بسم الله الرحمن الرحيم

Shendi University

Faculty of graduate studies and scientific research

# Evaluation of Haemostatic Changes in Patients with Haert Diseases in Shendi locality

Athesis submitted in fulfillment for the Requirement
of the M.Sc. degree in Medical Laboratory Sciences
(Haematology)

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# الآية

**قال تعالـــــى :**

" وَقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ وَرَسُولُهُ وَالْمُؤْمِنُونَ وَسَتُرَدُّونَ إِلَى عَـــالِمِ الْغَيْبِ وَالشَّهَادَةِ فَيُنَبِّئُكُمْ بِمَا كُنْتُمْ تَعْمَلُونَ " (١٠٥)

صدق الله العظيم

سورة التوبة– الآية (١٠٥)

# Dedication

To my dear mother and the spirit of my father

my sister and brothers

To my best friends Randa, ahamed,osman

To my Supervisor Dr. mohammedosman

To staff of shandi university -college medical laboratory sciences

*To the staff ofAlmeknaimr hospital*

## Acknowledgements

praise is to good first for enabling me to achieve this research .lam very grateful to my supervisor

**Dr.Mohammed Osman Ali Mohammed**

for being very keen to make us highly oriented in the field of hematology lam very grateful to other member in the medical field who help me a lot and paved the way for me to progress .

# List of abbreviation

| | |
|---|---|
| ACSC | **Acute coronary syndrome** |
| ADP | **Adenosine diphosphate** |
| CSF | **Colony stimulation factor** |
| CVD | **Cardio vascular disease** |
| DIC | **Disseminated Intravascular Coagulation** |
| EPI | **Epinephrine** |
| FPA | **Fibrino peptide** |
| GP | **Glycoprotein** |
| HIV | **Human Immunodeficiency virus** |
| HMW | **High molecule wight** |
| IHD | **Ischemic heart disease** |
| LDL | **Low-density Lipoprotein** |
| MI | **Myocardial infraction** |
| MPV | **Mean platelet volume** |
| PCT | **Platelets Crit** |
| PDW | **Platelet distribution width** |
| P-LCR | **Platelets large cell ratio** |
| PLT | **Platelet** |
| PT | **Prothrombin time** |
| PTT | **Partial thrombin time** |
| RBCs | **Red blood cells** |
| STIM | **Stromal interaction molecule** |
| TPO | **Thrompopotin** |
| TXA | **ThromboxanA2** |
| VWF | **Von will brand factor** |

## الخلاصة

مرض القلب والأوعية الدموية هو مصطلح عام للحالة التي تؤثر على القلب والأوعية الدموية، ودور الصفائح الدموية والفبرينوجين في عملية تصلب الشرايين، وفي وقت لاحق في الفسيولوجيا المرضية لأمراض القلب والأوعية الدموية أمر ضروري كما ان الصفائح الدموية بالإضافة إلى مساهمتها في تجلط الدم والأرقاء تعديل التفاعلات الالتهابية والاستجابة المناعية, هذه التفاعلات تنشئ استجابة التهابية موضعية تعزز عملية تصلب الشرايين.

أجريت هذه الدراسة في مستشفى الملك نمر الجامعي- ولاية نهر النيل- في الفترة ما بين شهر مارس 2015وحتى أغسطس في العام 2017 بهدف حساب قياسات عدد الصفائح الدموية ومعدل الفبيرينوجين وتأثيرها على أمراض القلب وهي دراسة تقدميه وصفيه.

أخذت حوالي 360 عينه عشوائية كان بينهم 271 من الرجال و89 من النساء تتراوح أعمارهم بين 40-60 سنه . وكانت النتائج علي النحو التالي :

حيث وجد ان عدد الصفائح الدمويه ونقاء الصفائح الدمويه علي حسب الجنس أكثراتأثرا وكانp.value (0,001,0,005) علي التوالي.

بينما توزيع عرض الصفائح الدمويه ، حجم الصفائح الدمويه، مستوي الفبرينوجين ،زمنالثرمبوبلاستين الجزئي وزمن الثرومبين: وكان ال p.value (0.153,0.272,0.909,0.514,0.510)علي التوالي.

علي حسب العمر لا يوجد تاثير علي عدد الصفائح الدمويه،نقاء الصفائح الدمويه ،توزيع عرض الصفائح الدمويه ، حجم الصفائح الدمويه، مستوي الفبرينوجين،زمن الثرمبوبلاستين الجزئي وزمن الثرومبين:وكان الp.value (0,228,0,951,0,743,0,067,0,581,0,762,0,877) علي التوالي.

اما علي حسب فتره المرض ايضا لا يوجد أي تاثير عدد الصفائح الدمويه،نقاء الصفائح الدمويه ،توزيع عرض الصفائح الدمويه ، حجم الصفائح الدمويه، مستوي الفبرينوجين ،زمنالثرمبوبلاستين الجزئي وزمنالثرومبين:وكان p.value (0.289,0.173,0.139,0.644,0.334,0.473,0.874) علي التوالي.

عدد الصفائح الدمويه هو الوحيد الذي تاثر بتناول الدواء من عدمه في مرضي القلب وكان (0.002) p.value .

بينما لم يحدث أي تاثيرعلي باقي المعدلات وكان p.value (0,190,0,394,0,159,0,523,0,543,0,878) علي التوالي.

ومن هذه الدراسة اتضح انهتاثيرالعمر عند مرضي القلبكان واضحا علي معدلات الصفائح الدمويه ونقاء الصفائح الدمويه وكان p.value (0.001,0.005) علي التوالي,كما ان الدواء له تاثير عند مرضي القلب ويظهر هذا التاثير علي معدل عدد الصفائح الدمويه وكان ال (0.002)p.value.

## Abstract

Cardiovascular disease is a general term for condition affecting the heart or blood vessels,the role of platelets and fibrinogen in atherosclerotic process and subsequently in the pathophysiology of cardiovascular disease is essential as platelets in addition to their contribution to thrombosis and hemostasis modulating inflammatory reactions and immune response, these interactions establish alocalized inflammatory response that promotes the atherosclerotic process.

This study was done in elmaknamiruniversityhospital, the study was conducted at period of time from march 2015 to august 2017,to assess of platelet count, platelet indices a, fibrinogen levels, prothrombintime,partialprothrombinamongSudanese patients with cardiovascular disorders,wasdescriptive cross sectional based study carried on patients with heart diseases.

The study include 360 samples selected randomly 271 patients were male and 89 females, and age of this patient ranged between 40 – 60 years.

In gender platelete count and PCT significant with p.value (0.001, 0.005) respectively, while PDW ,MPV,,fibrinogen level ,PTTand PT no significant variation p.value (0.153, 0.272, 0.909, 0.514, 0.510)respectively.

according to age found has no any effect in platelet count,platelet indices (PDW,MPV,PCT), fibrinogen level , PTT ,PT with p.value (0.228, 0.951, 0.743, 0.067, 0.581, 0.762, 0.877) respectively.

While according to duration of diseases no significantvariation in platelet count, platelet indices(PDW,MPV,PCT), fibrinogen level, PTT and PT with p.value (0.289, 0.173, 0.139, 0.644, 0.334, 0.473, 0.874) respectively.

Only one parameter was effect by treatmen platelet count withp.value (0.002) in patients under treatment or not , while other parameters no significant platelet

indices (PDW,MPV,PCT), fibrinogen level, PTT and PT with p.value (0.190, 0.394, 0.159, 0.523, 0.543, 0.878) respectively .

Platelet count and fibrinogen level always effect with Cardiovascular diseases andincease when compare with normal range.

In gender platelet count and pct was significantly diffrent with p.value(0.001, 0.005) and under treatment was significantly different with p.value (0.002).

