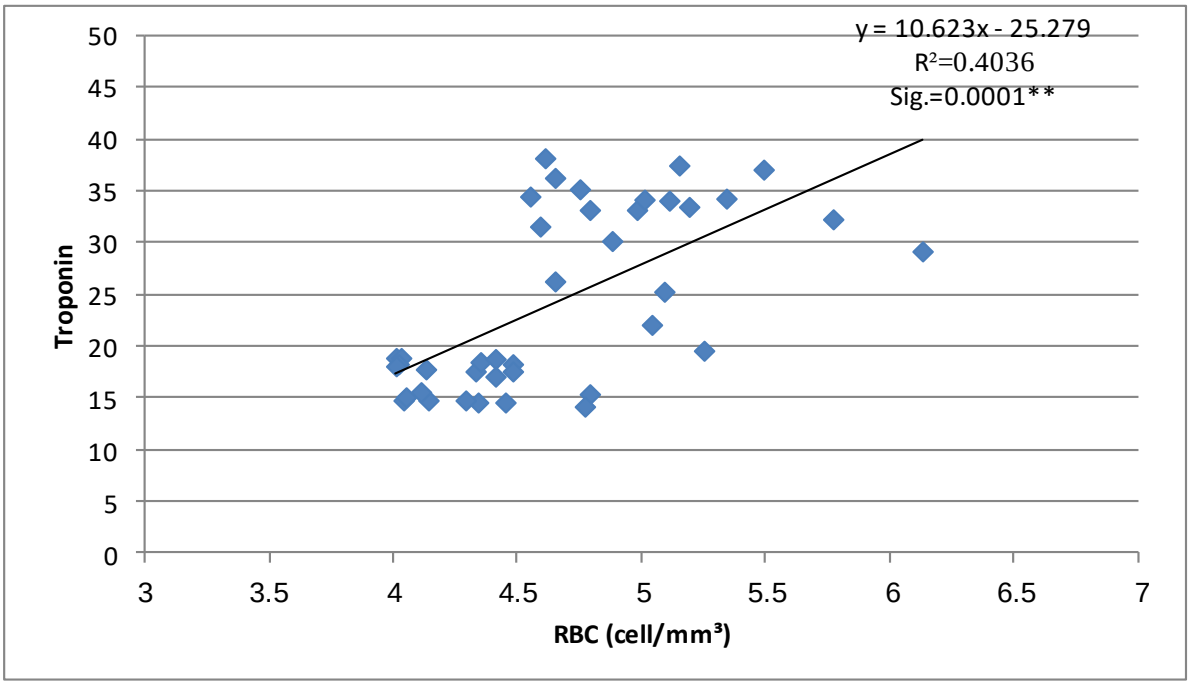

Figure (4.10): Correlation Coefficient Between RBCs and Troponin of patients with myocardial infarction.

The significant negative correlation (R^2=0.132 , sig = 0.021) recorded between Hb and PLT of patients with myocardial infarction.

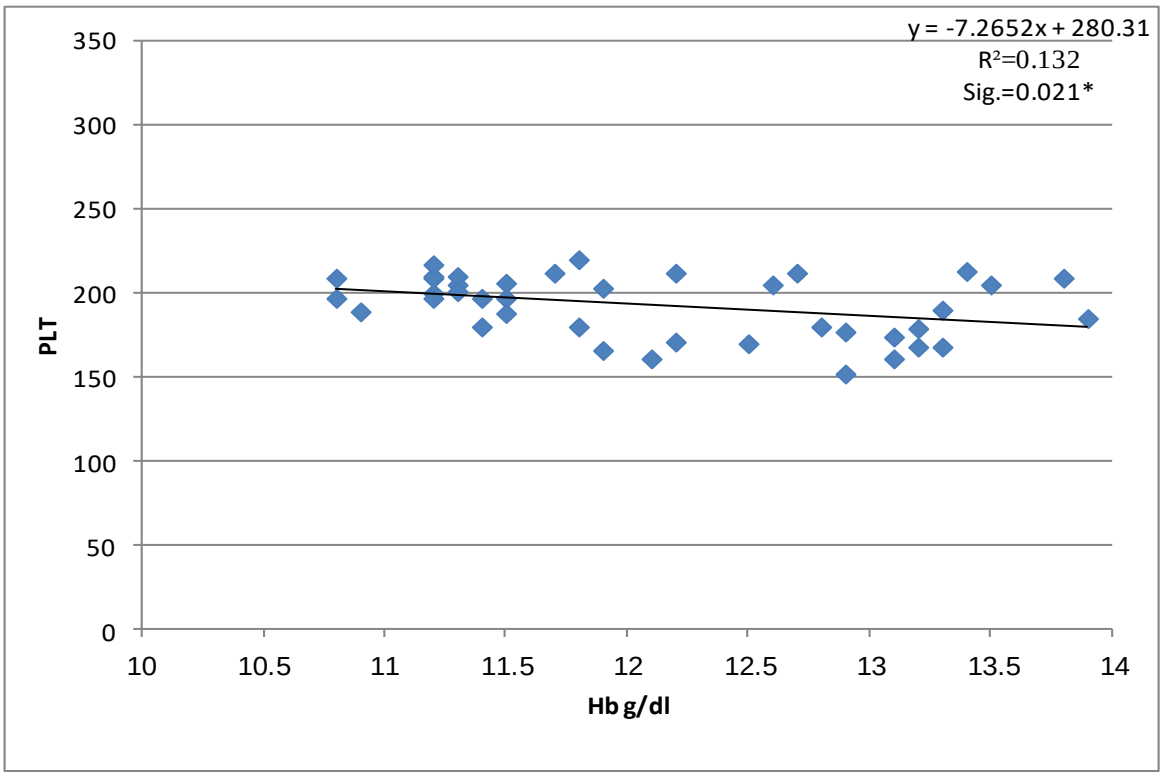

Figure (4.11): Correlation Coefficient Between Hb and PLT of patients with myocardial infarction.

It was well documented that there was a significant negative correlation (R^2=0.4382 , sig = 0.0001) recorded between PLT and troponin of patients with myocardial infarction.

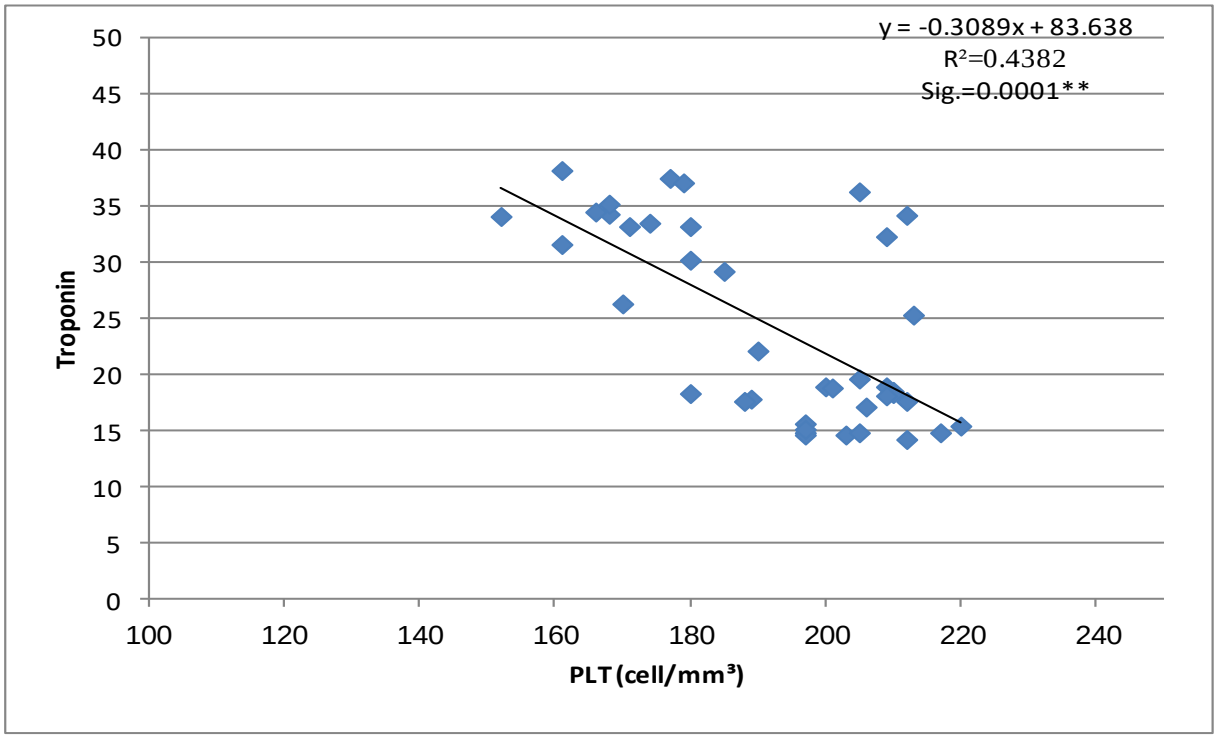

Figure (4.12): Correlation Coefficient Between PLT and Troponin of patients with myocardial infarction.

Table (4.9): the best cut off, sensitivity and specificity for prediction of the disease activity by parameters.

Parameter	Sensitivity	Specificity	AUC	Cut off	95% confidence	p-value
D-dimer (ng/ml)	80	0.58	0.740	298.5	0.629-0.851	≤0.0001
Troponin (pg/ml)	0.825	0.700	0.813	1.650	0.716-0.910	≤0.0001
tPA (ng/ml)	0.78	0.60	0.724	5.175	0.608-0.840	0.001
Fibrinogen (mg/dl)	0.93	0.63	0.816	253	0.715-0.917	≤0.0001
CRP (mg/dl)	0.825	0.625	0.724	6.150	0.612-0.837	0.001
IL-6 (pg/ml)	0.800	0.750	0.767	8.950	0.661-0.874	≤0.0001

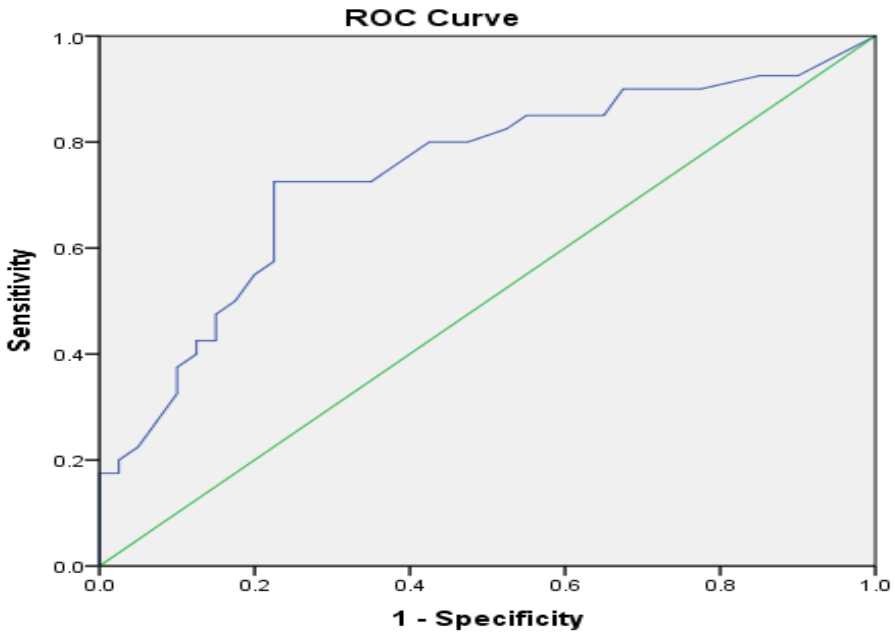

Figure (4.13): ROC Curve for Prediction of the Disease Activity by D-dimer (ng/ml)

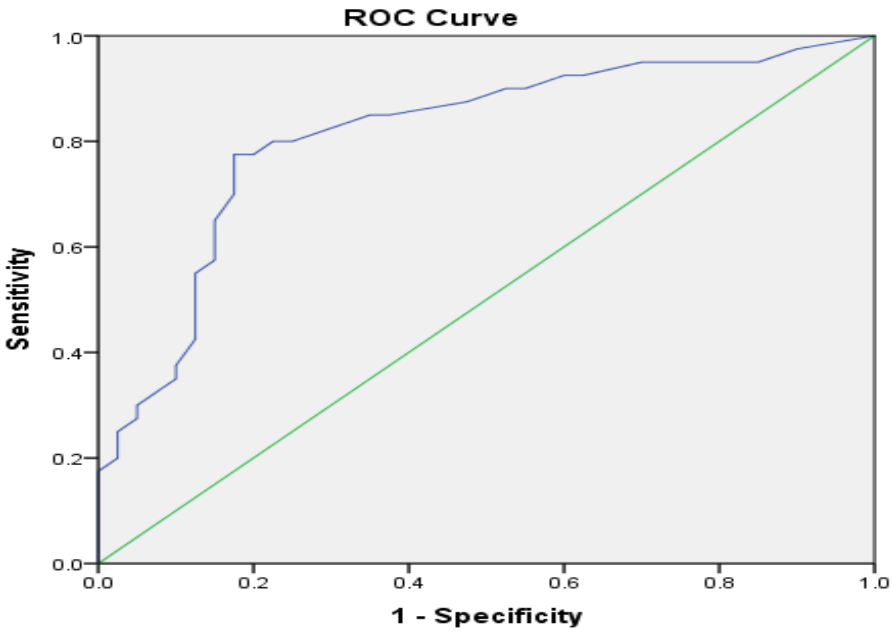

Figure (4.14): ROC Curve for Prediction of the Disease Activity by Troponin (pg/ml).

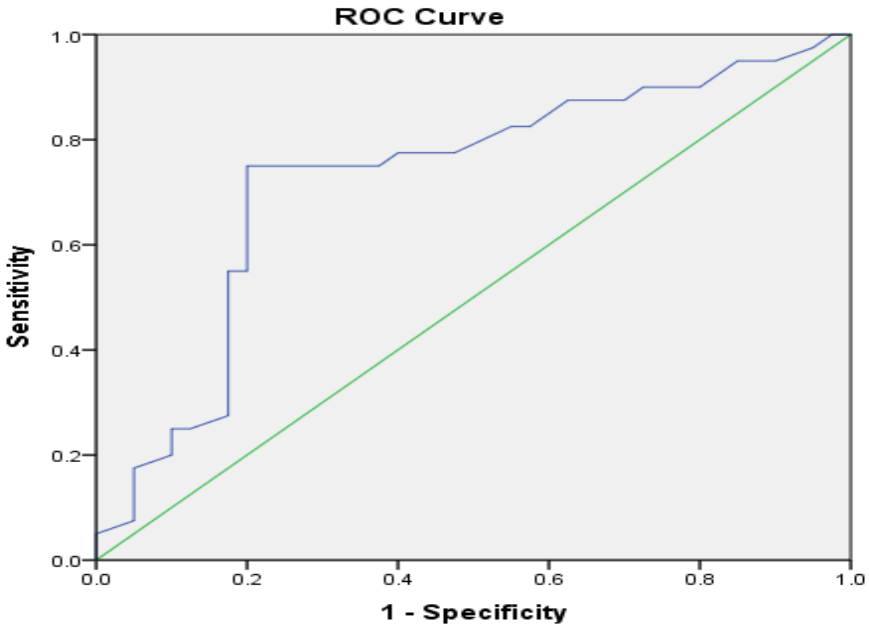

Figure (4.15): ROC Curve for Prediction of the Disease Activity by tPA (ng/ml).