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# ChapterOne

**Introduction**

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## 1-1 : INTRODUCTION

Cardiovascular disease refers to any disorder of the heart and blood vessels, including hypertension, coronary artery disease (CAD), cardiac dysrhythmias, cerebrovascular disease, valvular heart disease, cardiomyopathies, peripheral vascular disease, and congenital cardiac abnormalities,each disorder has been characterized epidemiologically; incidence and prevalence rates vary widely by country and culture. Because hypertension, coronary artery disease, cardiac dysrhythmias, and cerebrovascular disease account for the majority of cardiovascular morbidity and mortality in developed countries, For each of the disease categories, the epidemiology, etiology, risk indicators and primary prevention, diagnostic assessment, and treatment and prognosis are discussed.[1]

Coagulation process has evolved over the past decade from one in which platelets and the triggering of one of two very separate protein cascade systemsthe intrinsic and extrinsic pathwayswould ultimately produce clot formation, to the present understanding that places more emphasis upon the final common pathway and the proteolytic systems that result in the degradation of formed clots and the prevention of unwanted clot formations.[2]

cardiovascular disease, abnormal clotting occurs that can result in heart attacks or stroke. It very well known that platelets play a vital role in the pathophysiology mechanism underlying many cardiovascular diseases.

These are implicated in atheromatous formation and plaques rupture. Even though no bleeding is occurring, platelets sense the plaque rupture and are confused, thinking that an injury has taken place that will cause bleeding. Instead of sealing the vessel to prevent bleeding as would occur with a cut, a clot forms in an intact blood vessel, causing a blockage of blood flow without blood, a portion of the heart muscle can die, leading to a heart attack, Several epidemiological studies have provided prospective data on plasma fibrinogen levels in relation to cardiovascular disease. According to these studies, the risk of developing a cardiovascular event such asischemic Heart Disease or stroke is 1.8 to 4.1 times higher in subjects with fibrinogen levels in the top third than in those with levels in the lower third[(3)]

## 1.2:RATIONALE

Nowadays heart problems do not bind with certain age, as they can occur at any level or step of human's life span and factors may lead to them have to be found, as obesity and smoking beside family history and coagulation imbalanced has become harbored among many body system disorders including the heart. So in this study, trying to bind existence cardiac dysfunctions with haemstatic changes , Prothrombin Time and Activated Partial ThromboplastinTime in Patients with Heart Diseases in shendi localityand trying to anticipate what stage of the disease according to the different data of platelet and fibrinogen.

## 1.3OBJECTIVES:-

### 1.3.1GENERAL OBJECTIVES

To evaluation of haemstatic changes in patients with Heart Diseases in shendi locality.

### SPECIFIC OBJECTIVES

1.To evaluate platelet count, platelet indices, plasma fibrinogen level Prothrombine time and partial Prothrombine time according age of patients with heart diseases.

2.To evaluate platelet count, platelet indices, plasma fibrinogen level Prothrombine time and partial Prothrombine time according gender of patients with heart diseases.

3.To evaluate platelet count, platelet indices, plasma fibrinogen level Prothrombine time and partial Prothrombine time according duration of diseases.

4.To evaluate plateletcount, platelet indices, plasma fibrinogen level Prothrombine time and partial Prothrombine time accordring with treatment.

# Chapter Two

## Literature Review

## 2. Literature Review

**2.1**Hemostasis is the physiological process that stops bleeding at the site of an injury while maintaining normal blood flow else where in the circulation. Blood loss is stopped by formation of a hemostatic plug ,the endothelium in blood vessels maintains an anticoagulant surface that serves to maintain blood in its fluid state, but if the blood vessel is damaged components of the subendothelial matrix are exposed to the blood. Several of these components activate the two main processes of hemostasis to initiate formation of a blood clot, composed primarily of platelets and fibrin. This process is tightly regulated such that it is activated within seconds of an injury but must remain localized to the site of injury.[(4)(5)]

There are two main components of hemostasis, Primary hemostasis refers to platelet aggregation and platelet plug formation. Platelets are activated in a multifaceted process and as a result they adhere to the site of injury and to each other, plugging the injury. [(4)(5)]

Secondary hemostasis refers to the deposition of insoluble fibrin, which is generated by the proteolytic coagulation cascade. This insoluble fibrin forms a mesh that is incorporated into and around the platelet plug. [(4)(5)]

This mesh serves to strengthen and stabilize the blood clot,these two processes happen simultaneously and are mechanistically intertwined,the fibrinolysis pathway also plays a significant role in hemostasis. Pathological thrombus formation, called thrombosis, or pathological bleeding can occur whenever this process is dis-regulated. The complexity of these systems has been increasingly appreciated in the last few decades.[(4)(5)]

Multiple anticoagulant mechanisms regulate and control these systems to maintain blood fluidity in the absence of injury and generate a clot that is proportional to the injury. The proper balance between procoagulant systems

and anticoagulant systems is critical for proper hemostasis and the avoidance of pathological bleeding or thrombosis.[4][5]

**2.1.1Cardiovascular diseases** involve the blood vessels, the heart, or both.

The cardiovascular or circulatory system supplies the body with blood,it consists of the heart, arteries, veins, and capillaries,there are several types of cardiovascular disease, but treatment, symptoms, and prevention often overlap.[7]

**Symptoms:-**

There are many different types of cardiovascular disease. Symptoms will vary, depending on the specific type of disease a patient has.

However, typical symptoms of an underlying cardiovascular issue include:

- pains or pressure in the chest, which may indicate angina
- pain or discomfort in the arms, the left shoulder, elbows, jaw, or back
- shortness of breath, also known as dyspnea
- nausea and fatigue
- light-headed or faint
- cold sweat

**Causes:-**

Important causes of cardiovascular disease include atherosclerosis, when fatty deposits accumulate in the arteries,damage to the circulatory system can also result from diabetes and as the result of other health conditions, such as a virus, an infection, or a structural problem that the person was born with.[7]

**Types**:-Cardiac, or heart-related, diseases and conditions include:

- angina, considered both a cardiac and vascular disease
- arrhythmia, where there is an irregular heartbeat or heart rhythm
- congenital heart disease, when a problem with heart function or structure is present from birth
- coronary artery disease (CAD), which affects the arteries that feed the heart muscle
- dilated cardiomyopathy
- heart attack
- heart failure, when the heart does not work properly
- hypertrophic cardiomyopathy
- mitral regurgitation
- mitral valve prolapse
- pulmonary stenosis
- rheumatic heart disease, which can be a complication of strep throat

Vascular diseases are diseases that affect the blood vessels: the arteries, veins, or capillaries. [7]

They include:

- peripheral artery (arterial) disease
- aneurysm
- atherosclerosis
- renal artery disease
- Raynaud's disease (Raynaud's phenomenon)
- Buerger's disease
- peripheral venous disease
- stroke, a type of cerebrovascular disease
- venous blood clots
- blood clotting disorders

- **Prevention**

The majority of CVDs are preventable. It is important to address risk factors by:

- consuming less alcohol and tobacco
- eating fresh fruit and vegetables
- reducing salt intake
- avoiding sedentary lifestyles, particularly among children

Bad habits during childhood will not lead to cardiovascular disease while the individual is still young; but they can lead to the accumulation of problems that continue into adulthood, resulting in a greater probability of having a cardiovascular disease later in life. [7]

**TREATMENT:**

Treatment will depend on the type of condition the person has.

Options include:

- lifestyle adaptations, such as weight control, exercise, quitting smoking, and dietary changes
- medication, for example, to reduce LDL cholesterol
- surgery, such as coronary artery bypass grafting (CABG)
- cardiac rehabilitation, including exercise and counseling

Treatment aims to:

- relieve symptoms
- reduce the risk of the condition recurring or worsening
- prevent complications

Depending on the condition, it may also aim to stabilize heart rhythms, reduce blockages, and widen the arteries to enable a better flow of blood. [7]

**Coagulation and Thrombosis in Cardiovascular Disease:**

An occlusive thrombus in the coronary arteries is the critical pathological event that immediately precedes most cases of myocardial infarction. Often the thrombus originates with a bleed from a fissured atheroma. Atheroma formation, therefore, creates risk of thrombosis; asymptomatic episodes of thrombosis and healing contribute to the pathogenesis of atherosclerosis and the development of atherosclerotic plaques. Based largely on in vitro and animal model evidence, infectious agents and their products can activate the coagulation cascade enzymatically or by up-regulating tissue factor. By initiating a procoagulant response, infectious agents can indirectly trigger a prothrombotic response. Alternatively, some microbes can directly trigger platelet aggregation in vitro and in animal models, suggesting direct prothrombotic potential in human cardiovascular disease. Activation of coagulation and thrombosis characterizes the pathological response to infectious agents in human disseminated intravascular coagulation and infective endocarditis. Given the underlying biological plausibility, the cumulative lifetime burden of chronic pathogens may be expected to create risk of atherosclerosis and thrombosis, and, indirectly, signs ofcardiovascular disease.[8]

**2.2.1 Platelets** are a cellular blood component, which are play a major role in hemostasis. They are a disc-shape anucleated cell fragments that are shed from the bone marrow to the blood stream .[9]

**2-2-1-1 Development**:- They are produced in the bone marrow by fragmentation of the cytoplasm of megakaryocyte, one of the largest cells in body. The precursor of themegakaryocyte the megakaryoblast-arises by a process of differentiation from the haemopoietic stem cell. The megakaryocyte matures by endomitotic synchronous replication (i.e. DNA replication in the absence of nuclear or cytoplasmic division) enlarging the cytoplasmic volume as the number of nuclear lobes increase in multiples of two. Very early on invaginations of plasma membrane are seen, called the demarcation membrane, which evolves through the development of the megakaryocyte into a highly branched network. At a variable stage in development, most commonly at the eight nucleus stage, the cytoplasm becomes granular. Mature megakaryocytes are extremely large, with an eccentric placed single lobulated nucleus and a low nuclear to cytoplasmic ratio.

Platelets form by fragmentation from the tips megakaryocyte cytoplasmic extensions, approximately each megakaryocyte giving rise to 1000-5000 platelets. (9)

The time interval from differentiation of the human stem cell to the production of platelets averages approximately 10 days. The thrombopoietin is the major regulator of platelet production and is constitutively produced by the liver and kidneys. Thrombopoietin increases the number and rate of maturation of megakaryocytes via c-MpL receptor.(10)

Platelets also have c-MpL receptors for thrombopoietin and remove it from the circulation. Therefore, levels are high in thrombocytopenia as a result of marrow aplasia and vice versa. The normal platelet count is approximately 250 x $10^9$/L (range 150-400 x $10^9$/L) and the normal platelet lifespan is 7-10 days. Up to one-third of the marrow output of platelets may be trapped at any one time in the normal spleen but this rises to 90% in cases of massive

splenomegaly. Platelets are extremely small and discoid, 3.0 x0.5 mm in diameter, with a mean volume 7-11 fl . The glycoproteins of the surface coat are particularly important in the platelet reactions of adhesion and aggregation which are the initial events leading to platelet plug formation during hemostasis. Adhesion to collagen is facilitated by glycoprotein la (GP la). Glycoproteins Ib and IIb/IIIa are important in the attachment of platelets to von Willebrand factor (VWF) and hence to vascular subendothelium where signaling interactions occur The binding site for lib /IIIa is also the receptor for fibrinogen [12].

**2.2.1.2 Platelet physiology:-** platelet has a critical physiological process to stop bleeding. Platelet accumulation at the site of injury is considered the first wave of hemostasis and the second wave of hemostasis is mediated by the blood coagulation pathway [13]. Platelets play a central role in a series of sequential events during the platelet accumulation (i.e. platelet adhesion, activation, and aggregation) and are also actively involved in cell-based thrombin generation, which markedly amplifies the blood coagulation cascade. Thus, platelets contribute to both the first and the second waves of hemostasis[11][12] .

**2.2.1.3 Platelet adhesion**:-. Following vascular injury, subendothelial matrix proteins such as collagens are exposed to the blood components. Plasma von Willebrand Factor (VWF), originated from endothelial cells, megakaryocytes, and platelets, can then anchor onto the collagen. The VWF receptor on platelets GPIba, via interaction with the immobilized VWF, subsequently initiates platelet tethering to the site of injury[13].This binding is essential for platelet adhesion at high shear (e.g. Coronary arteries), although the GPIba-VWF interaction may also contribute to platelet adhesion at low shear[14][15]. Following platelet tethering, GPVI and integrin a2b1 may interact with collagen and deliver activation signals to platelets [13] [16] [17].

Stable adhesion is subsequently mediated by binding of several integrins to their ligands on the vessel wall, e.g.integrinαIIbβ3 to fibrinogen/fibrin and fibronectin, α5β1 to fibronectin or collagen, andα2β1 to collagen [18].

**2-2-1-4 platelet activation :-**The primary interactions between platelet surface receptors (e.g. GPIba, integrins) and their ligands (e.g.vWF, collagen, fibrinogen/fibrin, fibronectin and others), can lead to platelet activation[19]. The release of $Ca^{2+}$ from the endoplasmic reticulum and the dense granules via the $Ca^{2}$sensor,stromal interaction molecule (STIM)1, and the $Ca^{2}$channel contribute in platelet activation[20] [21].There are many positive feedback loops during platelet activation/granule release. Not ably ADP likely via interaction with its receptors on platelets, initiates cell-based thrombin generation and further platelet activation/granule release[22]. These secretion events act as secondary messengers and, in combination with the generation of thromboxane $A_2$ ($TXA_2$) and reactive oxygen species, amplify the activation process andintegrinαIIbβ3 inside-out signaling, which in turn recruits more platelets for aggregation[23][24].

**2-2-1-5 platelet aggregation:-** Following platelet activation, integrin αIIbβ3 binds fibrinogen and other ligands (i.e. fibrinogen-dependent and -independent pathways [15] , which leads to platelet aggregation. It is not able that following the engagement of ligands, integrin αIIbβ3 can deliver out-side-in signals, which further enhance platelet activation, cytoskeleton rearrangement, and granule secretion. These signal events facilitate hemostatic plug and thrombus formation [22].In addition to their central roles in the platelet adhesion, activation, and aggregation (the first wave of hemostasis), platelets also contribute to coagulation pathway, which is the second wave of hemostasis.[22].

**2-2-1-6 Platelet indices:-**

2-3-1-Mean platelet volume (MPV) is average size of the platelets in blood normal range of MPV = (7.5-11.5 fl). Usually MPV >13 occurs in hyperdestruction& MPV <8 in hypoproduction of platelet, best cut off value for MPV for ITP was greater than 9.7 fl.[25]

**2.2.9.PDW**:- platelet Distribution Width (PDW) is an indication of Platelet Iindicesvariation in platelet size which can be a sign of active platelet releasemedian was 13.3%, with a reference range of 10.0%-17.9% for the 5th-95th percentiles, with a confidence interval of 95%.

**2.3. Platelet-crit (**P-LCR):- is a measure of total platelet mass,the cut off value in thrombocytopenias3 is 0.2-0.36%. Platelet-crit is an effective screening tool for detecting platelet quantitative abnormalities to PDW and MPV.

Platelet large cell ratio if properly utilised can be a good aid in the differential diagnosis of conditions associated with abnormal platelet counts

P-LCR was greater than 33.6%, with a diagnostic accuracy of 70.1 and 99.6% respectively.

To evaluate the efficiency of platelet indices to differentiate hypoproductive type from hyperdestructivethrombocytopenias[25]

**2.3.1 Platelet disorder**

Platelets may be abnormal either quantitatively (too many or too few) or qualitatively (the right number but they do not work correctly). The number of platelets is routinely tested as part of the complete blood count (CBC). Normal counts range from 150 000 to 450 000. A decrease in the number of platelets indicates a condition known as thrombocytopenia and may result in increased bleeding, the first signs of which may include gum bleeding, nose bleeds, and increased bruising. In cardiology, the most frequent cause of a low platelet count is an abnormal immune response caused by drug therapy,

particularly with the intravenous blood thinner heparin (heparin-induced thrombocytopenia), and rarely with other drugs to control high blood pressure or symptoms of congestive heart failure (diuretics), to control diabetes (antidiabetic medications), or to regulate your blood clotting (antiplatelet drugs). Elevated platelet counts can also occur, usually in association with diseases in the elderly, and can result in either excess clotting or even abnormal bleeding.[26]

### 2.3.2 Platelet Dysfunction

Because platelets are so important in stopping bleeding from everyday injuries such as cuts or bruises, severe inherited disorders of platelets are quite rare. Researchers, however, have discovered more subtle genetic variations in platelets called polymorphisms that may alter platelets in subtle ways to raise the risk of cardiovascular disease when combined with other risk factors, but which on their own do not result in overt disease. These polymorphisms may also be important in understanding who may gain the greatest benefit from drugs such as aspirin that alter platelet function. Because abnormal clots cause heart attack, your doctor can prescribe drugs (antiplatelet agents) to inhibit clot formation and reduce the risk of cardiovascular disease.[25]