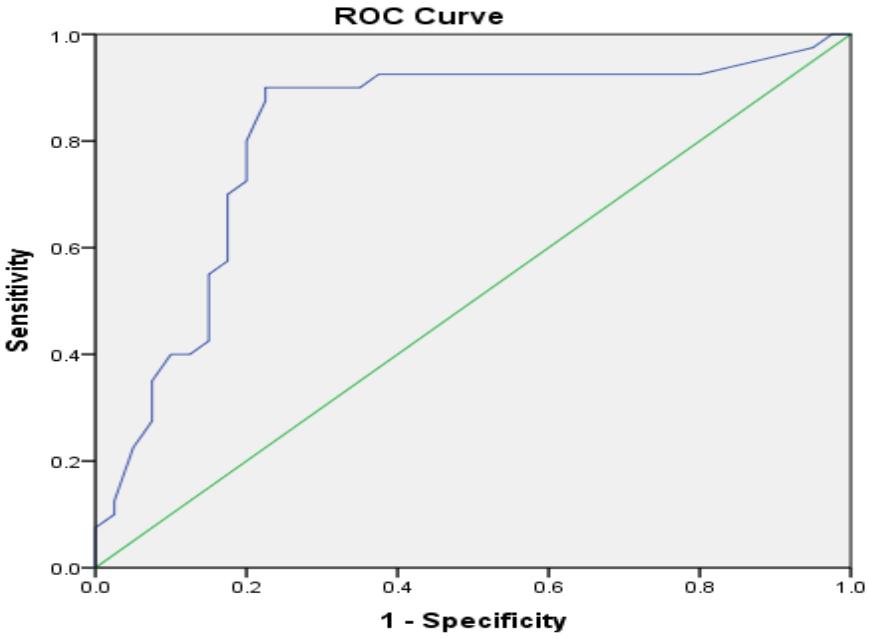

Figure (4.16): ROC Curve for Prediction of the Disease Activity by Fibrinogen (mg/dl).

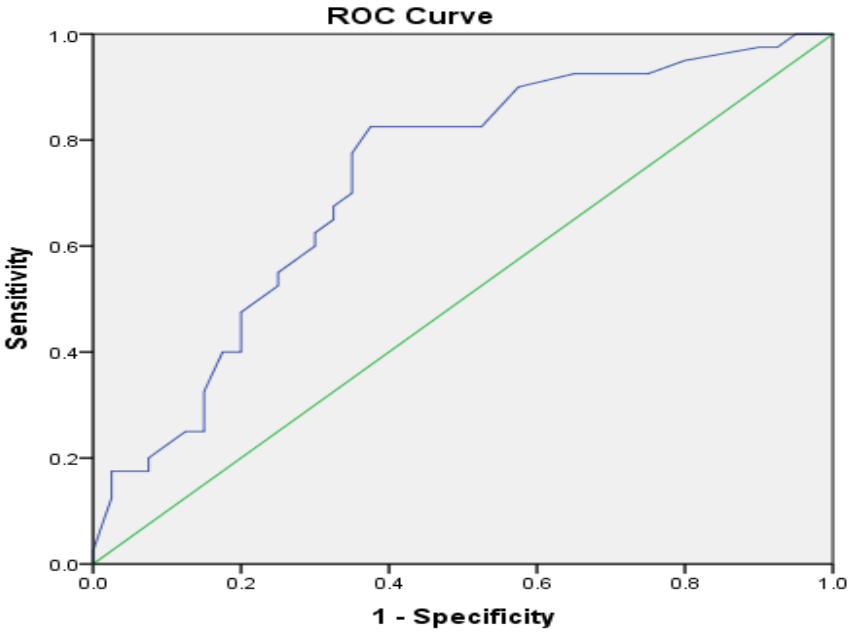

Figure (4.17): ROC Curve for Prediction of the Disease Activity by CRP (mg/dl).

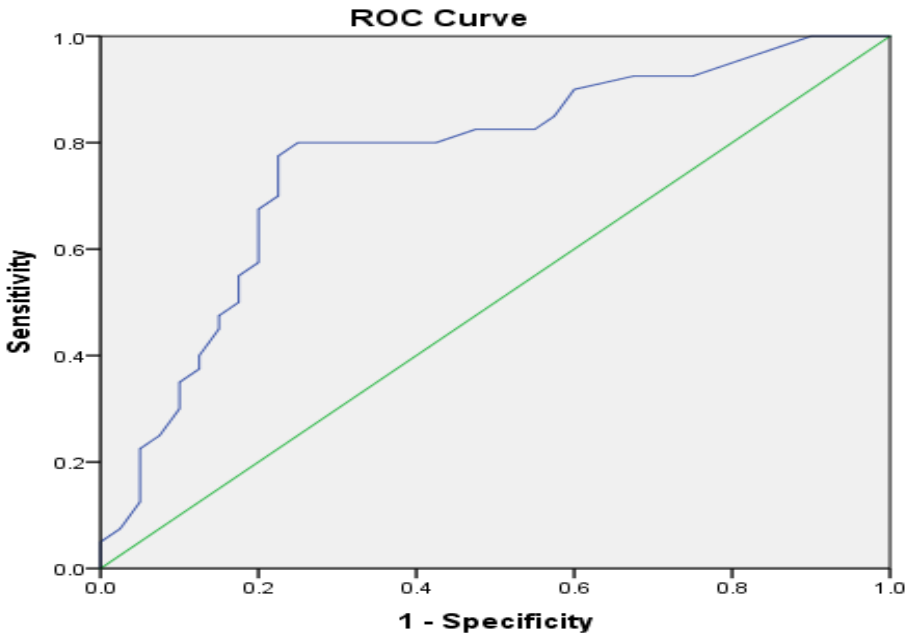

Figure (4.18): ROC Curve for Prediction of the Disease Activity by IL-6 (pg/ml).

Chapter Five
Discussion

5. Discussion

5.1. Relationship of myocardial infarction with age and gender

The result which were presented in Figure (4-1) explained the incidence of myocardial infarction disease in men is greater than of women, since the percentage ratio of men was 60%, while the percentage ratio of women was 40% and the values which were given in Figure 4-2 pointed out the age groups with MI most affected were 30% in (50-59,60-69 years old) compared to the age group (70-79 years old) were 25% and (40-49 years) were 15%.

When comparing with previous study, it was found that age is one of the risk factors in the development of heart disease, which is clearly associated with an increase in the mortality rate, as they found that 87% of those who die from heart disease are aged 60 and over, as indicated by the American Heart Organization, (Mackay *et al*., 2004) while indicated that the risk of heart disease and death from heart disease increases above 55 years, and the various explanations about the increase in the incidence of heart disease with advancing age was due to the increase in the proportion of cholesterol in the blood serum, in women, the increase in cholesterol begins at the age of 65-60 years (Jousilahti and Tuomilehto, 1999).

In another study, the high percentage of patients were between the ages of 79-75 years and this is due to the rate of previous heart injuries, which was around 27% (Selton *et al*., 2012).

Among the other reasons that are discussed is the increase in the incidence of heart disease with age due to mechanical changes to the vascular wall and thus lose its elasticity, which leads to coronary artery disease (Jani and Rajkumar, 2006).

The present study showed that the percentage of men with heart disease was more than that of women, where their ratio was 60%, while the ratio of women was 40%, and this is clearly related to physiological aspects and hormonal

variation if the male hormone testostrerone has an effective effect in increasing the amount of fat carried in the blood and with age, this hormone in the blood decreases, in females, there is the female hormone esterogen, which has a role in protecting and preventing CHD (Coronary heart disease), but when this hormone disappears after menopause, the incidence of coronary atherosclerosis increases CHD (Greenspan and Gardner, 2004).

In all age groups, men are at greater risk of a heart attack than women, especially before menopause (also called menopause), but because women generally have a longer life expectancy than men, ischemic heart disease causes slightly more deaths for women(Graham *et al*., 2007).

It was clearly shown that gender had an effect on the rates of heart diseases statistics. When the study took samples of similar ages from the young age, it revealed that the incidence of men is more than women by about 2-5 times, and this was explained by the difference in hormones in both sexes, in females the presence of the hormone esterogen , which has a protective role and the risk increases after menopause (Jousilahti and Tuomilehto ,1999).

The difference in the composition of the body of men from all women also plays a role in terms of height, body weight, distribution of fats in the body, and heart rate, older women are more susceptible to infection than men because of their small body mass index (Jani and Rajkumar 2006).

These observations suggedted the clear indicator that the incidence of cardiac disease is related to age ,most if not all physiological mechanism become disturbed with ageing of these disturbances including decrease elasticity of blood vessels because of decrease synthesis of collagen and drop number of fibroblasts. As well as ,sexual hormone (estrogen and testosterone) tend to be drop with advanced ages causing increase incidence of coronary artery diseases.

5.2. The relation of Body Mass Index and Association with myocardial infarction.

Results that explained in Figure (4-3) showed an increased incidence of MI was 70% in 25-33kg/m² compared with 19-23kg/m² was lower 30%. One clear suggestion is that the overweight and obese patients present first line in the development of acute myocardial infarction symptoms, this may be due to increased awareness of their risk of having an acute myocardial infarction or because of more severe symptoms due to increased myocardial demands that accompany excess weight, overweight and obese patients may also have less severe left ventricular dysfunction at presentation, in a subanalysis of acute myocardial infarction patients from the global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries (GUSTO-I) trial, found that increasing BMI was associated with greater preservation of left ventricular function and improved 30-day survival (Lundergan *et al*.,2001). Overweight and obese subjects in the present study also presented with lower rates of moderate and severe left ventricular systolic dysfunction and lower global registry of acute coronary events scores, which may be related to an earlier presentation and may partly explain the association between higher BMI and better prognosis.

Previous study was found that the relationship between BMI and incidence of MI, there is greater evidence that women and men who have high levels of BMI become predisposing factors to affected with MI (Yatsuya *et al*., 2010).

It is well recommended that high adiposity is related with increased secretion pro-inflammatory and inflammatory mediators from adipose tissues that have ability to progress of cardiovascular diseases.

5.3. Relationship of white blood cells to myocardial infarction

The results of hematological parameters (WBC cell/mm^3, Granulocytes% and Lymphocyte%) in Table (4-1), (4-3) and (4-5) showed data that are explained in the present study had been recorded a significant elevation ($p<0.05$) in the levels of WBCs in all patients group affected with MI compared to those control group. Data recorded a significant negative correlation in Figure (4-5) ($r = -0.99$, sig = 0.0001) between granulocyte and lymphocytes in patients and data that there was a significant negative correlation in Figure (4-6) ($r = -0.32$, sig = 0.042) recorded between lymphocyte and D-dimer of patient who had MI and a significant positive correlation in Figure (4-7) ($r=0.33$, sig= 0.035) occurring between granulocytes and d-dimer levels**.**

The levels of leukocytes is associated with myocardial infarction and can determine the prognosis of MI ,and there is found that leukocytes increases in patients suffering from MI (Ferrai *et al*.,2016).

It is well understanding that any inflammatory processes within the body is associated with increase inflammatory cells (WBCs) ,one of the ischemic heart diseases is MI and this disease results as a consequence of pathophysiological diseases accompanied with elevation nuclear factor KB ,inflammatory mediators ,and evoke adhesion of polymorphonuclear cells (Frangogiannis *et al*.,2002).

Moreover, the increase of WBCs after occurance of ischemic heart disease and this increment is higher significant (Coller,2002).

In spite of previous studies focused on the number of leukocytes in myocardial infarction but the count of WBCs no correlated with size of MI (Pesaro *et al*.,2009).

Previous epidemiological study established an association between increase leukocytes and incidence of acute myocardial infarction ,and it found the incidence of MI is there times higher in high range of WBCs 9000 cell/mm^3 compared with those have 6000 cell/mm^3 of WBCs (Blum *et al*.,2002).

One of the most prominent indicator associated with coronary artery disease is both total WBCs and differential WBCs ,in addition ,there is association between WBCs count and mortality rate in patients with acute ischemic heart disease (Yan *et al*.,2020).

Marrugate *et al.* (2004) confirmed the mortality rate increase in elderly patients with MI older than 65 years old higher than 34-36 years old and so that it concluded the greater effects of high WBCs number in elderly more than of young one.

The development and progression of atherosclerotic cardiovascular diseases is related with inflammatory processes ,with this relation ,there is increase levels of inflammatory markers such as CRP ,IL-6 ,and TNF-α , there for there is a positive relationship occurring between WBCs and risk incidence of cardiovascular events (Rana *et al*.,2007). The white blood cells are accompanied with severity of coronary artery disease (Hong *et al*.,2014).

The systemic inflammation may be usually associated with increase production of leukocytes, this is results from secretion of inflammatory and pro-inflammatory cytokines such as IL-6, IL-4, TNF-α, and CRP which in turn evoke production of further number of leukocytes.

5.4. Relation of myocardial infarction on red blood corpuscles and hemoglobin:

Results that are mentioned in the present study in Tables (4-1), (4-3) and (4-5) had been recorded a significant elevation ($p<0.05$) in the levels of RBCs and Hb in all patients group affected with MI compared to those control group. Data appeared there was a significant positive correlation in Figure (4-8) ($r=0.90$, sig= 0.0001) occurring between Hb and RBCs, and there was a significant positive correlation in Figure (4-9) ($r = 0.71$, sig = 0.0001) recorded between Hb and troponin and a significant positive correlation in Figure (4-10) ($r = 0.63$,

sig = 0.0001) between RBCs and troponin, and there was significant positive correlation in Figure (4-11) (r = 0.36 , sig = 0.021) recorded between Hb and PLT.

Previous study had been shown decreased of red blood cells count , hematocrit ,hemoglobin and fibrinogen in patient suffering from myocardial infarction as well as it documented increase blood viscosity because of alterations of these studied parameters (kul *et al*.,2014).