### 2.3.3 : Quantitative Disorders Of Platelet:-

**1-Thrombocytopenia**is decreased in number of platelet count than normal range occur by Three categories Idiopathic thrombocytopenia , Hypo plastic thrombocytopenia , Acquired thrombocytopenia .[24][27][28]

### 2-Idiopathic Thrombocytopenic Purpura (Itp)

Refers to acute, chronic or recurrent form of thrombocytopenia result of non-etiological causes but considered to be due to immunological process of platelet destruction in RES .Autoimmune or ‘idiopathic’ thrombocytopenic

purpura is an acquired condition in which platelet survival is reduced by the presence of platelet directed auto antibodies.[24][27][28]

Autoimmune thrombocytopenia can also occur as one feature of a more generalized autoimmune disease such as systemic lupus erythematosus or the rare autoimmune lympho proliferative syndrome associated with Fas deficiency,There is an increased incidence in DiGeorge's syndrome. Autoimmune thrombo-cytopenia is a common complication of chronic lymphocytic leukaemia and a less common complication of other lymphoproliferative disorders. Idiopathic autoimmune thrombocytopenic purpura has generally been regarded as particularly likely to occur in young women but in one population-based survey the incidence in adults was 1.6/10 000/year overall, was similar in men and women and was higher above the age of 60 years. [24][27][28]

**3-Congenital Hypo Plastic Thrombocytopenia**

Due to bone marrow megakaryocytic hypoplasia seen in various of clinical situations including the Fanconi syndrome . [24][27][28]

**4-Acquired Thrombocytopenia**

Result from suppresser of megakaryocytic maturation by large number of agents e.g (Ionizing irradiation , Severe Alcoholic , Splenomegaly and Bone marrow infiltration) . [24][27][28]

**5-Drugs –induced thrombocytopenia**

Ingestion of certain drug such as quinine enhances formation of antibodies reacts with platelets in the presence of drug and cause thrombocytopenia .[24][27][28]

**6-Infectious Induced Thrombocytopenia**:

Thrombocytopenia at birth of lower than 70000/$mm^3$ of platelets counts with marked lack of bone megakaryocyte result from severe rubella infection. [24][27][28]

## 2.3.Heparin Induced Thrombocytopenia

- Represented as important causes of hospital –acquired morbidity of two separated syndromes:-

1- Most common benign and mild thrombocytopenia related to property of heparin induced platelet aggregation.

2- Less common and severe thrombocytopenia appears as drug related immune thrombocytopenia associated with serious thrombotic complications. Other factor of thrombocytopenia like pregnancy, post transfusion and autoimmune disease .[30]

### 2.3.4 Thrombocytosis :

- Defined as abnormal high platelet count above 400000/$mm^3$ in whole blood.
- 1-Reactive thrombocytosis often secondary to inflammation or trauma rarely exceeds 8000000/$mm^3$.
- 2-Marked persist thrombocytosis of myeloproliferative disorders of count exceed 1000000/$mm^3$
- 3-Essential Thrombocythemia in which counts are between 1000000/$mm^3$ and 2000000/$mm^3$. [24][27][28]

### 2.3.4.1Secondary Reactive Thrombocytosis:

- Of platelet counts between 440000 and 800000 with normal platelet function. And not associated with thrombosis or bleeding, disappears with management of underlying disorder.[15][28][47]

### 2.3.4.2 Post- Splenectomy Thrombocytosis:

- Counts reaches 1000000/$mm^3$ regardless of the clinical reason for spleen removal, there is no sequestration of platelet occurs.
- IDA related thrombocytosis:

- Result from mild IDA with chronic blood loss, iron deficiency inhibits thrombopoietin production. Counts may be as high as 2000000/$mm^3$, while thrombocytopenia is more common in severe IDA. [24][27][28]

**2.3.4.3 Inflammatory Thrombocytosis**

- Thrombocytosis is indicator for inflammation results from infectious, systemic or collagenic disease and usually correlated with the activation of inflammatory process. [24][27][28]

**2.3.4.4 Exercise Thrombocytosis**

- Results from hemoconcentraion due to transfer of plasma water to extravascular compartment causing reversible thrombocytosis. [24][27][28]

**2.3.5Essential Thrombocythemia**

- Essential or primary Thrombocythemia results from proliferation of bone marrow megakaryocytes with platelet counts between 1000000/$mm^3$ and 2000000/$mm^3$, and occasional hemorrhage and occasional thrombosis.
- Prevalent in middle aged and older both males and females affected equally. [24][27][28]

**2.4.1 :Qualitative Disorders Of Platelets**

General feature:

State of prolonged bleeding time in a patient's with normal platelet count indicates an acquired or a congenital platelet dysfunction result of four phases platelet abnormalities involves adhesion, aggregation, secretion and elaboration of procoagulant activity .[30]

**2.4.2 Bernard- Souliersyndrome :**

Platelet quantitative disorder associated with defective platelet adhesion and aggregation result from inability to interact with vWF at site of injury.[30]

### 2.4.3 Von Will Brand's Disease (Vwf):

- Heterogeneous familial bleeding syndrome that result from a quantitative or qualitative abnormality of vWF (with distinct minor variants).
- VWF is glycoprotein, synthesized by endothelial cells and megakaryocytes.[30]

### 2.4.4 Glanzmann'sThrombasthenia :

Bleeding disorder associated with abnormal clot retraction.[30]

### 2.4.5 Storage Pool Diseases

Dense granules deficiencies:

-decrease storage intracellular granules include ADP, ATP, Ca, P and serotonin. With marked BT prolonged. And in response to collagen secondary to ADP absent.[30]

-decreased number of dense bodies.

-greater decrease ADP with increased ATP: ADP ratio higher than in normal platelets is diagnostic.

-acquired forms found in leukemia, SLE and acute alcoholic toxicity.

Acquired form result from auto antibodies.

Alpha granule deficiency (gray platelet syndrome):-Inability to release PF4, VIIIreceptor,beta- thromboglobulin, acid hydrolases, Rare disorder with feature of large gray platelets appear on a Wright's stained blood film.[30]

### 2.4.6Anticoagulant Therapy

Anticoagulant medications are widely used in the prevention and treatment of thromboembolism. For many years, the antithrombotic therapeutic armamentarium was limited essentially to heparin, warfarin,and aspirin, but over the past several years the number of medications has increased significantly, with a consequent demand for better understanding of the laboratory aspects of therapeutic monitoring. Laboratory monitoring falls

into the two broad categories of general monitoring and specific monitoring. General monitoring is directed toward the assessment of bleeding or other untoward effects of therapy.These tests include hematocrit, hemoglobin, platelet count, occult blood ,and so forth. The need for general monitoring is common to all anticoagulants.[25]

**2-4-7- Platelet disorder in general** Thiscould numerical or functional or physiological.

**2-4-8- numerical platelet disorder :-** The number could be low and known as thrombocytopenia, or high and known as thrombocytosis. Thrombocytopenia ir reduction I the number of platelet could be due to platelet disorder production, decrease platelet survive, sequestration, or dilution. Different types of thrombocytopenia can be determine like immune thrombocytopenic purpura (chronic or acute), drug induced, HIV-Associated thrombocytopenia, and thrombotic micro-angiopathic. [24][27][28]

**2-4-9- Platelet disorder in cardiac diseases:-** It is a very well known that platelet play a vital role in the pathophysiology of cardiovascular disease, especially acute coronary syndrome(ACSs), since they are implied in thrombus formation after atheroma plaque rupture. This is the reason why molecules involved in platelet activation and aggregation are primary target for treatment of acute coronary syndromes. Platelet is a key word in thrombous formation mechanism, as it starts with platelet plug formation followed by stabilization of this plug through fibrin deposition (coagulation).Cardiovascular diseases include number of conditions which affect structure and function of the cardiovascular system. They comprise coronary acute diseases, vascular diseases, arrhythemias, heart failure, heart valvular disease, congenital heart disease, cardiomyopathy, pericardial and aorta diseases. There are many risk factors associated with cardiovascular diseases such as family history, ethinicity, and age which cannot be changed.