Complete blood viscosity results from friction blood molecules and blood cells ,and this viscosity is dependent particularly on cellular compartments of blood such as RBCs ,WBCs ,blood platelets (Koening *et al*.,1991).

Recent study conducted by Hamaza *et al*.(2021) ,it pointed out that red cell distribution width can related positively with different disease such as cardiovascular disease ,diabetes mellitus ,and hypertension.

There is an evidence confirms the links occurring between cardiovascular events and red blood cells from point of pathophysiological status ,and there is high incidence of cardiovascular disease development associated with anemia or polycythemia conditions (Mozos, 2015).

The relation between RBCs and MI incidence remains controversial ,it is found that RBCs transfusion is occasionally associated with incidence of MI especially when hemoglobin levels at 10 mg/dl (Wang *et al*.,2018).

The current results may be returned to effects of RBCs count on the viscosity of blood and its friction on wall of vessels causing injuries and enhance atherosclerotic plaquies.

5.5. Relation of myocardial infarction to Blood Platelets:

Values that are obtained in the present study in Table (4-1), (4-3) and (4-5), had been recorded non-significantly different ($p>0.05$) in the levels of PLT in all patients group affected with MI compared to those control group. Data recorded a significant negative correlation in Figure (4-12) ($r = -0.66$, $sig = 0.0001$) between PLT and troponin, and a significant positive correlation in Figure (4-11) ($r = 0.36$, $sig = 0.021$) recorded between Hb and PLT.

To explain whether the platelets count influences or can be associated with MI, it was documented that platelets count was lower and mean of platelets volume (MPV) recorded a significant increase in those patients with MI, also, it was found from the obtained findings of the preious study that indicated these changes may be persist or changed after MI and these changes do not distinguish between thrombotic and the non-thrombotic MI (Amraotkar *et al*.,2017).

According to pathological point view ,the formation of vascular plaque during atherosclerosis leads to activation of platelets and incidence of occlosion of blood vessels by thrombi ,later ,damage to plaque lesions can evoke further platelets activation because of release of storage coagulant molecules with in platelets (Borissoff *et al*.,2011).

Plaques of atherosclerosis activate more aggregation and activated platelets and also enhance formation and release of new blood platelets from bone marrow (Ranjith *et al*.,2009).

The ischemic and bleeding disorders are mostly associated with platelets ,it is well known that thrombocytes have essential roles in thrombotic events or damage to plaque of atherosclerotic lesion which represents the prominent factor in mechanism of acute myocardial infarction ,as well as ,there are several mechanisms enhance and evoke platelets formation and activation through systemic inflammation and degree of myocardial damage (Roh *et al*.,2020).

There is a recent study which indicated that the platelets contribute in development the MI pathogenesis ,the take part in the formation of thrombus and of that micro thrombi ,inflammatory mediators ,immune modulators ,and vasoconstrictive agents ,however ,increase inflammatory events and thrombotic risk factors are associated with increase formation and platelet activities (Halucha *et al*.,2021).

The results of the present study recorded non-significant increase of PLT in patients of MI and this results might resulted from increase thrombotic events are related with triggering of new production of platelets from bone marrow as well as the increase levels of pro-inflammatory mediators can excelerated of platelets production.

5.6. Relation of myocardial infarction to D-dimer levels:

Results that are showed in the present study in Table (4-2), (4-4), (4-6) and (4-7) had been recorded a significant elevation ($p<0.01$) in the levels of D-dimer in all patients groups according to sex, age, and BMI affected with MI compared to those of control group. Data recorded a significant negative correlation in Figure (4-6) ($r = -0.32$, $sig = 0.042$) between lymphocyte and D-dimer of patient who had MI and a significant positive correlation in Figure (4-7) ($r=0.33$, $sig= 0.035$) occurring between granulocytes and d-dimer levels. ROC analyses of the disease activity by D-dimer ,AUC result in Table (4-9) was (0.740).

It is not surprising that D-dimer represents a diagnostic parameter in patients affected with MI and other thrombotic problems ,the present results were consistent with previous study of Reihani *et al*.(2019) which indicated that there are higher levels of D-dimer in patients with MI indendently on gender ,age and other risk factors.

It is well known that fibrin degradation (clotlysis) by plasmin produces D-dimer ,the clot formation and fibrinolysis (D-dimer production) represent the

activity of coagulation and fibrinolysis mechanisms (Wada and Sakuragawa ,2008).

D-dimer production is released faster or proceed the production other cardiac biomarker during ischemic heart diseases (Righini *et al*., 2015).

As well as ,it documented that patients who have D-dimer a bove one –third of D-dimer levels they undergo from 70% risk factor of cardiac heart diseases (Baye-Genis *et al*.,2000).

D-dimer remains the essential marker for determining the activity of fibrinolytic system that carried out by plasmin also it used in identification of disseminated intravascular coagulation (DIC) ,it was found that D-dimer level ,creatin kinase-MB ,and troponin I were significantly higher in patients with a cut coronary diseases compared to healthy people (Mansour and El-shakhawy,2020).

Previous study was measured the levels of D-dimer in patients with pulmonary embolism and this study found increase of D-dimer level three fold higher than of control and concluded that fibrinolytic system become active when thrombosis occurs (Robert-Ebadi *et al*., 2021).

According to gender ,the young people have high risk chance in recurrent thromboembolism than high of women and it found that D-dimer results give positive relation in male than those women (Palareti *et al*., 2019).

The severity of D-dimer is positively correlated with levels of D-dimer and this marker is remarkable elevated during hyper coagulability state particularly in a cute coronary artery (Türkoglu *et al*.,2020).

5.7. Relation of myocardial infarction to Fibrinogen (FI)

The results of the present study in Tables (4-2), (4-4) and (4-6) indicated a significant elevation ($p<0.05$) in all tested groups of patient affected with MI of

both sexes and related with BMI. ROC analyses of the disease activity by fibrinogen, AUC result in table (4-9) was (0.816).

These findings were consistent with recent study who carried out by Surma and Banach ,(2022) ,which elaborated that increased plasma fibrinogen and a cute phase proteins in atherosclerotic cardiovascular disease such as myocardial infarction and angina pectoris.

Another study pointed out there is an association between cardio vascular events convential high risk factors and also predisposing factor of coronary artery disease and the results of this study showed higher levels of fibrinogen levels as a pro inflammatory biomarker in addition ,it is essential role in clotting mechanism (Jiang *et al*.,2019).

Previous study investigated the increase gene encoding of fibrinogen such fibrinogen gamma ,alph ,and beta and this study proved a relationship between these gene expressions and incidence of thrombotic events (Mannila *et al*.,2006).

As long as the present study involved the gender groups (men and women) ,its well documented that estrogen can to decrease LDL and increase HDL as well as it causes vasodilation but on the other hand ,it was recognized the estrogen therapy disturps homeostatic mechanisms causing decrease coagulation inhibitors with the same time activation of coagulation factors and thrombosis incidence (Williams *et al*.,2016).

Another study indicated that levels of clotting factors and coagulation inhibitor in particular tissue plasminogen activator inhibitor are associated with incidence of coronary diseases (Meilahn *et al*.,1996).

In order to determine the effects of testosterone wether can affect or increased thrombosis, it was found that testosterone does not or has not adverse effects on blood coagulation mechanisms (Smith *et al*.,2005).

There is growing evidence indicates an association between levels of fibrinogen and risk of thrombosis of more concern of early CAD of women than of other clotting factors of hemostatic mechanism including stable factor (VII) and anti-hemophilic factor (VIII), tPA-1, and tPAI-1, moreover, increase concentration of fibrinogen during inflammatory processes is often associated with IL-6, however, fibrinogen level is higher in women and increase IL-6 production that can exacerbates incidence of CAD (Kryczka *et al*.,2021).

The effects of body mass index on coagulation ,Kornblith *et al*.(2015) showed that increase in Table (4-7) coagulability when body mass index increases and this effects is not associated with age and gender ,also this study confirm the patients with CAD have higher number of platelets and fibrinogen in obese patients.

The relationship between visceral obesity and levels of fibrinogen are associated with increased incidence of inflammatory processes ,hypertension ,and prothrombotic status and these effects are occurred in children and elderly (Hafez *et al*.,2016).

In addition, there is a relationship had been found between inflammation and incidence of thrombosis ,it found that inflammation evoks coagulation and inhibits the natural anti-coagulants ,this processes are mediated by inflammatory cytokines such as CRP and IL-6 that directly or indirectly influence clotting mechanisms (Esmon ,2005).

Inflammatory mediators (IL-6) triggers fibrinogen production by hepatocytes and then after the higher levels of fibrinogen can increase risk of thrombotic events (Hulshof *et al*.,2021).

The relationship between age and clotting and fibrinolytic system was studied ,it had been found there is a positive correlations occurring between old ages and levels of D-dimer and fibrinogen so that this study concluded that hyper coagulable activities progress at old ages (Ochi *et al*.,2016).

5.8. Relation of myocardial infarction to Troponin:

Results of the present study in Tables (4-2), (4-4) and (4-6) had recorded a significant elevation ($p<0.05$) in the levels of troponin in all patients group affected with MI compared to those control group. Data recorded a significant positive correlation in Figure (4-9) ($r = 0.71$, sig = 0.0001) between Hb and troponin and a significant positive correlation in Figure (4-10) ($r = 0.63$, sig = 0.0001) between RBCs and troponin, and that there was a significant negative correlation in Figure (4-12) ($r = -0.66$, sig = 0.0001) recorded between PLT and troponin. ROC analyses of the disease activity by troponin ,AUC result in Table (4-9) was (.813). Findings that were Yield from the present study ,they had been a significant increase in the levels of troponin in all studied patients group compared to those healthy one.

The results of the present study are consistent with study of Negahdary *et al*.(2016) that focused on the levels of troponin ,a cardiac biomarker and explained elevation levels of troponin in patients with MI and other cardiac diseases.

There are many factors can contribute in the incidence of MI ,of these ,obesity ,high cholesterol , hypertension , and high blood sugar that in turn lead to injury of cardiac muscle and increase level of troponin (Jokela *et al*.,2014).

Another study showed that troponin canbe used as predictable markers with new and early events of ischemic heart disease such as MI and this study established that return of troponin concentration to normal values is associated with positive outcome of patient status (Wanamaker *et al*.,2019).

Furthermore, study of Eidizadeh *et al*.(2021) confirmed that in spite of troponin is important diagnostic factor for MI ,but this study was confirmed that no recommendations or instructions concerne to the two types of troponin ,including troponin I (cTnI) and troponin T (cTnT) in diagnostic severity of disease also ,this study demonstrated that a sex dependent of these parameters

by using ROC analysis improved and increase sensitivity with specifity of those troponin types.

Troponin remains the the one of important factors in diagnostic cardiac events ,and there for many studies focused on this biomarker and its interactions and complications ,and develops of troponin such as Tt and TI (Alaour *et al*.,2018).

There are several causes that take part in elevation of cardiac troponin including cTnT and cTnI ,ischemic heart disease especially acute myocardial infarction are implicated in this problem either reversible or irreversible injuries of heart muscle, from the mechanism which increase subtypes of cardiac troponin are inflammation of cardiac disease ,physical exertion, and pshyco-emotional stress (Chauin ,2021).

Regard the age ,it had been found that high sensitive troponin T values recorded significant heightening in men with age over 40 years old compared to those men who have ages less than 40 years old in patients with MI, In addition to that , it was found women have lower level of hsTnT when they compared to those men with the matched ages (Isilksacan *et al*.,2018).

Also another studies investigated the effects of age of levels of troponin and found that the old age especially more than 60 years old have higher levels of troponin when they are affected with a cute MI compared to those counter parts of healthy one (Ichise *et al*.,2017and Sedighi *et al*.,2019).

Study of vavik *et al*.(2021) it explained there is strong relationship occurring among cardiac troponin ,endothelial abnormalities ,inflammatory biomarkers and obesity ,these factors consider a risk factors in incidence of cardiovascular abnormalities.

Concerning body mass index ,recent study investigated whether BMI affect on cardiovascular events and cardiac biomarker ,and this study in Table (4-7) was established that cardiac troponin ,atrionatriuritic peptid ,and pro natriuretic peptid were positively associated with body mass index (Suthahar *et al*.,2021).

5.9. Relation of myocardial infarction to Tissue Plasminogen Activator -1 (tPA-1):

Results that are obtained from the present study in Tables (4-2), (4-4) and (4-6) indicated a significant increase ($p<0.05$) in the levels of tPA-1 in all patients groups according to sex ,age and asspciated with increase body mass index in Table (4-7) in all patients affected with MI and this biomarker is not correlated with studied parameters. ROC analysis of the disease activity by TPA-1 ,AUC result in Table (4-9) was (0.724).

Previous study was conducted by Lowe *et al*, (2004) ,this study had been established that there was a strong relationship between tPA and other factors including cardiac heart diseases, body mass index, age, blood pressure, inflammatory markers (CRP) and white blood cells.

It was documented that tPI and tPA levels were associated with progressire development acute myocardial infarction and this relation was confirmed in both sexes ,men and women ,moreover ,it was found that tPA and tPI were much higher in patients with MI and this increment is not affected with smoking habits ,BMI , and blood pressure (Thögersen *et al*,1998).

Another study carried out by Mulder *et al*,(2018) indicated that tPA and tPI are associated with increase incidence of stroke and atrial fibrillation, also these observations do not dependent on sex.

Recent study established the fact that fluctuation levels of tPA-1 diminish the regulation mechanism of the hemostatic system and lead to either sever bleeding or incidence of thrombosis ,furthermore ,it was found a strong effect of PAI-1 on cardiovascular complication ,since ,the high levels of circulating pro-inflammatory mediators that are released in to blood stream such as IL-6 ,TNF-α ,these factors affect PAI-1 with the same context obesity was also found to increase levels of PAI-1 (Morrow *et al*,2021) .

Habib *et al*.(2012) confirmed that patients suffering from myocardial infarction and those with angina pectoris having significant elevation in the levels of plasminogen activator ,fibrinogen and C-reactive proteins compared to those healthy subjects ,tissue plasminogen activator is antagonized by the tissue plasminogen in hibitor-1 ,there for the levels of tPAI-1 is associated with cardiovascular events ,so as the fibrinolytic activity become encountered by pro-coagulant factor and these effects may be equal on interactions between coagulation and fibrinolytic system (Jung *et al*.,2018).

Obesity and overweight are more related with high incidence of cardiovascular incidence ,it is well documented that there are many effects of obesity on different mechanisms including fibrinolysis ,inflammatory status ,and thrombotic events ,of those parameters that CRP ,tPA-1,tPAI-1 and IL-6 were remarkably associated with high BMI and represent high risk factors in increment of cardiovascular events of young and older man (Orenes-pinero *et al*.,2015).