Other risk factors which are modifiable include smoke, hypertension, high cholesterol, obesity, physical inactivity, diabetes, unhealthy diets, and harmful use of alcohol.[19][27][31]

**2-2-2 Fibrinogen** is a soluble glycoprotein present in plasma that has a variety of physiological functions. Fibrinogen has an important role in the process of thrombus formation and evolution. It is a major determinant of blood viscosity and erythrocyte aggregation. Fibrinogenis both constitutively expressed and inducible during areaction of acute phase. It is also important in cellular and matrix interactions, wound healing, inflammation,tumor development and atherogenesis.The recent years have considerably advanced our understanding of fibrinogen structure, functions, genetic and extrinsic determinants and involvement in pathogenesis of many disease conditions[32][33].Fibrinogen is acomplex multifunctional glycoprotein composed of two identical molecular halves, each consisting of three non-identical subunit polypeptides designated as alpha (α), beta (β), and gamma (γ) chains held together by multiple disulfide bridges[33]. Fibrinogen has atrinodular structure; one central dimeric E domain in which each dimer contains the three amino-terminal regions of polypeptides, and two distal D domains. These three nodules are linked by two coiled-coil regions[34] and contain multiple binding sites[35]. The amino terminal ends of and chains represent fibrino peptides A and B(FPA and FPB).Most of the fibrinogen is found in plasma, where it exists as a population of slightly different molecules3.Under normal conditions, about 70% of the fibrino gen molecules are high molecular weight fibrinogen (HMW fibrinogen), with molecular weight (mw) of 340,000 Dalton (Da). The remaining molecules are the consequence of the proteolysis of the α chains of fibrinogen molecule4:loss of the C-terminal end of one α chain creates low weight fibrinogen (LMW-fibrinogen, mw 305,000 Da, about 26% of total

fibrinogen), and loss of both chains creates LMW'-fibrinogen (mw 270,000 Da, about 4% of total fibrin)[36][37], resulting in impaired fibrin polymerization [39].Fibrinogen has a biological half-life of about 100hours, and is synthesized predominantly in the liver but also in megakaryocytes The production of fibrinogen by lung and intestinal epithelium requires an inflammatory stimulus ,Fibrinogen polypeptide chains α ,β and γ are encoded by three different genes named α, β and γ, clustered on the chromosome 4 in region q23–32of approximately 50 kb, with the direction of transcription of the gene opposite to that of the other two [38].

Many cytokines and other molecules influence biosynthesis of fibrinogen. For example, interleukin 1 and 6(IL-1 and IL-6), tissue necrosis factor α (TNF-α), freefatty acids and on costatin M stimulate fibrinogen synthesis, while interleukin 4, 10, and 13 (IL-4, IL-10, andIL-13), vitamin E, and high plasma albumin decrease synthesis of fibrinogen.[38]

Fibrinogen and cholesterol may share a novel common regulatory pathway, because Oxysterols, which suppress cholesterol biosynthesis and the uptake of LDL-cholesterol, also down-regulates constitutive fibrinogen expression[54],It is accepted that the normal range of plasma levels of fibrinogen is from 1.5to3.5g/l.[36]

Fibrinogen has an important role in the process of thrombogenesis, being the precursor of fibrin. Most of fibrinogen functions are assigned to certain structures of fibrin including double-stranded fibrin protofibrils and highly cross-linked fibrin networks. Fibrin formation is a series of highly ordered molecular interactions – a complex cascade of enzymatic reactions of blood coagulation. That cascade is comprised of two arms, the intrinsic and extrinsic pathways that converge at factor Xa to form the common pathway.[38]

Factor Xa activates prothrombin to thrombin. Thrombin, which is a protease enzyme, induces cleavage of FPA from α chain, what is considered to be the initial step in the conversion of fibrinogen to fibrin. Removal of the FPA and also FPB from the fibrinogen α and chains leads to spontaneous polymerization of the monomers. Lateral growth produces protofibrils, and cross-linking further creates fibrin strands. Thrombin-activated factor XIIIa introduces covalent cross links into polymers to complete and stabilize the formed thrombi [(34) (37)]. Fibrinogen and fibrin are degraded by plasmin, an enzyme that is activated from plasminogen18. High fibrinogen levels lead to formation of larger and less lysable clot with tight and rigid network structure [(39) (40)]. Moreover, elevated Fibrinogen levels interact with the binding of plasminogen to its receptor, causing impaired fibrinolysis[(38)]

the interaction of platelets with fibrinogen is an important event in the maintenance of hemostatic response. Fibrinogen binding to the GP IIb–IIIareceptorin activated platelets leads to platelet aggregation and formation of platelet-rich thrombi[(25)(26)].

Fibrinogen's major role is as aprecursor of fibrin through the action of thrombin. It is also known as the coagulation Factor I and it's concentration in plasma ranges between 2 and 4 g/L. The fibrinogen concentration is increased in infections, tissue necrosis, estrogen ingestion, diabetes,obesity and pregnancy. High levels of fibrinogen are also a significant independent risk factor for coronary artery disorders and cerebrovascular diseases. Low concentrations of fibrinogen in plasma are associated with liver diseases (cirrhosis, jaundice) or with fibrinolysis and disseminated intravascular coagulation (DIC).[(26)]

**2-2-2-1 fibrinogen disorder :**Fibrinogen disorders can be classified as quantitative or qualitative, congenital or acquired .The following terms will be used here:

- Dysfibrinogenemia ─ Presence of a dysfunctional fibrinogen molecule.
- Hypodysfibrinogenemia **:** inherited fibrinogens that are both functionally abnormal as well as associated with low plasma levels (<150 mg/dL) as measured by immunologic techniques.
- Hypofibrinogenemia **:**Any condition associated with a reduction in the circulating level of normal fibrinogen to <150 mg/dL.
- Afibrinogenemia **:**A rare autosomal recessive condition in which there is a complete lack of circulating fibrinogen.
- Cryofibrinogenemia **:** A phenomenon in which there is the presence in plasma, but not serum, of a fibrinogen that precipitates on exposure to low temperatures (eg, 4°C).[(22)]

**2-2-2-2 CONGENITAL DISORDERS** :

Congenital disorders of fibrinogen take the form of either the production of an abnormal fibrinogen (dysfibrinogenemia) or the complete lack of production of fibrinogen (afibrinogenemia). Each will be described below.Inheriteddysfibrinogenemia is the result of mutations in the coding region of the fibrinogen FGA, FGB, or FGG genes. Over 400 affected families have been reported in the literature. Over 90 percent are point missense mutations, leading to the production of a dysfunctional protein product. An updated online database of fibrinogen mutations is available, which also provides data on their associated clinical manifestations.These modifications result in alteration of fibrinopeptide release, fibrin polymerization, fibrin crosslinking, or fibrinolysis, and may be associated with a clinical phenotype.[(36)(38)(41)]

Structure and function correlations can be made for several of these mutations significant number of these mutations are located at positions Aalpha 16 Arg (the FPA cleavage site) and gamma 275 Arg (the fibrin polymerization site) .These mutations account for 45 percent of dysfibrinogenemia mutations. Overall, dysfibrinogenemias can be silent (55 percent), or lead to a hemorrhagic (25 percent) or thrombotic diathesis (10 to 20 percent) .About 2 percent of the mutations may be associated with both thrombotic and bleeding complications. Asymptomatic dysfibrinogenemia is often diagnosed incidentally following the finding of abnormal coagulation tests or as part of family screening studies. [36][38][41]

Inherited dysfibrinogenemias are named after the city where the patient was first identified or evaluated. Roman numerals are added after the city name when there are several dysfibrinogens from the same city (eg, Caracas V). With rare exceptions, the mode of inheritance of the congenital dysfibrinogenemias is autosomal dominant.