The relationship between body mass index and several fibrinolytic ,inflammatory ,and pro thrombotic and anti pro thrombotic biomarker was conducted by El-kader and Jiffiri (2018) ,they in vestingated tPA-1,TNF-α ,fibrinogen ,IL-6 ,pro thrombin time (aptt) and the authors concluded that reduction of body weight to normal values can modulate or regulate fibrinolysis mechanism and inflammation processes of those obese subjects affected with cardiovascular diseases.

5.10. Relation of myocardial infarction to Interleuken-6 (IL-6):

Results of the present study in Tables (4-2), (4-4), (4-6) and (4-7) had been recorded a significant elevation ($p<0.01$) in the levels of IL-6 in in all patients groups according to sex, age, and BMI affected with MI compared to those

control group. ROC analysis of the disease activity by IL-6, AUC result in Table (4-9) was (0.767).

Recent studies were conducted to explore the association occurring between cardiovascular diseases and IL-6 especially acute coronary syndrome, however, there are many cytokines are involved with incidence of acute coronary syndrome, of those, TNF-α, interleukins, adipokines, chemokines and interferons, in particular, IL-6 was found to have prominent prognostic levels in patients with acute coronary syndrome (Mourouzis *et al*.,2020; Yang *et al*.,2021).

It is well noticeable that IL-6 values are at maximum levels and significantly increased in patients who have coronary heart disease and also constitutes three times higher than those normal healthy people, at the same times, these values of IL-6 are strong associated with inflammatory markers particularly c-reactive protein (Cao *et al*.,2020 ;Chan and Ramji,2020).

Furthermore, previous researches indicated that the patients having long term affected with cardiovascular disease such as IL-6 their blood samples have elevated levels of IL-6 and these levels are independent and not associated with other risk factors including diabetes, total cholesterol, and hypertension, from these studies, it was found that prominent evidence refers to fact that IL-6 initiates activations of macrophages and their infiltration and excelerate expressions of low density lipoprotein receptors that lead to increase libration of tissue factor (an extrinsic clotting factor) which in turn propagate and worse inflammatory and atherosclerosis processes (Libby and Bornfeldt, 2020).

Recent study confirmed that increased release of inflammatory mediators control whatever the vascular plague remain or dissolved and progressive of cardio and cerebrovascular events ,of those inflammatory markers, IL-6 which is largerly cytokines and implicated in development of inflammatory process and oxidative stress that in turn can lead to incidence and progress atherosclerosis and myocardial infarction (Su *et al*.,2021).

In addition, inflammation processes of blood vessels trigger the development and progression of plague deposits which implicated in increased thrombosis events and damage to myocardial muscle, as well as, IL-6 plague a central role in signaling to accelerate and destabilization of vascular plague (Schieffer *et al*.,2004 and Ridker ,2016).

Also, it was demonstrate the relationship between IL-6 and cellular events emerging from myocardial infarction ,it found that IL-6 mediates and potentiate remodeling of affected cardiac muscle ,apoptosis and lowering contractile activity of heart muscle and these effects are resulted by attraction of inflammatory cells to injured area of cardiac muscle (Souza *et al*.,2008).

The study of Arakawa *et al*. (2014) had also explained the role of sexual hormones especially 17 β-estradiol and progesterone in central nervous system to regulate the level of inflammatory cytokines such as IL-1 and IL-6 and this study confirmed that treatment with estrogen replacement therapy attenuate inflammatory effects through decrease the response to stressful conditions.

The relationship between sexual hormones and inflammatory cytokines was demonstrated by Talaat *et al*. (2018), who proved that estrogen, testosterone, IL-6, IL-10, TNF are significantly elevated in patients of MI compared to control and those authors concluded that estrogen exerts anti-inflammatory role on inflammatory cytokine effects.

To explain the effect of age on inflammatory processes further study investigated whatever the old age affect the levels of inflammatory mediators or no ,it is well found that TNF-α, IL-6, IL-2 were positivily correlated with advanced ages compared to young human (Bruunsgaard *et al*.,2000).

5.11. Relation of myocardial infarction to C-reactive Protein (CRP):

Data obtained from the present work had been established significant increase in Tables (4-2), (4-4) , (4-6) and (4-7) of inflammatory cytokine (CRP) in all patients groups according to sex, age, and BMI compared to those of healthy control groups. ROC analysis of the disease activity by CRP, AUC result in Table (4-9) was (0.724).

It is well known that inflammation can evoke and increase initiation and development of coronary artery disease, there for, the levels of CRP is at higher level with severity of cardiovascular diseases, it increases two fold in patients with CAD compared to healthy subjects, so that CRP consider the powerful indicator to evaluate the severity of MI (Bouzidi *et al*.,2020).

On the basis of molecular point view, the increase adhesion molecules (CAM) and activation of inflammatory cells can co-operate to induce release of inflammatory mediators and pro coagulant molecules, these event eventully enhance thickening of atherosclerotic lesions and progress of acut coronary disease in panticular MI (Razi *et al*.,2017 and Ma *et al*.,2018).

Physiologically, CRP is synthesized by hepatocytes and its synthesis is dependent on the other pro-inflammatory biomarkers especially IL-6, IL-6 and TNF-α previous study have shown higher up regulation of CRP levels in patients complained from angina pectoris, MI, obesity, insulin resistance (Kaur *et al*.,2013).

Another recent study is designed to evaluation of high sensitivity CRP levels in heart disease and it established that the levels of CRP are increased three times in MI and heart failure and it concluded that systemic inflammation can worse of the MI and cardiac failure (Magielski and Kubica ,2021).

As well as, during myocardial infarction occurs activation for inflammatory mediators and this process is accompanied with heart damage and repairing

mechanism, so that increase inflammatory mediators can lead to several cardiac damage and dysfunction (Swiatkiewicz *et al*.,2020).

Study of Milano *et al*.(2019), was designed to determine the association between high sensitive CRP concentrations and myocardial infarction patients, this study was found increase levels of CRP in patients with MI in matching with those healthy people, at the same time, it concluded that the major response of inflammation for tissue damage and CRP is prognostic factor to this response.

In regards, the relationship between body mass index and c-reactive protein ,it had been documented that obesity represents chronic low level of inflammatory condition and this is recognized by elevation of specific inflammatory parameter that is c-reactive proteins, these facts were confirmed by study which indicated a significant positive correlation occurring between CRP and BMI (Farooq *et al*.,2017).

Conclusions and Recommendations

Conclusions :

From the present data the following can be concluded:-

1. There is a relationship between BMI and incidence of MI.
2. Gender affects incidence of MI, the males was affected more than females.
3. Ageing considers the predisposing factor in development of MI.
4. Increase fibrinolytic activity in patients with MI.
5. Elevation of inflammatory markers may be implicated in development and progression of MI.

Recommendations:

1. Study the relationship between sexual hormone (estrogen and testosterone) and incidence of cardiovascular disease.
2. Effects of age, gender, BMI on the activity of other fibrinolytic components.
3. Perform molecular study to investigate gene expression of tissue plasminogen activator.
4. Individuals with advanced age should be avoided obesity and control their BMI with normal values.

References

References:

Ait-Oufella, H.; Sage, A.P.; Mallat, Z.; and Tedgui, A. (2014). Adaptive (T and B cells) immunity and control by dendritic cells in atherosclerosis. Circ. Res.,114(10):1640–1660.

Alaour, B. ; Liew, F. ; and Kaier, T.E. (2018). Cardiac troponin–diagnostic problem and impact on cardio vascular disease. Annals of Med., 50(8): 655–665.

Alberts, B.; Johnson, A.; Lewis, M.; Raff, M.; Roberts, K.; and Walter, P. (2002). Leukocyte also known as macrophagesfunctions and percentage breakdown. Molecular Biology of the Cell (4th Ed.). New York: Garland Science.

Alomari, M.; Bratton, H.,; Musmar, A.; Al Momani, L.A.; and Young, M. (2019). Ticagrelor-induced Diarrhea in a Patient with Acute Coronary Syndrome Requiring Percutaneous Coronary Artery Intervention. Cureus., 11(1):e3874.

Amraotkar, A.R.; Song, D.D.; Otero, D.; Trainor, P.J.; and Ismail, I. (2017). Platelet count and mean platelet volume at the time of and after acute myocardial unfarction. Clin. Appl. Thromb. Hemost., 23(8): 1052–1059.

Arakawa, K.; Arakawa, H.; Hueston, C.M.; and Deak, T. (2014). Effects of the estrus cycle and ovarian hormones on central expression of interleukin-1 evoked by stress in female rats. Neuroendocrinology., 100: 162–177.

Avolio, A.; Butlin, M.; Liu, Y. Y.; Viegas, K.; Avadhanam, B.; and Lindesay, G. (2011). Regulation of arterial stiffness: Cellular, molecular and neurogenic mechanisms. Artery Research., 5(4), 122-127.

Aznaouridis, K. A. and Stefanadis, C. I. (2007). Inflammation and arterial function. Artery Research., 1(1), 32-38.

Bach, R.R. (2006). Tissue factor encryption. Arterioscler. Thromb. Vasc. Biol.; 26: 4561-461.

Bailey, K. (1946). Tropomyosin: A new asymmetric protein component of muscle. Nature., 157:368–369.

Baloglu, U. B.; Talo, M.; Yildirim, O.; San Tan, R.; and Acharya, U. R. (2019). Classification of myocardial infarction with multi-lead ECG signals and deep CNN. Pattern Recognition Letters., 122: 23-30.

Bannish, B. E.; Chernysh, I. N.; Keener, J. P.; Fogelson, A. L.; and Weisel, J. W. (2017). Molecular and physical mechanisms of fibrinolysis and thrombolysis from mathematical modeling and experiments. Scientific reports., 7(1):1-11.

References .

Bayes–Genis, A.; Mateo, J.; Santaló, M.; Oliver, A.; and Guindo, J. (2000). D–dimer is an early diagnostic marker of coronary ischemia in patients with chest pain. Am. Heart J., 140(3): 379–384.

Bianconi, E.; Piovesan, A.; Facchin, F.; Beraudi, A.; Casadei, R.; Frabetti, F.; and Canaider, S. (2013). An estimation of the number of cells in the human body. Annals of human biology, 40(6):463-471.

Black, S.; Kushner, I.; and Samols, D. (2004). C-reactive protein. J. BiolChem.; 279:48487-48490.

Blum, A.; Sheiman, J.; and Hasin, Y. (2002). Leukocytes and acute myocardial infarction. IMAJ, 4: 1060–1064.

Boeder, N. F.; Nef, H. M.; and Bauer, T. (2017). Thebesian veins as drainage to the ventricle: A case report. Cardiovascular Revascularization Medicine, 18(3), 213-214.

Bodor, G.S.; Porter, S.; Landt, S.; and Ladenson, J.H.(1992). Development of monoclonal antibodies for an assay of cardiac troponin I and preliminary results in suspected cases of myocardial infarction. Clin Chem; 38:2203–2214.

Borissoff, J.I.; Spronk, H.M.; and Cate, H. (2011). The hemostatic system as a modulator of atherosclerosis. N. Engl. J. Med., 364(18): 1746–1760.

Bouzidi, N.; Messaoud, M.B.; Maatouk, F.; Gamra, H.; and Ferchichi, S. (2020). Relationship between high sensetivity C–reactive protein and angio graphic severity of coronory artery disease. J. Geriatric Cardial., 17(5): 256–263.

Bracey, A. and Meyers, H.P.(2021). Posterior Myocardial Ischemia. In: StatPearls [Internet].

Bridges, K. R. (2007).Iron Transport and Cellular, Information Center for Sickle Cell and Thalassemic Disorders.

Brummel-Ziedins, K. and Mann, K. G. (2018). Molecular basis of blood coagulationin. In: Hoffman R Hematology: Basic principles and practice. Elsevier, Philadelphia, :1885-1905.

Bruunsgaard, H.; Pedersen, A.N.; Schroll, M.; Shinho, P.; and Pedersen, B.K. (2000). TNF-alpha, leptin, and lymphocyte function in human aging. Life Sci., 67(22): 2721–2731.

Cao, D.; Chiarito, M.; and Mehran, R. (2020). Treating inflammation prior to precutaneous coronary intervention : Dose the heart care?. Circ. Cardiovasc. Interven., 13(4): e 009127.

Centers for disease control and prevention (2019). Coronary Heart Disease, Myocardial Infarction, and Stroke.

Chan, Y. H.; and Ramji, D. P. (2020). A perspective on targeting inflammation and cytokine actions in atherosclerosis. *Future Medicinal Chemistry*, *12*(7),

613-626.

Chaturvedi, S.; Brodsky, R.A.; and Mc Care, K.R. (2019). Complement in the pathophysiology of the antiphospholipid syndrome. Front. Immunol., 10:449.

Chauin, A. (2021). Concentration other than acute myocardial infarction (part1): Physical exertion, inflammatory heart disease, pulmonary embolism, renal failur sepsis. J. Vasc. Health and Risk Management, 17: 601–617.

Christersson, C.; Oldgren, J.; Bylock, A.; Siegbahn, A.; and Wallentin, L. (2007). Early decrease in coagulation activity after myocardial infarction is associated with lower risk of new ischaemic events: observations from the ESTEEM Trial. European heart journal, 28(6),692-698.

Chung, D.W.; Harris, J.E.; and Davie, E.W. (1990). Nucleotide sequences of the three genes coding for human fibrinogen. Adv. Exp. Biol., 39-48.

Cimmino, G. and Cirillo, P. (2018). Tissue factor. Newer concepts in thrombosis and its role beyond thrombosis and hemostasis. Cardiovasc. Diagn. Ther.; 8 (5): 581-593.

Cohn, L.; Catherine, H.; and Anuradha, R. (2014). Biology of Lymphocytes. Middleton's Allergy: Principles and Practic. 203–214. doi:10.1016/B978-0-323-08593-9.00013-9.

Colledge, N. R.; Walker, B. R.; Ralston, S.; and Davidson, S. (2018). Davidson's principles and practice of medicine. Edinburgh: Churchill Livingstone/Elsevier.

Coller, B.S. (2002). Leukocytosis and ischemic vascular disease morbidity and mortality: is it to intervenes. Arterioscler Thromb.Vas.Biol., 25: 658–670.

Cummins, B.; Auckland, M.L.;and Cummins, P.(1987). Cardiac-specific troponin I radioimmunoassay in the diagnosis of acute myocardial infarction. Am Heart J; 113:1333–1344.

Daniel, W.W. (1999). Biostatistics: a foundation for analysis in the health science. 7th. ed. John Wily. Philadelphia.

Davie, E.D. and Ratnoff, O.D. (1964). Waterfall sequence for intrinsic blood clotting. Science, 145: 1310-1312.

Dawn, B.; Xuan, Y. T.; Guo, Y.; Rezazadeh, A.; Stein, A. B.; Hunt, G.; and Bolli, R. (2004). IL-6 plays an obligatory role in late preconditioning via JAK–STAT signaling and upregulation of iNOS and COX-2. Cardiovascular research, 64(1), 61-71.

De Lemos, J. A.; Newby, L. K.; and Mills, N. L. (2019). A proposal for modest revision of the definition of type 1 and type 2 myocardial infarction. Circulation, 140(22), 1773-1775.

Demaerschalk, B. M.; Kleindorfer, D. O.; Adeoye, O. M.; Demchuk, A. M.;

References .

Fugate, J. E.; Grotta, J. C.; and Smith, E. E. (2016). Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke, 47(2), 581-641.

Docherty, A.; Turgeon, A. and Walsh, T. (2018). Best Practice In Critical Care: Anaemia In Acute and Critical Illness. Transfusion Medicine, 28, 181-189.

Dorfleutner, A. and Ruf, W. (2003). Regulation of tissue factor cytoplasmic domain phosphorylation by palmitoylation. Blood, 102: 3998-4005.

Drechsler, M.; Megens, R. T.; van Zandvoort, M.; Weber, C.; and Soehnlein, O. (2010). Hyperlipidemia-triggered neutrophilia promotes early atherosclerosis. Circulation, 122(18):1837-1845.

Ebashi, S.; Kodama, A.;and Ebashi, F.(1968). Troponin I. Preparation and physiological function. J. Biochem.; 64:465–477.

Eidizadeh, A. ; Fraune, L. ; Leha, A. ; Wachter, R. ; and Bender, L. (2021). In consistent findings of cardiac troponin T and I in clinical routin diagnostics: factors of influence. J. Clin. Med., 10: 3148.

El–Kader, S.M. and Jifferi, O.H. (2018). Coagulation, fibrinolytic and cytokines parameters response to weight reduction in obese subjects. Eur. J. Med., 15(1): 27–32.

Erkol, A.; Oduncu, V.; Turan, B.; Kılıçgedik, A.; Sırma, D.; Gözübüyük, G.; and Kırma, C. (2014). The value of plasma D-dimer level on admission in predicting no-reflow after primary percutaneous coronary intervention and long-term prognosis in patients with acute ST segment elevation myocardial infarction. Journal of thrombosis and thrombolysis, 38(3), 339-347.

Esmon, C.T. (2005). The interaction between inflammation and coagulation. British J. Haematol., 131:417–430.

Falcone, F. H.; Haas, H.; and Gibbs, B. F. (2000). The human basophil: a new appreciation of its role in immune responses. BLOOD-NEW YORK-, 96(13), 4028-4038.

Farooq, S.N.; Ahmed, A.; Mustafa, M.A.; Safi, M.I., Serafi, A.H.; and Khan, A.A. (2017). High sensitivity C–reactive protein level increases with rise in body mass index and not affected by perceived stress in young saudis. Annals Med. Health Sci. Res., 7: 224–229.

Ferrari, J. P.; Lueneberg, M. E.; Silva, R. L.; Fattah, T.; and Gottschall, A. M. (2016). Correlatiion between leukocyte count and infarct size in ST segment elevation myocardial infarction. Arch. Med. Sci. Atherosclero. Dis., 1(1): e 44– e 48.

Ferraro, R.; Latina, J. M.; Alfaddagh, A.; Michos, E. D.; Blaha, M. J.; Jones, S. R.; and Arbab-Zadeh, A. (2020). Evaluation and management of patients with stable angina: beyond the ischemia paradigm: JACC state-of-the-art

review. J. Am. Coll. Cardiol. 76(19):2252-2266. doi:10.1016/j.jacc.2020.08.078.

Florholmen, G.; Thoresen, G. H.; Rustan, A. C.; Jensen, J.; Christensen, G.; and Aas, V. (2006). Leukaemia inhibitory factor stimulates glucose transport in isolated cardiomyocytes and induces insulin resistance after chronic exposure. Diabetologia, 49(4), 724-731.

Fontes, J. A.; Rose, N. R.; and Čiháková, D. (2015). The varying faces of IL-6: From cardiac protection to cardiac failure. Cytokine, 74(1), 62-68.

Forbes, C.D. and Jackson, W.F. (2003). Color Atlas and Text of Clinical Medicine. ISBN 10: Lincoln, United Kingdom.

Fossel, C.; Luther, T.; Muller, M.; Albrech, S.; and Kasper, M. (1994). Immunohistochemistry detection of tissue factor (TF) on Paraffin selection of routinely fixed human tissue. Histochemistry, 10 (6): 449-453.

Frangogiannis, N. G. (2006). Targeting the inflammatory response in healing myocardial infarcts. Current medicinal chemistry, 13(16), 1877-1893.

Frangogiannis, N. G. (2014). The inflammatory response in myocardial injury, repair, and remodelling. Nature Reviews Cardiology, 11(5), 255-265.

Frangogiannis, N. G.; Smith, C. W.; and Entman, M. L. (2002). The inflammatory response in myocardial infarction. Cardiovascular research, 53(1), 31-47.

Gajsiewicz, J.M. and Morrissey, J.H. (2016). Structure-Function relationship of the interaction between tissue factor and factor VIIa. Semin. Thromb. Hemost., 41(7): 682-690.

Garmo, C.; Bajwa, T.; and Burns, B. (2021). Physiology, Clotting Mechanism. In: StatPearls. StatPearls Publishing, Treasure Island (FL). PMID: 29939572.

Ganong, W.F. (2010). Physiology of Coagulation. Review of Medical Physiology. 22: 647-660.

Giannitsis, E.; Mair, J.; Christersson, C.; Siegbahn, A.; Huber, K.; Jaffe, A. S.; and Biomarker Study Group of the European Society of Cardiology (ESC) Acute Cardiovascular Care Association (ACCA). (2017). How to use D-dimer in acute cardiovascular care. European Heart Journal: Acute Cardiovascular Care, 6(1), 69-80.

Gravanis, I.; and Tsirka, S. E. (2008). Tissue-type plasminogen activator as a therapeutic target in stroke. Expert opinion on therapeutic targets, 12(2), 159-170.

Graham, I.; Atar, D.; Borch-Johnsen, K.; Boysen, G.; Burell, G.; Cifkova, R.; Dallongeville, J.; De Backer, G.; Ebrahim, S.; Gjelsvik, B.; Herrmann-

References .

Lingen, C.; Hoes, A.; Humphries, S.; Knapton, M.; Perk, J.; Priori, S.G.; Pyorala, K.; Reiner, Z.; Ruilope, L.; Sans-Menendez, S.; Scholte op Reimer, W.; Weissberg, P.; Wood, D.; Yarnell, J.; Zamorano, J.L.; Walma, E.; Fitzgerald, T.; Cooney, M.T.; Dudina, A.(2007). European guidelines on cardiovascular disease prevention in clinical practice: executive summary: Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by representatives of nine societies and by invited experts). Eur. Heart J. 28 (19): 2375–414.

Greenspan, F.S. and Gardner, D.G. (2004). Basic and clinical endocrinology. 7thed.McGraw Hill companies, Inclincal 70:324-341.

Grover, S.P. and Mackman, N. (2018). Tissue factor: an essential mediator of hemostasis and trigger of thrombosis. Arterioscler. Thromb. Vasc. Biol., 38(4): 709-725.

Guo, W.; Wang, H.; Zhao, W; Zhu, J.; JU, B.; and Wang, X. (2001). Effect of all-trans retinoic and arsenic trioxide on tissue factor expression in acute promyelocytic leukemia cells. Chinese Med. J., 114 (1): 30-40.

Gwechenberger, M.; Mendoza, L. H.; Youker, K. A.; Frangogiannis, N. G.; Smith, C. W.; Michael, L. H.; and Entman, M. L. (1999). Cardiac myocytes produce interleukin-6 in culture and in viable border zone of reperfused infarctions. Circulation, 99(4), 546-551.

Habib, S.S.; Gader, A.G., Kurdi, M.I. and Suriya, M.O. (2012). Tissue plasminogen activator inhibitor-1 levels in patients with acute myocardial infarction and ustable angina pectoris. J. Pakistan Med. Assoc. 62(7): 681–685.

Hafez, M. ; El–Masry, S.; Musa, N. ; and Fathy, M. ; (2016). Relationship between viszeral obesity and plasma fibrinogen in obese children. J. Pediatr. Endocrinol. Metab. , 29(3):289–296.

Halucha, K.; Pasikowska, A.R.; and Lula, I.B. (2021). Protective role of platelets in myocardial infarction and iscemia/reperfusion injury (2021). Cardiol. Res. Practice, 25(1): 1–8.

Hamza, M.A.; Mahmoud, M.; Abd–el Ghaffar, M.; and El–Tayeb, A. (2021). Relationship between Red Blood cell Distribution Width and Extent of Coronary Artery Disease in Patient with ST Elevation Myocardial Infarction.

Hansson, G. K. (2005). Inflammation, atherosclerosis, and coronary artery disease. New England journal of medicine, 352(16), 1685-1695.

Head, J.F.; Weeks, R.A.;and Perry, S.V.(1977). AYnity chromatographic isolation and some properties of troponin C from diVerent muscle types.

Biochem. J.; 161:465–471.

Heiferman, D. M.; Li, D. D.; Pecoraro, N. C.; Smolenski, A. M.; Tsimpas, A.; and Ashley Jr, W. W. (2017). Intra-arterial alteplase thrombolysis during mechanical thrombectomy for acute ischemic stroke. Journal of Stroke and Cerebrovascular Diseases, 26(12), 3004-3008.

Hillman, R. S.; Ault, K. A.; and Rinder, H. M. (2005). Hematology in Clinical Practice: A Guide to Diagnosis and Management (4 ed.). McGraw-Hill Professional, 4th edition.

Hjortoe, G.M.; Petersen, L.C.; and Albrektsen, T. (2004). Tissue factor-factor VII-specific up-regulation of IL-8 expression in MDA-MB 231 cells is mediation by PAR-2 and results in increased cell migration. Blood, 103 (8): 3029-3037.

Hoebe, K.; Janssen, E.; and Beutler, B. (2004). The interface between innate and adaptive immunity. Nature immunology, 5(10), 971-974.

Hong, L.F.; Li, X.L.; Luo, S.H.; Guo, Y.L.; Liu, J.; Zhu, C.G.; Qing, P.; Xu, R.X.; Wu, N.Q.; Jiang, L.X.; and Li, J.J. (2014). Relation of leukocytes and its subsets counts with the severity of stable coronary artery disease in patients with diabetic mellitus. PLoS One, 9(3), e90663.

Hong, J., Maron, D. J., Shirai, T., and Weyand, C. M. (2015). Accelerated atherosclerosis in patients with chronic inflammatory rheumatologic conditions. International journal of clinical rheumatology, 10(5), 365-381.

Huang, L. H.; Lavine, K. J.; and Randolph, G. J. (2017). Cardiac lymphatic vessels, transport, and healing of the infarcted heart. Basic to Translational Science, 2(4), 477-483.

Hulshof, A.M. ; Hemker, H.C. ; Spronk, H.M.H., Henskens, Y.M.C. ; and cate, H.T. (2021). Thrombin–fibrinogen interactions, host defense and risk of theombosis. Int. J. Mol. Sci., 22(5):2590(Article).

Ichise, T. ; Tada, H. ; Sakata, K. ; Kawashkri, M. ; and Yamagishi, M. (2017). Impact of aging on high–sensetivity cardiac troponin T in patients suspected of acute myocardial infarction. Inter. Med., 56(18): 2087–2102.

Isilksacan, N.; Biyik, I. ; Opan, S. ; Cagar, F.N.T. ; and Yazan, S. (2018). Effect of age and gender differences on high sensitive troponin T measurement in the diagnosis of acute myocardial infarction. J.Lab.Med., https://doi.org/10.1515/labmed–218–0102.

Janeway, C.A.; Travers, P.; Walport, M.; and Shlomchik, M.J. (2001). Immunobiology (5th ed.). New York and London: Garland Science. ISBN-10: 0-8153-3642.

Jani, B. and Rajkumar, C. (2006). Ageing and vascular ageing. Postgrad Med. J. 82: 357–362.

References .

Jardins, T. D. (2020). Cardiopulmonary anatomy & physiology: Essentials for respiratory care 7th Edition.

Jiang, P. ; Gan, Z. ; Zhao, W. ; Song, Y. ; Tang, Xu, J.J. ; and Wang, H.H. (2019). Relationship between Fibrinogen levels and cardiovascular events in patients recieving precutaneous coronary intervention: a large single–center study. Chin. Med. J. (Engl), 132(8): 814–921.

Jilani, T. N.; and Siddiqui, A. H. (2021). Tissue plasminogen activator. In StatPearls [Internet]. StatPearls Publishing.

Johnson, E. D.; Schell, J. C.; and Rodgers, G. M. (2019). The D-dimer assay. American journal of hematology, 94(7), 833-839.

Jokela, M.; Pukki–Raback, L.; Elovaino, M.; and Kivimaki, M. (2014). Personality traits as risk factor for stroke and coronary heart disease mortality : pooled analysis of three cohort studies. J.behavioral Med., 37(5): 881–889.

Jones, S. A. (2005). Directing transition from innate to acquired immunity: defining a role for IL-6. The Journal of Immunology, 175(6), 3463-3468.

Jousilahti,V. and Tuomilehto, P.(1999). Sex, Age, Cardiovascular Risk Factors, and coronary heart disease. Circulation 99: 1165–1172.

Jung, R.G.; Motazedian, P.; Ramirez, D.; Simared, T.; Santo, P.D.; and Visitini, S. (2018). Association between plasminogen activator inhibitor-1 and cardiovascular events: a systematic review and meta- analysis. Thromb. J., 16: 12.

Kant, J.A.; Forace, A.J.; Saxe, D.; Simon, M.I.; Mcbride, O.W.; and Crabtree, G.R. (1985). Evolution and organization of the fibrinogen locus on chromosome 4: gene duplication accompanied by transposition and inversion. Proc. N atl. Acad. Sci. USA., 185: 1- 19.

Kaplanski, G.; Marin, V.; Montero-Julian, F.; Mantovani, A.; and Farnarier, C. (2003). IL-6: a regulator of the transition from neutrophil to monocyte recruitment during inflammation. Trends in immunology, 24(1), 25-29.

Kar-mun, C. W.; and Schneider, J. I. (2009). High-risk chief complaints I: chest pain—the big three. Emergency Medicine Clinics, 27(4), 685-712.