**2-2-2-3 Thrombotic variants** : Dysfibrinogenemia is a rare cause of thrombophilia; the other more common causes of thrombophilia should be excluded before the patient is evaluated for the presence of an abnormal fibrinogen. The prevalence of congenital dysfibrinogenemia in patients with a history of venous thrombosis has been estimated at 0.8 percent. [36][38][41]

The true prevalence of thrombosis among patients with dysfibrinogenemia is unknown, but is estimated to be around 10 to 20 percent .Venous thrombosis of the lower extremity dominates the clinical picture; arterial thrombosis or both venous/arterial thrombosis have also been reported. The findings of a registry of dysfibrinogenemia and thrombophilia established by the Scientific and Standardization Subcommittee on Fibrinogen of the International Society on Thrombosis and Haemostasis were published in 1995. The registry reported 26 cases with thrombosis at young age and gathered information on

family members. The mean age of first thrombosis was 27 years. A highly convincing association between dysfibrinogenemia and thrombophilia could be established for five families (Caracas V, Melun, Naples, Paris V, Vlissinger/Frankfurt IV). There was a high rate of pregnancy-related complications such as postpartum thrombosis and spontaneous abortions; 3 of the 26 families experienced severe postpartum bleeding Fibrinogen concentrations were normal or low. [36][38][41]

Resistance to fibrinolysis due to the presence of an abnormal fibrinogen is a potential mechanism in the development of chronic thromboembolic pulmonary hypertension (CTEPH) following pulmonary embolism. Five patients with dysfibrinogenemias were identified in a cohort of 33 patients with CTEPH. Functional studies showed abnormal fibrin structure and/or resistance to lysis in all five. [36][38][41]

**2-2-2-4 Hemorrhagic variants** : Patients with fibrinogen levels less than 50 to 100 mg/dL have a higher frequency of bleeding complications. Bleeding is also associated with fibrinogen mutations impairing fibrinopeptide release or fibrin monomer polymerization. Most bleeding manifestations are moderate, but some can be severe. [36][38][41]

The clinical presentation is heterogeneous, and may include epistaxis, menorrhagia, easy bruisability, soft tissue hemorrhage, postoperative bleeding, antepartum and postpartum bleeding, as well as hematomas and hemarthrosis. Bleeding often manifests after trauma, surgery, or during the postpartum period. [36][38][41]

**2-2-2-5 Silent mutations** : Half of the reported cases of dysfibrinogenemia remain asymptomatic as observed in family members who share the defect with the proband. [36][38][41]

### 2-2-2-6 Other disease manifestations:

- Hereditary renal amyloidosis :Renal amyloidosis secondary to deposition in the kidney of a mutant fibrinogen alpha chain has been reported. Inheritance is autosomal dominant and most affected individuals develop renal failure
- disease In four hypofibrinogenemia mutations, all located in exon 8 of the fibrinogen gamma gene, the abnormal fibrinogen may remain within the endoplasmic reticulum of the hepatocyte, leading to a form of hepatic storage disease .
- Dysfibrinogenemia can rarely cause delayed wound healing and/or wound dehiscence. [36][38][41]

### 2-2-2-7 Congenital afibrinogenemia/hypofibrinogenemia:

Afibrinogenemia, or a complete or virtually complete lack of circulating fibrinogen, is a rare condition, most often with autosomal recessive inheritance in association with consanguinity ,The estimated incidence is one per million in the general population. Hemorrhagic manifestations vary from minimal to catastrophic, and may include fatal umbilical cord hemorrhage as the first disease manifestation. In later life, the disorder may be associated with bleeding from mucosal surfaces (eg, epistaxis, menorrhagia, gastrointestinal bleeding), hemorrhage into muscles and joints, intracranial bleeding, spontaneous abortions, and/or spontaneous splenic rupture.[54][55][59]

The vast majority of patients with afibrinogenemia are homozygous or compound heterozygous for truncating mutations in the fibrinogen alpha chain gene ,while patients with hypofibrinogenemia are usually asymptomatic carriers (heterozygotes) of afibrinogenemia mutations. Comprehensive reviews of the molecular mechanisms of congenital hypo- and a-fibrinogenemia have been published . [36][38][41]

Heterogeneity of the disease was confirmed by the observations of a survey of 100 patients with congenital hypo- or a-fibrinogenemia. The annual incidence of bleeding episodes was 0.7, with a range from zero to 16.5 episodes per year .[37][54]

The diagnosis is established by demonstrating trace or absent immunoreactive fibrinogen in the plasma. Patients with hypofibrinogenemiaare usually asymptomatic, except during pregnancy or when exposed to trauma.

**2.2.2.8 ACQUIRED DISORDERS:-**

**2.2.2.8.1Acquired dysfibrinogenemia** : A number of clinical conditions can lead to the production of an abnormal fibrinogen:

**2.2.2.8.2 Liver disease** :The most common cause of acquired dysfibrinogenemia is liver disease. It is observed in the majority of patients with cirrhosis, acute or chronic hepatitis, and also in those with metastatic hepatoma .Fibrinogen dysfunction in this setting is manifested by prolongation of thrombin and reptilase times; fibrinogen levels are normal when measured by immunologic methods. [36][38][41]

The abnormal fibrinogen in this setting is characterized by an increased content of sialic acid residues and delayed fibrin polymerization .Both cleavage of the A and B fibrinopeptides and the crosslinking of fibrin by factor XIII are normal. Removal of the sialic acid from the abnormal fibrinogen normalizes the thrombin time and corrects the polymerization defect .Normal fetal fibrinogen also exhibits an increased content of sialic acid residues and similar laboratory changes are found . [36][38][41]

Whether the abnormal fibrinogen seen in liver disease is associated with an increased bleeding risk is difficult to evaluate, since most of these individuals have other associated abnormalities of hemostasis (eg, thrombocytopenia, diminished synthesis of other coagulation factors) and/or other causes for

bleeding (eg, varices, peptic ulceration). No increase in thrombotic risk has been observed. [36][38][41]

**2.2.2.8.3 Other causes** :- Acquired dysfibrinogenemia has also been reported in association with renal carcinoma , isotretinoin therapy and biliary obstruction, and in one case resulted in red cell aggregation, digital arterial occlusion, and digital gangrene. The abnormal fibrinogen may disappear with treatment of the underlying condition ,or may disappear spontaneously.[45]

**2.2.2.9.Fibrinogen antibodies or inhibitors**:-Autoantibodies inhibiting specific functions of fibrinogen have been described. These antibodies can block fibrinopeptide release, fibrin monomer polymerization, or fibrin crosslinking. They have been reported in systemic lupus erythematosus, ulcerative colitis, multiple myeloma, therapy with isoniazid, or without any underlying condition. Presence of such antibodies is more commonly associated with bleeding manifestations. Clinical thrombosis associated with fibrinogen autoantibodies has been reported, although many of those patients had other risk factors for thrombosis. [36][38][41]

Antibodies can also be clinically silent, such as in one patient in whom the antibody interfered with fibrinopeptide B release. Blockage of fibrinopeptideA release seems to be associated with the most severe clinical manifestations. Spontaneous remissions have been reported. [36][38][41]

Fibrin sealant (fibrin glue) has been used during various surgical procedures for decades. Patients exposed to fibrin glue prepared from bovine sources can develop antibodies against bovine fibrinogen, which may cross-react with human fibrinogen Current FDA-approved commercial fibrin sealants made of human coagulant factors (Hemaseel APR or Tisseel kit VH) should eliminate this potential complication. [36][38][41]

**2.2.2.10 Hypofibrinogenemia**:

Low levels of fibrinogen may occur when there is reduced synthesis or increased turnover of fibrinogen. As an example, patients with hepatic failure or decompensated cirrhosis may have low levels of fibrinogen for a number of reasons.