Kattula, S.; Byrnes, R., J.; and Wolberg; A.S. (2017). Fibrinogen and fibrin in hemostasis and thrombosis. Arterioscler. Thromb. Vasc. Biol., 37: e13-e21.

Katus, H.A.; Remppis, A.; Looser, S.; Hallermeyer, K.; ScheVold, T.;and Kubler, W.(1989). Enzyme linked immunoassay of cardiac troponin T for the detection of acute myocardial infarction in patients. J. Mol. Cell. Cardiol.; 21:1349–1353.

Kaur, R.; Matharoo, K.; and Sharma, R. (2013). CRP+1059GNC polymorphism

in type 2 diabetes and coronary artery disease patients. Meta. Gene., 1: 82–92.

Kerneis, M.; Nafee, T.; Yee, M. K.; Kazmi, H. A.; Datta, S.; Zeitouni, M.; and Gibson, C. M. (2019). Most promising therapies in interventional cardiology. Current Cardiology Reports, 21(4), 1-8.

Kloner, R. A. and Chaitman, B. (2017). Angina and its management. Journal of Cardiovascular Pharmacology and Therapeutics, 22(3), 199-209.

Koening, W.; Sand, M.; Ernst, E.; Keil, V.; and Rosenthal, J. (1991). Association between plasma viscosity and blood pressure. Am.J. Hypertens., 4(6): 529–536.

Kornblith, L. ; Howard, B. ; Kunitake, R. ; Redick, B. ; and Nelson, M. (2015). Obesity and clotting: BMI independently contributes to hyper coagulability after injury. J. Trauma Acute Care Surg., 78(1): 30–38.

Kramer, A. H.; Jenne, C.; Holodinsky, J. K.; Todd, S.; Roberts, D. J.; Kubes, P.; and Wong, J. H. (2015). Pharmacokinetics and pharmacodynamics of tissue plasminogen activator administered through an external ventricular drain. Neurocritical care, 23(3), 386-393.

Kryczka, K.E. ; Kruk, M. ; Demkow, M. ; and Lubiszewska, B. (2021). Fibrinogen and a triad of thrombosis , inflammation and the renin–angiotensin system in prature coronary artery disease in women : a new insight in to sex–related differences in pathogenesis of the disease. Biomolecules, 11:1036 (Review).

Kul, A.N.; Ozdemir, S.; Helvaci, A.; Bulut, C.; and Dursun, S. (2014). The relationship of acute myocardial infarction with or without ST–segment elevation and viscosity. Clin.Appl.Thrombo. Henost., 20(8): 779–782.

Lacolley, P.; Challande, P.; Regnault, V.; Lakattac, E.G.; Wang, M. (2015). Cellular and molecular determinants of arterial aging. In: Nilsson P, Olsen M, Laurent S, editors. Early Vascular Aging. Academic Press, Elsevier p. 7–13.

LaFleur-Brooks, M. (2008). Exploring Medical Language: A Student-Directed Approach (7th ed.). St. Louis, Missouri, US: Mosby Elsevier. p. 398.

Lanza, G.A. and Crea, F.(2010). Cardiopatia ischemica. In Medicina Interna. Sistematica, Edra-Masson; Elselvier Italia srl: Milan, Italy, 2010; 1:103–149.

LaPelusa, A.; and Dave, H. D. (2021). Physiology, Hemostasis. In StatPearls. StatPearls Publishing.

Lawson, J.H.; Butenas, S.; and Mann, K.G (1992). The evalution of complex-dependent alterations in human factor VIIa. J. Biol. Chem., 767 (7): 4834-4843.

Legein, B.; Temmerman, L.; Biessen, E. A.; and Lutgens, E. (2013).

Inflammation and immune system interactions in atherosclerosis. Cellular and Molecular Life Sciences, 70(20), 3847-3869.

Levy, J.H.; Sziam, F.; Tanaka, K.A.; and Snieciski, R.M. (2011). Fibrinogen and hemostasis: a primary hemostatic target for the management of a quired bleeding. Anethesia and Analgesia, 114(2): 261-274.

Li, Y.; Li, H.; and Zhang, D. (2020). Timing of Norepinephrine Initiation In Patients With Septic Shock: A Systematic Review and Meta-Analysis. Critical Care, 24, 1-9.

Libby, p. and Bornfeldt, K.E. (2020). How far we have come, How far we have yet to go in atherosclerosis resesrch. Circ. Res., 126(9): 1107–1111.

Libby, P.; Ridker, P. M.; and Maseri, A. (2002). Inflammation and atherosclerosis. Circulation, 105(9), 1135–1143.

Lin, Z. Q.; Kondo, T.; Ishida, Y.; Takayasu, T.; and Mukaida, N. (2003). Essential involvement of IL-6 in the skin wound-healing process as evidenced by delayed wound healing in IL-6-deficient mice. Journal of leukocyte biology, 73(6), 713-721.

Loukas, M.; Bilinsky, S.; Bilinsky, E.; El-Sedfy, A.; and Anderson, R. H. (2009). Cardiac veins: a review of the literature. Clinical Anatomy: The Official Journal of the American Association of Clinical Anatomists and the British Association of Clinical Anatomists, 22(1), 129-145.

Lowe, G.D.O.; Danesh, J.; Lewington, S.; Walker, M.; Lenon, L.; and Thomas, A. (2004). Tissue plasminogen activator antigen and coronary heart disease: Prospective study and meta-analysis. Eur. Heart J., 25(3): 252–259.

Lundergan, C.F.; Ross, A.M.; and McCarthy, W.F. (2001). Predictors of left ventricular function after acute myocardial infarction: effects of time to treatment, patency, and body mass index. Am. Heart J. 142(1):43-50.

Ma, C.Y.; Xu, Z.Y.; and Wang, S.P. (2018). Change of inflammatory factors in patients with acute coronary syndrome. Chin. Med. J., 131: 1444–1449.

Mackam, N. (2004). Role of tissue factor in Hemostasis, Thrombosis, and vascular development. Arteriosclerosis, Throm., and Vasc. Biol., 24: 1015-1022.

Mackay, J. ; Mensah. G. ; Mendis, S.; and Greenland, K.(2004) .The Atlas of Heart Disease and Stroke. World Health Organization.

Magielski, P. and Kubica, J. (2021). C–Reactive protein as a risk marker for post–infarct heart failnre over a multi–year period. Int. J. Mol. Sci., 22: 3169 (article).

Mannila, M.N.; Erikson, P. ; Ericsson, C.G.; Hamsten, A. ; and Silveira, A. (2006). Epistatic and pleiotropic effects of polymorphisms in the fibrinogen and coagulation factor Xlll genes on plasma fibrinogen concentration, fibrin

gel structure and risk of myocardial infarction. Thromb. Haemost., 95: 420–427.

Mansour, H.M. and El–Sakhawy, Y.N. (2020). Initially presented acute coronary syndrome: does D-dimer imply any clinical significans? . Egyptian J. Haematol., 45(1): 23–27.

Marrugat, J.; Sala, J.; Manresa, J.M.; Gill, M.; Elosua, R.; and Perez, G. (2004). Acute myocardial infarction population incidence and in–hospital management factors. Eur.J. Epidemiol., 19(3): 231–237.

Mast, A.E. (2016). Tissue factor or pathway inhibitor multiple anticoagulant activities for single protein. Arterioscler. Thromb. Vasc. Biol., 36: 9-14.

Maton, D.; Hopkins, J.; McLaughlin, C.W.; Johnson, S.; Warner, M.Q.; LaHart, D.; Wright, J.D.; and Kulkarni, D.V. (1997). Human Biology and Health. Englewood Cliffs, New Jersey, US: Prentice Hall.

McEniery, C. M.; Qasem, A.; Schmitt, M.; Avolio, A. P.; Cockcroft, J. R.; and Wilkinson, I. B. (2003). Endothelin-1 regulates arterial pulse wave velocity in vivo. J. Am. Coll. Cardiol., 42(11):1975–1981.

Meilahn, E.; Cauley, J.A. ; and Tracy, R.P. (1996). Association of sex hormones and diposity with plasma levels of fibrinogen and PAI-1 in postmenopausal women. Am. J. Epidiol., 143(2): 159–166.

Miao, J. H.; and Makaryus, A. N. (2021). Anatomy, Thorax, Heart Veins. In StatPearls [Internet]. StatPearls Publishing. NCBI Bookshelf. A service of the National Library of Medicine, National Institutes of Health.

Milano, S. S.; Junior, O.V.; Bordin, A.A.S.; and Lenci, G. (2019). C–reactive protein is predictor of mortality in ST–segment elevation acute myocardial infarction. Int. J. Cardiovas. Sci., 32(2) 118–124.

Monore, Hoffman, M.; and Roberts, H.R. (2010). Molecular Biology and Biochemistry of the coagulation factors and pathways of Hemostasis. In: Williams Hematology. 8th ed., New York NY: Mc Graw-Hill professional publishing P: 614-630.

Morrow, G. B.; Whyte, C. S.; and Mutch, N. J. (2021). A serpin with a finger in many PAIs: PAI-1's central function in thromboinflammation and cardiovascular disease. *Frontiers in cardiovascular medicine*, *8*, 653655.

Mourouziz, K.; Oikonomou, E.; Siasos, G.; and Tsalamdris, S. (2020). Pro-inflammatory cytokines in acute coronary syndrome. Curr. Pharm. Des., 26(36): 4624–4647.

Mozos, I. (2015). Mechanisms linking red blood cell disorders and cardiovascular diseases. Biomed. Res. Int., 2015: 682054.

Mozos, I.; Malainer, C.; Horbańczuk, J.; Gug, C.; Stoian, D.; Luca, C. T.; and

References .

Atanasov, A. G. (2017). Inflammatory Markers for Arterial Stiffness in Cardiovascular Diseases. Frontiers in immunology, 8: 1058.

Mulder, B.A.; Geelhoed, B.; Harst, P.V.; Spronk, H.M.; and Gelder, I.C.V. (2018). Plasminogen activator inhibitor-1 and tissue plasminogen activator and incident AF: Data from the prevend study. Inter. J. Cardiol., 272: 208–210.

Negahdary, M. ; Namayandeh, S.M. ; Ardekan, M.B. ; Ghobadzadeh, S. ; and Deghani, H. (2016). The importance of the troponin biomarker in myocardial infarction. J. Biol. To day's World, 5(1): 1–12.

Niedermeyer, J.; Meissner, E.; and Fabel, H. (1993). Thrombolytic therapy in pulmonary embolism. Indications and therapeutic strategies. Zeitschrift fur die gesamte innere Medizin und ihre Grenzgebiete, 48(6-7), 332-343.

Niessner, A.; and Weyand, C. M. (2010). Dendritic cells in atherosclerotic disease. Clinical immunology, 134(1), 25-32.

Ochi, A. ; Adachi, T. ; Inokuchi, K. ; Ogawa, K. ; Nakamura, Y. ; and Chiba, Y. (2016). Effects of aging on the coagulation fibrinolytic system in outPAtients of the cardiovascular department. Circulation J. , 80(10): 2133–2140.

Ohman, E. M. (2016). Chronic stable angina. New England Journal of Medicine, 374(12), 1167-1176.

Oldgren, J.; Linder, R.; Grip, L.; Siegbahn, A.; and Wallentin, L. (2001). Coagulation activity and clinical outcome in unstable coronary artery disease. Arteriosclerosis, thrombosis, and vascular biology, 21(6), 1059-1064.

Olson, J.D.(2015). D-dimer: an overview of hemostasis and fibrinolysis, assays, and clinical applications. Adv Clin Chem. 69:1-46.

Omman, R. A.; and Kini, A. R. (2020). Leukocyte development, kinetics, and functions. Rodak’s Hematology: Clinical Principles and Applications; Keohane, EM, Otto, CN, Walenga, JM, Eds, 117-135.

Orenes–Pinero, E., pineda, J.; Roldon, V.; and Romero, D.H. (2015). Effects of body mass index on the lipid and profil and Biomarkers of inflammation and fibrinolytic and prothrombotic state. J. Atheros.Thromb., 22(6): 610–617 (original article).

Orkin, S. H.; and Zon, L. I. (2008). Hematopoiesis: an evolving paradigm for stem cell biology. Cell, 132(4), 631-644.

Orn, S.; Manhenke, C.; Ueland, T.; Damås, J. K.; Mollnes, T. E.; Edvardsen, T.; and Dickstein, K. (2009). C-reactive protein, infarct size, microvascular obstruction, and left-ventricular remodelling following acute myocardial infarction. European heart journal, 30(10), 1180-1186.

Ortale, J. R.; Gabriel, E. A.; Iost, C.; and Marquez, C. Q. (2001). The anatomy

of the coronary sinus and its tributaries. Surgical and Radiologic Anatomy, 23(1), 15-21.

Owen, D.R.; Lindsay, A.C.; Choudhury, R.P.; and Fayad, Z.A. (2011). Imaging of atherosclerosis. Annu Rev Med. 62:25–40.

Pai, J. K.; Pischon, T.; Ma, J.; Manson, J. E.; Hankinson, S. E.; Joshipura, K.; and Rimm, E. B. (2004). Inflammatory markers and the risk of coronary heart disease in men and women. New England Journal of Medicine, 351(25), 2599-2610.

Pallister, C.J. and Watson, M.S. (2010). Haematology. second edition 2nd Edition.

Palareti, G.; Legnani, C.; Antonucci, E.; Cosmi, B.; Poli, D.; Testa, S.; and Prandoni, P. (2020). D-dimer testing, with gender-specific cutoff levels, is of value to assess the individual risk of venous thromboembolic recurrence in non-elderly patients of both genders: a post hoc analysis of the DULCIS study. *Internal and emergency medicine*, *15*(3), 453-462.

Palta, S.; Saroa, R.; and Palta, A. (2014). Overview of the coagulation system. Indian journal of anaesthesia, 58(5), 515.

Pendurthi, U.R.; and Rao, V.M. (2008). Factor VIIa interaction with tissue factor and endothelial cell protein C receptor on cell surfaces. Semin. Hematol., 45 (Suppl 1): S21-S24.

Pepys, M.G. and Hirschfield, G.M. (2003). C-reactive protein: a critical update. J. Clin. Invest.;111(12).

Periayah, M. H.; Halim, A. S.; and Saad, A. Z. M. (2017). Mechanism action of platelets and crucial blood coagulation pathways in hemostasis. International journal of hematology-oncology and stem cell research, 11(4), 319.

Perry, S.V.(1999). Troponin I: Inhibitor or facilitator. Mol. Cell. Biochem.; 190:9–32.

Perry, S.V.(1998). Troponin T: Genetics, properties and function. J. Muscle. Res. Cell. Motil.; 19:575–602.

Pesaro, A.E.P.; Nicolau, J.c.; and Serrano, C.V. (2009). Influence of leukocytes and glycemia on the prognosis of patients with acute myocardial infarction. Arg.Bras.Cardiol., 92: 88–93.

Pierigè, F.; Serafini, S.; Rossi, L.; and Magnani, M. (2008). Cell-based drug delivery. Advanced drug delivery reviews, 60(2), 286-295.

Pillay, J.; Den Braber, I.; Vrisekoop, N.; Kwast, L. M.; De Boer, R. J.; Borghans, J. A.; and Koenderman, L. (2010). In vivo labeling with 2H2O reveals a human neutrophil lifespan of 5.4 days. Blood, The Journal of the

American Society of Hematology, 116(4), 625-627.

Pop, C.; Matei, C.; and Petris, A. (2019). Anticoagulation in acute coronary syndrome: review of major therapeutic advances. American journal of therapeutics, 26(2), e184-e197.

Prabhu, S. D. (2004). Cytokine-induced modulation of cardiac function. Circulation research, 95(12), 1140-1153.

Prabhu, S. D.; and Frangogiannis, N. G. (2016). The biological basis for cardiac repair after myocardial infarction: from inflammation to fibrosis. Circulation research, 119(1), 91-112.

Rafieian-Kopaei, M.; Setorki, M.; Doudi, M.; Baradaran, A.; and Nasri, H. (2014). Atherosclerosis: process, indicators, risk factors and new hopes. International journal of preventive medicine, 5(8), 927.

Rana, J.S.; Boekholdt, S.M.; Ridker, P.M.; Jukema, J.W.; Luben, R.; and Bingham, S.A. (2007). Differential Leukocyte count and the risk of future coronary artery disease in healthy men and women. J.Intern.Med., 262(6): 678–689.

Ranjith, M.P.; Divya, R.; Metha, V.K.; Krishnan, M.G.; KamalRaj, R.; and Kavishwar, A. (2009). Significance of platelet volume Indices and platelet count in ischemic heart disease. J. Clin. Pathol., 62(9): 830–833.

Rao, L.V. and Pendurthi, U.R. (2005). Tissue factor VIIa signaling. Arterioscler. Thromb. Vasc. Biol., 25: 47-56.

Razi, M.M.; Abdali, N.; and Asif, S.M. (2017). Association of inflammatory cytokines/biomarkers with severity and hospital outcome. J. Clin. Prev. Cardiol.,6: 44–49.

Reed, M.; Kerndt, C. C.; and Nicolas, D. (2021). Alteplase. In StatPearls [Internet]. StatPearls Publishing.

Reihani, H.; Sephehri Shamloo, A., and Keshmiri, A. (2018). Diagnostic value of D-dimer in acute myocardial infarction among patients with suspected acute coronary syndrome. Cardiol. Res., 9(1): 17–21.

Reindl, M.; Reinstadler, S. J.; Feistritzer, H. J.; Klug, G.; Tiller, C.; Mair, J.; and Metzler, B. (2017). Relation of inflammatory markers with myocardial and microvascular injury in patients with reperfused ST-elevation myocardial infarction. European Heart Journal: Acute Cardiovascular Care, 6(7), 640-649.

Rezkalla, S. H.; Dharmashankar, K. C.; Abdalrahman, I. B.; and Kloner, R. A. (2010). No-reflow phenomenon following percutaneous coronary intervention for acute myocardial infarction: incidence, outcome, and effect of pharmacologic therapy. Journal of interventional cardiology, 23(5), 429-436.

References .

Ridker, P. M., Hennekens, C. H., Buring, J. E., and Rifai, N. (2000). C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. New England journal of medicine, 342(12), 836-843.

Ridker, P. M.; Danielson, E.; Fonseca, F. A.; Genest, J.; Gotto Jr, A. M.; Kastelein, J. J.; and Glynn, R. J. (2008). Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. New England journal of medicine, 359(21), 2195-2207.

Ridker, P.M. (2016). From C-Reactive Protein to Interleukin-6 to Interleukin-1: Moving Upstream To Identify Novel Targets for Atheroprotection. Circ Res. 118(1):145-56.

Righini, M.; Robert-Ebadi, H.; and Le Gal, G. (2015). Diagnosis of pulmonary embolism. Presse. Med., 44(12): 385–391.

Rivera-Bou, W. L. ; Cabañas, J. G.; and Villanueva S. E. (2021).Thrombolytic Therapy. eMedicine.

Robert–Ebadi, Robin, P.; Hugi, O.; Verschuren, F.; Thrinh–Duc, A.; and Roy, P.M. (2021). Impact of the age –adjusted D–dimer cutoff to exclude Pulmonary embolism. Circulation, 143: 1828–1830.

Rogers, S.D.; Riemersma, L.B.; and Clements, S.D. (1987). Tissue plasminogen activator: an evaluation of clinical efficacy in acute myocardial infarction. Pharmacotherapy. 7(4):111-21.

Rogers, W.J.; Canto, J.G.;and Lambrew, C.T. (2000).Temporal trends in the treatment of over 1.5 million patients with myocardial infarction. J. Am. Coll. Cardiol.; 36:2056–2063.

Rosalki, S.B.; Roberts, R.; Katus, H.A.; Giannitsis, E.;and Ladenson, J.H. (2004).Cardiac biomarkers for the detection of myocardial infarction: Perspectives from past to present. Clin Chem; 50: 2205–2213.

Roh, J.W.; Lim, S.; Hwang, Y.; Lee, K.Y.; Choo, E.H.; Choi, I.J.; and Hwang, B.H. (2020). Ischemic and bleeding events associated with thrombocytopenia and thrombocytosis after precutaneous coronary intervention in patients with acute myocardial infarction. J. Clin. Med., 9(10): 3370.

Saladin, K. (2012). Anatomy and Physiology: the Unit of Form and Function (6 ed.). New York: McGraw Hill.

Saran, R. K.; Sethi, R.; and Nagori, M. (2009). " Tenecteplase--the best among the equals.". Indian Heart Journal, 61(5), 454-458.

Sedighi, S.M. ; Homme, P.P. ; Ghachem, A. ; Lepage, S. ; Nguyen, M. ; and Fulop, T. (2019). Increased level of high sensitivity cardiac troponin T in a geriatric population is determined by comorbidities compared to age. Int. J.

Cardiol. Heart. Vascul. 22: 187–191.

Selton-Suty, C.; Célard, M. ; LeMoing, V. ;Doco-lecompte ,T. ;Chirouze C. ;Lung, B.; and Strady, C. (2012). Preeminence of Staphylococcus aureus in infective endocarditis: a 1-year population-based survey. Clin Infect Dis 2012; 54:1230.

Severino, P.; D'Amato, A.; Netti, L.; Pucci, M.; De Marchis, M.; Palmirotta, R.; and Fedele, F. (2018). Diabetes mellitus and ischemic heart disease: the role of ion channels. International Journal of Molecular Sciences, 19(3): 802.

Shakur, H. and Roberts, I. (2010). Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage: a radomised, placebocontrolled trial. Lancet, 376 (9734): 23-32.

Sharifi, M.; Bay, C.; Nowroozi, S.; Bentz, S.; Valeros, G.; and Memari, S. (2013). Catheter-directed thrombolysis with argatroban and tPA for massive iliac and femoropopliteal vein thrombosis. Cardiovascular and interventional radiology, 36(6), 1586-1590.

Sharma, L.; Melis; E.; and Hickey, M.J. (2004). The cytoplasmic domain of tissue factor contributes to leukocyte recruitment and death in endotoxemia. Am. J. Pathol., 165: 331-340.

Schieffer, B.; Bunte, C.; Witte, J.; Hoeper, K.; Boger, R.H.; Schwedhelm, E.; and Drexler, H. (2004). Comparative effects of AT1-antagonism and angiotensin-converting enzyme inhibition on markers of inflammation and platelet aggregation in patients with coronary artery disease. J Am Coll Cardiol**.** 44: 362–368.

Shirai, T.; Hilhorst, M.; Harrison, D. G.; Goronzy, J. J.; and Weyand, C. M. (2015). Macrophages in vascular inflammation–from atherosclerosis to vasculitis. Autoimmunity, 48(3), 139-151.

Shirwany, N. A. and Zou, M. H. (2010). Arterial stiffness: a brief review. Acta pharmacologica Sinica, 31(10): 1267–1276.

Singh, A.; Museedi, A.S.; Grossman, S.A.(2022). Acute Coronary Syndrome. In: StatPearls. StatPearls Publishing, Treasure Island (FL);. PMID: 29083796.

Sirajuddin, A.; Chen, M. Y.; White, C. S.; and Arai, A. E. (2020). Coronary venous anatomy and anomalies. Journal of Cardiovascular Computed Tomography, 14(1), 80-86.

Smani, T.; Mayoral-Gonzalez, I.; Galeano-Otero, I.; Gallardo-Castillo, I.; Rosado, J. A.; Ordoñez, A.; and Hmadcha, A. (2020). Non-coding RNAs and ischemic cardiovascular diseases. Non-coding RNAs in Cardiovascular Diseases, 259-271.

References .

Smart, N.; Mojet, M. H.; Latchman, D. S.; Marber, M. S.; Duchen, M. R.; and Heads, R. J. (2006). IL-6 induces PI 3-kinase and nitric oxide-dependent protection and preserves mitochondrial function in cardiomyocytes. Cardiovascular research, 69(1), 164-177.

Smith, A.M. ; English, K.M. ; Malkin, C.J. ; and Jones, R.D. (2005). Testosterone dose not adversely affect fibrinogen or tissue plasminogen activator (tPA) and plsaminogen activator inhibitor (tPAI) levels i 46 men with chronic stable angina. Eur. J. Endocrinol., 152: 285–291.

Smith, S. A.; Travers, R. J.; and Morrissey, J. H. (2015). How it all starts: Initiation of the clotting cascade. Critical reviews in biochemistry and molecular biology, 50(4), 326-336.

Soomro, A. Y.; Guerchicoff, A.; Nichols, D. J.; Suleman, J.; and Dangas, G. D. (2016). The current role and future prospects of D-dimer biomarker. European Heart Journal-Cardiovascular Pharmacotherapy, 2(3), 175-184.

Souza, J.R.; Oilveira, R.T.; Blotta, M.H.; and Coelho, O.R. (2008). Serum levels of IL-6, IL-18, and CRP in patients with type-2 diabetes and acute coronory syndrome without elevation of ST–Segment. Arq. Bras. Cardiol. 90(2): 86–90.

Spencer, J.H.; Anderson, S.E.; and Iaizzo, P.A.(2013). Human coronary venous anatomy: implications for interventions. J Cardiovasc Transl Res. 6(2):208-17.

Stary, H.C.; Chandler, A.B.; Dinsmore, R.E.; Fuster, V.; Glagov, S.; Insull, W. Jr.; Rosenfeld, M.E.; Schwartz, C.J.; Wagner, W.D.; and Wissler, R.W. (1995). A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Circulation. 92(5):1355-74.

Stevens, A.; Lowe, J. S.; and Young, B. (2002). Wheater's basic histopathology: a colour atlas and text . Edinburgh: Churchill Livingstone.

Streetz, K. L.; Luedde, T.; Manns, M. P.; and Trautwein, C. (2000). Interleukin 6 and liver regeneration. Gut, 47(2), 309-312.

Su, J. H.; Luo, M. Y.; Liang, N.; Gong, S. X.; Chen, W.; Huang, W. Q.; and Wang, A. P. (2021). Interleukin-6: a novel target for cardio-cerebrovascular diseases. *Frontiers in pharmacology*, 2183.

Surma, S. and Banach, M. (2022). Fibrinogen and atherosclerotic cardiovascular diseases–review of the literature and clinical studies. Int. T. Mol. Sci., 23:193 (Review).

Suthahar, N. ; Mees, L.M.G. ; Groothof, D. ; Bakker, S.L. ; and Gansevoort, R.T. (2021). Relationship between body mass index, cardiovascular biomarkers and incident heart failure. Eur. J. H. Fail., 23(3): 396–402.

References .

Swiatkiewicz, I., Magielski, P.; Kubica, J.; Zadourian, J.; and Demaria, A.N. (2020). Enhanced inflammation is a marker for risk of post–infarct ventricular dysfunction and heart failnre. Int. J. Mol. Sci., 21: 807.

Tak, T.; Tesselaar, K.; Pillay, J.; Borghans, J. A.; and Koenderman, L. (2013). What's your age again? Determination of human neutrophil half-lives revisited. Journal of leukocyte biology, 94(4), 595-601.

Talaat, F.M.; Abokrysha, N.T.; Labib, D.M.; and El–khateeb, E. (2018). Egy.J.Neurol. Psych. Neurosurgery, 54: 30.

Tamura, T.; Arais, S.; Nagaya, H.; Mizuguchi, J.; and Wada, I. (2013). Stepwise assembly of fibrinogen is assisted by the endoplasmic reticulum lectin chaperon system in HePG2 cells. PLOS one, 8: e 74580.

Terrell, A. M.; Crisostomo, P. R.; Wairiuko, G. M.; Wang, M.; Morrell, E. D.; and Meldrum, D. R. (2006). Jak/STAT/SOCS signaling circuits and associated cytokine-mediated inflammation and hypertrophy in the heart. Shock, 26(3), 226-234.

Thakare, S. M.; Wandre, R. A.; and Hingane, L. D. (2021). Blood disorders. World Journal of Pharmaceutical Research, Review Article, 10(3), 830-853.

Thögersen, A.M.; Jansson, J.H.; Boman, K.; Nilsson, T.K.; and Weinehall, L. (1998). High plasminogen activator inhibitor and tissue plasminogen activator levels in plasma precede a first acute myocardial infarction in both men and women: evidence for the fibrinolytic system as an independent primary risk factor. Circulation, 98(21): 2241–2247.

Thygesen, K.; Alpert, J. S.; Jaffe, A. S.; Chaitman, B. R.; Bax, J. J.; Morrow, D. A.; and Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. (2018). Fourth universal definition of myocardial infarction. Journal of the American College of Cardiology, 72(18), 2231-2264.

Thygesen, K.; Alpert, J. S.; Jaffe, A. S.; Simoons, M. L.; Chaitman, B. R.; and White, H. D. (2012). Tercera definición universal del infarto de miocardio. Circulation, 126, 2020-2035.

Tillett, W.S. and Francis, T. J.r. (1930). Serological reactions in pneumonia with a non-protein somatic fraction of pneumococcus. J Exp Med; 52:561-571.

Turgeon, M. L. (2004). Clinical Hematology: Theory and Procedures. Lippincott Williams & Wilkins. p. 100.