- Production of an abnormal fibrinogen (see 'Liver disease' above)
- Decreased hepatic synthesis
- Increased turnover (consumption) due to the concomitant presence of disseminated intravascular coagulation[36][38][41]

Fibrinogen is an acute phase reactant, with levels increasing as part of the acute inflammatory response. (See "Acute phase reactants".) Thus, a plasma fibrinogen of 200 mg/dL, although within the normal range, may represent a significant decrease in a patient whose baseline level, because of underlying malignancy, sepsis, or inflammation, should be 800 mg/dL. [36][38][41]

- The most common clinical condition associated with hypofibrinogenemia is acute disseminated intravascular coagulation (DIC), a disorder in which there is an excessive turnover of fibrinogen, due to increased consumption Plasma levels of fibrinogen are usually normal or increased in chronic DIC.
- Less common causes of hypofibrinogenemia include administration of drugs that may impair hepatic synthetic function, such as L-asparaginase and valproicacid . [36][38][41]

**2.2.2.11 Cryofibrinogenemia** Primary fibrinolytic states leading to hypofibrinogenemia are rare.: Cryofibrinogenemia refers to the presence in plasma (but not serum) of an abnormal cold-insoluble protein, composed of a combination of fibrinogen, fibrin, and fibronectin. This condition is seen most frequently in autoimmune disorders, malignancy, thrombotic disorders, and infections (eg, hepatitis C virus infection), and

may be accompanied by disseminated intravascular coagulation. Symptoms, when present, include sensitivity to cold, Raynaud's phenomenon, purpura, urticaria, skin ulcerations or gangrene, and arterial or venous thromboses. [36][38][41]

**2.2.2.12 fibrinogen in cardiac diseases :**

Mounting data support a causal connection between high-normal fibrinogen levels and atherosclerotic cardiovascular disease. There is clearly a thrombogenic component to atherosclerosis and the onset of clinical manifestations. This offers the possibility to better identify high-risk candidates and also to protect them by reducing blood fibrinogen concentration or blocking its action.[22][38]

The relationship of antecedent fibrinogen to the subsequent development of cardiovascular disease is examined, based on 18 years of surveillance of a cohort of 1274 men and women aged 47 to 79 years who participated in the Framingham Study. The association with the development of peripheral arterial disease and cardiac failure is now examined in addition to previously studied relationships to coronary heart disease and stroke. In men and women, there is a significant age-adjusted relationship of fibrinogen level to coronary heart disease and to cardiovascular disease in general. In women, a significant relationship to cardiac failure and peripheral arterial disease, but not to stroke, was also found. These data on women are unique as they are not available elsewhere.[38]

Age-adjusted cardiovascular, all-cause, and coronary heart disease mortality were all related to fibrinogen in both sexes. In men, fibrinogen impact was the greatest for stroke and the least for peripheral arterial disease. For women, the impact on coronary heart disease was greatest. The absolute risk for an elevated fibrinogen level was greatest for coronary heart disease in both sexes. [38]

Average fibrinogen values are higher in women and in persons with other risk factors, including hypertension, cigarette smoking, diabetes, obesity, and elevated hematocrit. However, there is an independent contribution of fibrinogen to cardiovascular disease in general and coronary disease in particular, on adjustment for coexistent risk factors. Fibrinogen enhances the risk of cardiovascular disease in hypertensives, diabetics, and cigarette smokers. About half the cardiovascular risk of cigarette smoking appears due to the higher fibrinogen values.[38]

Now, five prospective studies document the excess incidence of cardiovascular events in persons with elevated fibrinogen levels within the "normal range." Each standard deviation increase in fibrinogen is associated with a 30% increment of coronary heart disease in men and a 40% increase in women. Fibrinogen should be added to the list of major cardiovascular risk factors. Trials of intervention to lower fibrinogen in high-risk coronary candidates are needed.[38]

**2.3 Prothrombin Time (PT):**

Prothrombin Time (PT) is commonly used for screening for extrinsic factor deficiency, monitoring oral anticoagulant therapy and quantitative determination of the extrinsic coagulation factors.

Tissue thromboplastin, in the presence of calcium ions and Factor VII, activates the extrinsic pathway of coagulation.

When a mixture of tissue thromboplastin and calcium ions is added to normal anticoagulant plasma, the clotting mechanism is initiated and a clot will form within aspecified time period. If a deficiency exists within the

extrinsic pathway, the time required for clot formation will be prolonged. The degree of prolongation is proportional to the severity of single factor deficiency, or in a cumulative deficiency of all the factors involved.

Normal control sample: (11-16 seconds).[25][26]

**2.4Activated Partial ThromboplastinTime :-**

(PTT) is commonly used for pre-surgical screening for intrinsic factor deficiency, monitoring heparin therapy, in the detection of Lupus Anticoagulants, and quantitative determination of the Factor VIII, IX, XI, and XII relevant with the intrinsic coagulation system In the test, citrated test plasma is mixed with PTT reagent,for a specified period of time. The time required for clotting formation is the activated partial thromboplastin time (PTT). The degree of prolongation is proportional to the severity of single factor deficiency, or in a cumulative deficiency of all the factors involved,normal control sample 26-36 seconds ,PT, PTT, TT , and FIB assay procedure are routinely used to identify and quantitate deficiencies in clotting mechanism as well as to monitor anticoagulant Ttherapy. [25][26]

**2.5 Previous study:**

(1)**Turk U, Tengiz I, Ozpelit E and etal the relationship between platelet indices and clinical features of coronary artery disease**, found that there was no statistical difference for platelet count, MPV and PDW values among the groups, Correlation analysis showed a positive association between platelet count and Gensiniscoringand also age in patients with coronary artery disease. However, there was no significant correlation between Gensini scoring and MPV or PDW values in these patients.[42]

(2)**Thompson SG, Kienast J and etal Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris, European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group**,the extent of coronary artery disease and other risk factors, an increased incidence of myocardial infarction or sudden death was associated with higher base-line concentrations of fibrinogen .[43]

(3) **Khandekar MM, Khurana AS and etal Platelet volume indices in patients with coronary artery disease and acute myocardial infarction: an Indian scenario**,found that the platelet volume indices:mean platelet volume (MPV), platelet distribution width (PDW), and platelet large cell ratio (P-LCR) were significantly raised in patients with acute myocardial infarction and unstable angina(mean MPV, 10.43 (SD, 1.03) fL; mean PDW, 13.19 (SD, 2.34) fL; mean P-LCR, 29.4% (SD, 7.38%)) compared with those with stable coronary artery disease(mean MPV, 9.37 (SD, 0.99) fL; mean PDW, 11.35 (SD, 1.95) fL; mean P-LCR, 22.55% (SD, 6.65%)) and the control group (mean MPV, 9.2 (SD, 0.91) fL; mean PDW, 10.75 (SD, l.42) fL; mean P-LCR, 20.65% (SD, 6.14%).[44]

**(4)Khan HA, Alhomida AS and etal alterations in prothrombin time and activated partial thromboplastin time in patients with acute myocardial infarction, international journal of clinical and experimental medicine** found PT and aPTT are significantly increased in AMI patients on anticoagulation therapy, the elevations in PT values were more than 2.5-fold higher than aPTT suggesting a greater responsive potential of PT for predicting blood clotting tendency in patients receiving anticoagulation therapy.[52]

# Chapter Three

## Materials and Methods

# 3.Materials and Methodology:

## 3.1 Study design:

Prospective Descriptive cross sectional, conducted during the period from march 2015 to august 2017 that aimed to evaluate platelet count, platelet indices, fibrinogen levels, Prothrombine time and partial Prothrombine time among Sudanese patients with cardiovascular disorders in elmaknair hospital in shendi locality.

## 3.2 Study area:

This study was carried out among patients of cardiac center MicNimier hospital, Shandi state.

## 3.3 Study population:

Atotal of 360 patients ,who professionally diagnosed with cardiovascular disorders, were encountered in this study Subjects.

## 3.4 Inclusion criteria

Individual with established diagnosis of heart issues.

## 3.5 Exclusion criteria

Individuals with other disorders than cardiac, as Anemia, renal disorders or liver's and any disease that associated with haemostatic change.

## 3.6 Data collection

Data was collected by direct questionnaire.

## 3.7 Ethical consideration

-This study is approved by the ethical committee of Shandi University, faculty of medical laboratory science. Every subject involved in this study should be informed with the study and its importance and formal consent elmek nimir.