Türkoglu, C.; Harbalioglu, H.; Seker, T.; Baykan, A.O.; and Uysal, O.K. (2020). D-dimers are associated with coronary artery disease severity assessed using syntax and syntax II scores. Revista Portuguesa de Cardiologia, 39(12): 687–693.

References .

Valentine, C. M.; Tcheng, J. E.; and Waites, T. (2018). Translating the translation: what clinicians should know about the Fourth Universal Definition of Myocardial Infarction. Journal of the American college of cardiology, 72(21), 2668-2670.

Vavik, V. ; Aakre, K.M. ; Pedersen, E.K.R. ; Tveitevag, F. ; Tell, G.S.; Nygard, O. ; and Vikenes, K. (2021). The association between serum high–sensetivity cardiac troponin T and acute myocardial infarction in patients with suspected chronic coronary syndrome modified by body mass index. Int. J. Cardiol. Cardiovascul. Risk and prevention, 11: 200124.

Versteeg, H.H.; Schaffner, F.; and Kerver, M. (2008). Inhibition of tissue factor signaling suppresses tumor growth factor. Blood, 11 (1): 190-199.

Vilar, R.; Fish, R. J.; Casini, A.; and Neerman-Arbez, M. (2020). Fibrinogen in human disease: both friend and foe. *Haematologica*, *105*(2), 284.

Vita, J. A.; Keaney Jr, J. F.; Larson, M. G.; Keyes, M. J.; Massaro, J. M.; Lipinska, I.; and Benjamin, E. J. (2004). Brachial artery vasodilator function and systemic inflammation in the Framingham Offspring Study. Circulation, 110(23): 3604-3609.

Von Lüdinghausen, M. (2003). The venous drainage of the human myocardium. Adv Anat Embryol Cell Biol.; 1-104.

Von Lüudinghausen, M.; Ohmachi, N.; Besch, S.; and Mettenleiter, R. (1995). Atrial veins of the human heart. Clinical Anatomy: The Official Journal of the American Association of Clinical Anatomists and the British Association of Clinical Anatomists, 8(3), 169-189.

Voudris, K.V.; and Kavinsky, C.J. (2019). Advances in Management of Stable Coronary Artery Disease: the Role of Revascularization? Curr Treat Options Cardiovasc Med. 21(3):15.

Wada, H. and Sakuragawa, N. (2008). Are fibrin related markers useful for the diagnosis of thrombosis? Semin Thromb. Hemost., 34(1): 33–38.

Wanamaker, B.L. ; Seth, M.M. ; Sukul, D. ; Dixon, S.R. ; Bhatt, D. ; Madder, R.D. ; Rumsfeld, J.S., and Gurm, H.S. (2019). Relationship between troponin on presentation and in–hospital mortality in patients with ST–Segment elevation myocardial infarction. J. Am. Heart Associo., 8: e 013551.

Wang, W.; Zhao, X.; Ren, Y.; and Qiao, P. (2018). Therapeutic effect evaluation of reteplase on acute pulmonary embolism. Pakistan journal of pharmaceutical sciences, 31(3), 899-906

Wang, Y.; Shi, X.; Du, R.; Chen, Y.; and Zhang, Q. (2018). Impact of red blood cell transfusion on acute coronary syndrome. Intern. Emerg. Med., 13(2): 231–241.

References .

Watson, J.; Jones, H. E.; Banks, J.; Whiting, P.; Salisbury, C.; and Hamilton, W. (2019). Use of multiple inflammatory marker tests in primary care: using Clinical Practice Research Datalink to evaluate accuracy. The British journal of general practice : the journal of the Royal College of General Practitioners, 69(684): e462–e469.

Weasel, J.W. and Litvinov, R.I. (2017). Fibrin formation, structure and properties Subcellular Biochemistry, 82: 405-456.

Weber, C.; and Noels, H. (2011). Atherosclerosis: current pathogenesis and therapeutic options. Nature medicine, 17(11), 1410-1422.

Whitmore, I. (1999). Terminologia anatomica: new terminology for the new anatomist. The Anatomical Record: An Official Publication of the American Association of Anatomists, 257(2), 50-53.

Williams, M.S.; Cushman, M.; Ouyang, P.; Heckbert, S.R. ; and Kalyani, R.R. (2016). Association of serum sex hormones with hemostatic factors in women. J. Women Healthy, 25(2): 166–172.

Wineski, L. E. and Snell, R. S. (2019). Snell's clinical anatomy by regions (Tenth). Wolters Kluwer.

Wollert, K. C.; and Drexler, H. (2001). The role of interleukin-6 in the failing heart. Heart failure reviews, 6(2), 95-103.

Wollert, K. C.; Taga, T.; Saito, M.; Narazaki, M.; Kishimoto, T.; Glembotski, C. C.; and Chien, K. R. (1996). Cardiotrophin-1 Activates a Distinct Form of Cardiac Muscle Cell Hypertrophy: Assembly of sarcomeric units in series via gp130/leukemia inhibitory factor receptor-dependent pathways. Journal of Biological Chemistry, 271(16), 9535-9545.

Wong, B. W.; Meredith, A.; Lin, D.; and McManus, B. M. (2012). The biological role of inflammation in atherosclerosis. Canadian Journal of Cardiology, 28(6), 631-641.

Yamauchi-Takihara, K.; and Kishimoto, T. (2000). Cytokines and their receptors in cardiovascular diseases—role of gp130 signalling pathway in cardiac myocyte growth and maintenance. International journal of experimental pathology, 81(1), 1-16.

Yan, X. N.; Jin, J. L.; Zhang, M.; Hong, L. F.; Guo, Y. L.; Wu, N. Q.; and Li, J. J. (2020). Differential leukocyte counts and cardiovascular mortality in very old patients with acute myocardial infarction: a Chinese cohort study. *BMC cardiovascular disorders*, *20*(1), 1-12.

Yang, C.; Deng, Zhiyong, Li, J.; Zhilei, Ren ; and Liu, F. (2021). Meta–analysis of the relationship between inter leukin-6 levels and the prognosis and severity of acute coronary syndrome. Clinic (Sao paulo): 76: e 2690.

Yang, S.; Zheng, R.; Hu, S.; Ma, Y.; Choudhry, M. A.; Messina, J. L.; and Chaudry, I. H. (2004). Mechanism of cardiac depression after trauma-

hemorrhage: increased cardiomyocyte IL-6 and effect of sex steroids on IL-6 regulation and cardiac function. American Journal of Physiology-Heart and Circulatory Physiology, 287(5), H2183-H2191.

Yatsuya, H.; Toyoshima, Yamagishi, k. ; and Tamakoshi, K. (2010). Body mass index and risk of stroke and myocardial infarction in relatively lean population. Circ. Cardiovas. Qual. Outcome, 3:398–505.

Zègre-Hemsey, J. K.; Asafu-Adjei, J.; Fernandez, A.; and Brice, J. (2019). Characteristics of prehospital electrocardiogram use in north carolina using a novel linkage of emergency medical services and emergency department data. Prehospital Emergency Care.

Zhao, H. G.;Wang, S. X.; Lu, Z. N.; Yan, X. X.; Lyu, Z. C.; Peng, F. H.; and Xu, X. Q. (2017). Clinical efficacy and safety of thrombolytic treatment with reteplase in patients with intermediate-risk acute pulmonary embolism. Zhonghua Xin Xue Guan Bing Za Zhi, 45(4), 314-317.

الخلاصة

احتشاء عضلة القلب (MI) هو أحد أكثر أمراض القلب الإقفارية التي تؤدي إلى تلف عضلة القلب. استُخدمت الدراسة الحالية للتحري عن بعض المتغيرات الدموية والمؤشرات الحيوية لدى مرضى احتشاء عضلة القلب من كلا الجنسين ، وللتحقق من نشاط نظام تحلل الفبرين ونسبة حدوث المرض ، وقد أجريت الدراسة في مواقع مختلفة بما في ذلك مستشفى مرجان التعليمي (مرض القلب الإقفاري). وحدة) ومستشفى الامام الصادق وبعض المعامل الخاصة وجامعة بابل / كلية العلوم للبنات. تراوحت مدة الدراسة بين تشرين الثاني (نوفمبر) 2021 وأبريل (نيسان) 2022. وكان إجمالي عدد الأشخاص الذين شاركوا في الدراسة الحالية ثمانين (80) فردًا. من بين هؤلاء ، أصيب عشرون رجلاً وعشرون امرأة بمرض MI. أما الأفراد المتبقون (40) فكانوا عشرين رجلاً وعشرين امرأة وكانت صحتهم طبيعية وتم تجنيدهم كمجموعات ضابطة.

تراوحت أعمار جميع الأفراد (المرضى والضابطة) بين 40 إلى 70 سنة. كما تم تصنيف المرضى ومرضى السيطرة لديهم وفقًا لأعمارهم إلى أربع مجموعات على النحو التالي (40-49 ، 50-59 ، 60-69 ، 70-79 سنة).

باختصار ، أظهرت النتائج التي توصلت إليها هذه الدراسة أن الذكور المصابين بمرض احتشاء عضلة القلب يشكلون 60٪ أعلى من الإناث التي شكلت 40٪. كما كانت النسب المئوية لمرضى احتشاء عضلة القلب حسب أعمارهم هي المجموعة الأولى 15٪ ، المجموعة الثانية 30٪ ، المجموعة الثالثة 30٪ ، المجموعة الرابعة 25٪ على التوالي.

فيما يتعلق بمؤشر كتلة الجسم (BMI) ، فإن المرضى الذين لديهم مؤشر كتلة الجسم 25-33 كجم / م 2 يشكلون حوالي 70٪ أعلى من أولئك الذين لديهم مؤشر كتلة الجسم 29-23 كجم / م 2 بنسبة مئوية 30٪.

فيما يتعلق بالمعايير الدموية ، كانت نتائج خلايا الدم الحمراء (كرات الدم الحمراء) والهيموجلوبين (Hb) وإجمالي خلايا الدم البيضاء (WBCs) والخلايا المحببة ٪ ونسبة الخلايا الليمفاوية أعلى بشكل ملحوظ ($p < 0.05$) في جميع المرضى (رجال ونساء) من مجموعات التحكم. ومع ذلك ، فإن قيم Hb و RBCs تسجل فروقًا غير مهمة في جميع الفئات العمرية للمرضى الذين يعانون من MI في المطابقة مع التحكم الصحي.

وفقًا لمعاملات الارتباط ، سجلت المعلمات الدموية البيانات التالية: سجلت الخلايا الحبيبية ارتباطًا سلبيًا معنويًا ($r = -0.99$، $sig = 0.0001$) مع الخلايا الليمفاوية. أشار تركيز الهيموغلوبين إلى ارتباط إيجابي معنوي ($r = 0.90$، $sig = 0.0001$) مع كرات الدم الحمراء للمرضى المصابين بمرض MI. في المقابل ، أشارت مستويات الهيموغلوبين إلى ارتباط سلبي معنوي ($r = 0.36$ ، سيج = 0.021) مع الصفائح الدموية لمرضى MI.

فيما يتعلق بالعلامات الحيوية التي شاركت في هذه الدراسة والتي تضمنت D-dimer و fibrinogen و Troponin و tPA-1) Tissue plasminogen Activator -1) و - interleukin 6 و CRP) C-reactive protein) ، فقد أظهروا ارتفاعًا كبيرًا ($p < 0.01$).) في جميع الفئات المدروسة (رجال ونساء) من جميع الأعمار. علاوة على ذلك ، كانت هذه المعلمات مرتفعة بشكل كبير

(p <0.05) في المرضى الذين تراوح مؤشر كتلة الجسم لديهم بين 25-33 كجم / م 2 أعلى من مؤشر كتلة الجسم لديهم 19-23 كجم / م 2.

لم تسجل المؤشرات الحيوية الأكثر دراستها ارتباطات معنوية مع المتغيرات المدروسة الأخرى باستثناء D-dimer ، وأظهرت نتائجها ارتباطًا سلبيًا معنويًا (r = -0.32، sig = 0.042) مع الخلايا الليمفاوية لمرضى MI. عكسيا ، كان هناك ارتباط إيجابي معنوي (r = 0.33 ، سيج = 0.035) مع الخلايا المحببة للمرضى.

كان لقيم التروبونين علاقة إيجابية معنوية (r = 0.71 ، سيج = 0.0001) مع مستويات الهيموغلوبين في مرضى MI ، كما أن نتائجها لها علاقة إيجابية كبيرة (r = 0.63، sig = 0.0001) مع كرات الدم الحمراء من المرضى. ولكن من ناحية أخرى ، أظهرت نتائج التروبونين ارتباطًا سلبيًا مهمًا (r = 0.66 ، سيج = 0.0001) مع الصفائح الدموية لمرضى MI الذين تم اختبارهم.

تم إجراء تحليلات منحنى خصائص التشغيل المتلقاة (ROC) على المؤشرات الحيوية لشرح الحساسية وتحديد تلك المؤشرات الحيوية في مرض MI ، وأظهرت النتائج ما يلي: D-dimer كان القوس تحت المنحنى (0.740 (AUC وكان القطع 298.5 ، تروبونين 0.700 ، وكان القطع 0.813 ، وكان 0.724 tPA-1 وكان القطع 5.175 ، وكان الفيبرينوجين 0.816 AUC وكان القطع 0.816 ، وكان 0.724 CRP AUC وكان القطع 6.150 ، وكان 0.767 IL-6 AUC وكان القطع 8.950.

تم الحصول على خاتمة هذه الدراسة من هذه الدراسة والمذكورة أعلاه ، قد يعود ترطيب المعلمات الدموية وخاصة مكونات خلايا الدم البيضاء الالتهابية والتخثرية إلى الالتهاب الجهازي ، والشيخوخة ، وزيادة مؤشر كتلة الجسم ، والتقلبات التوافقية ، وقد تكون هذه التشوهات أسوأ وتتقدم في تطور مرض.

جمهوريـــــة العـــراق
وزارة التعليـم العـــالي والبحث العلمي
جامعـــــة بابل / كليـــة العلوم للبنات
قسم عـــلوم الحـــياة

التداخلات بين بعض عوامل التخثر والالتهاب في مرضى احتشاء عضلة القلب

رسالـــــــــة مقدمة إلى

مجلس كليــة العلوم للبنات / جامعـــة بابل

وهي جزء من متطلبات نيل درجة الماجستيرفي علوم الحياة

من قبل

سارة عبدالخالق مهدي الفتلاوي

بكالوريوس علوم الحياة , كلية العلوم للبنات/ جامعة بابل

2015

إشراف

أ . د . داخل غاني عمران الطائي

1444 هـ **2022 م**