**3.2 Method:**

- Sample collected venous blood 6 ml sepration into two tube 3ml EDTA(ethylene di amin tetra acetic acid) and 3ml trisodium citrate dihydrate anticoagulant, mix nine parts of blood with one part of $0.10^9$ mol/L trisodium citrate dehydrate(1: 9) and centrifuge at 1500xg during 15 min to obtain platelet poor plasma .
- **Platelet count** : in EDTA(ethylene di amin tetra acetic acid) tube is suitable for cellular counting, using CBC automated device(sysmexkx21), reagent ready to assessed platelets during running of EDTA added blood sample.
- **Fibrinogen** : measured via Clauss method measures the rate of conversion of fibrinogen into fibrin in a diluted plasma in the presence of an excess of thrombin , the measured clotting time is inversely proportional to fibrinogen concentration, using coagulometer devise.
- **Prothrombin time:**

1. Centrifuge anticoagulated blood at 2,500 rpm for 10 minutes as soon as possible after collection.
2. Pipet 0.2 ml of thromboplastin-calcium mixture into a set (4 – 6) of 12 x75test tubes. Warm the test tubes in the 37 C heat block for at least 1minute, until they have reached 37 C. The incubation period for this mixture is not critical once it reaches 37 C. (Thromboplastin reagent is good for 20 minutes at 37 C)
3. Incubate a portion of the plasma for approximately 2 to 3 minutes, until itreaches 37 C. Plasma should be incubated for no longer than 10 minutes after reaching 37 C.
4. Forcibly inject 0.1 ml of patient's plasma into the test tube containing 0.2ml of thromboplastin-calcium mixture and simultaneously start the stopwatch, allow clotting to start. The test is timed from the addition of the

calcium chloride until the plasma clots, this time is called the Prothrombin Time.

- **activated partial thromboplastin time**:-

1. Centrifuge anticoagulated blood at 2,500 rpm for 10 minutes as soon as possible after collection.
2. Incubate asufficient amount of 0.025M CaCl2 at 37 C.
3. Pipet 0.1 ml of normal control plasma (or patient's plasma) into a 12 x 75 testtube.
4. Pipet 0.1 ml of the partial thromboplastin (containing activator) into the test tube containing the control (or patient's) plasma, mix the contents of the tube quickly and place in a 37 C heat block for 5 minutes.
5. After exactly 5 minutes, forcibly inject 0.1 ml of the pre warmed CaCl2 and simultaneously start the stop watch, the partial thromboplastin time is the time it takes for a clot to form.

### 3.2.2 Data Analysis

The numerical data obtained from recent study were evaluate statistically with statistical package of social science program (SPSS) software program (version 21.0), T.test was used to detect significant difference on the data.

**Data Presentation**:-

The data were presented by using tables and figures .

# Chapter Four

## Results

## The result :

**Table ( 4-1 )** Distribuation of patients according to sex:

| Gender | Number | Precentage |
|---|---|---|
| **Male** | **271** | **75 %** |
| **Female** | **89** | **25 %** |

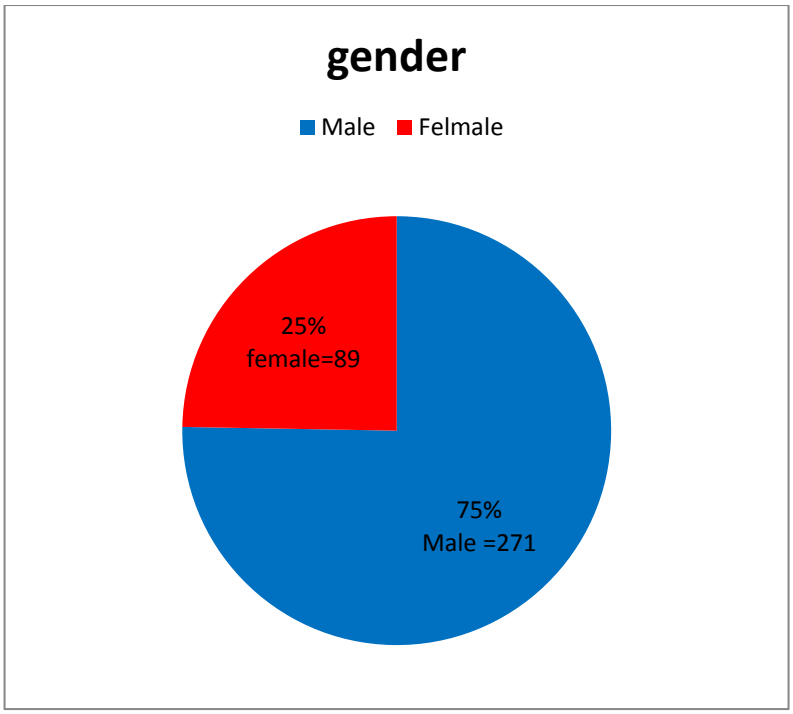


**Table (4-2) :** Distribuation of patients according to age :

| Age | Number | precentage |
|---|---|---|
| **40-49** | **82** | **22.8%** |
| **50-59** | **83** | **23.1%** |
| **> 60** | **195** | **54.1%** |

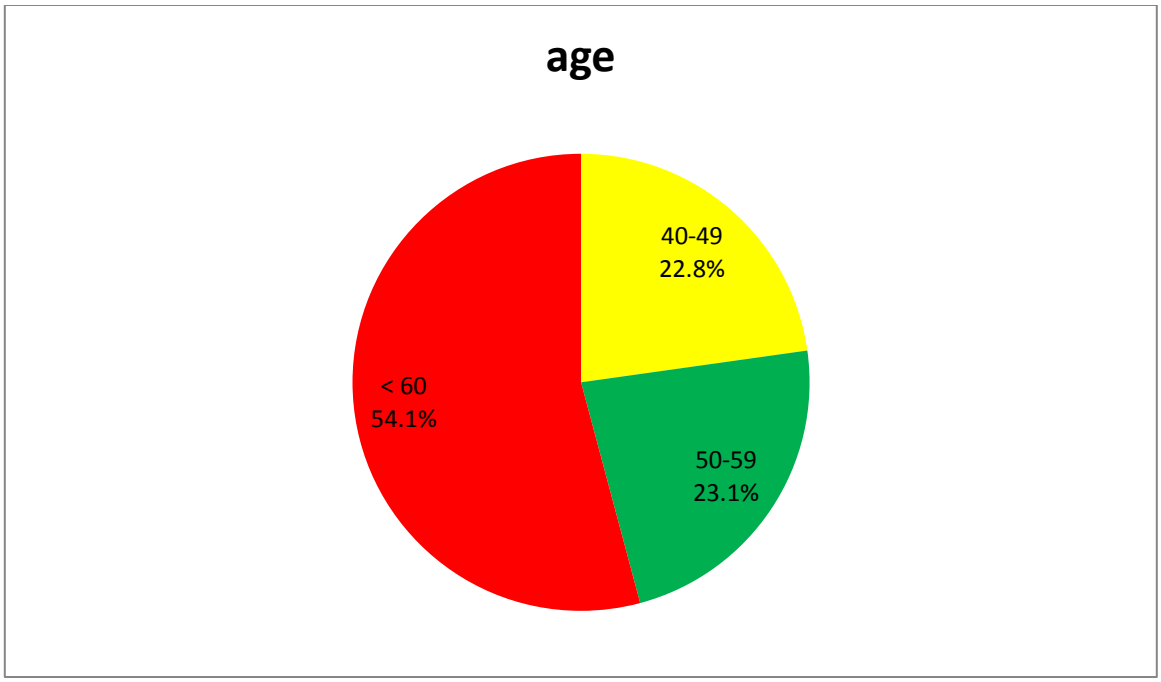


**Table (4-3):**Means of PLT count, Platelet indices (PDW,MPV, PCT) Fibrinogen level,PTT and PT in patients with cardiovascular diseases and Comparing with normal range:-

| Parameters/Normal value | Mean | P.value |
|---|---|---|
| PLT count (150-450) x$10^9$/L | 497 | 0.000 |
| PDW ( 10-17) FL | 18.0 | 0.000 |
| MPV (7-11.5) % | 16.0 | 0.000 |
| PCT (0.2-0.36 ) % | 0.6 | 0.000 |
| Fibrinogen level (150-450) mg/dl | 487 | 0.000 |
| PTT (26-36) second | 34.0 | 0.000 |
| PT (11-16) second | 12.0 | 0.000 |

**Table (4-3):**revealed that the means of platelet count , platelet indices (PDW, MPV, PCT) fibrinogen level ,PTT and PT according to normal range were(497, 18.0, 16.0, 0.6, 487, 34.0, 12.0) respectively,when compared with normal range weresignificant variation with p.value (0.000).

**Table(4-4):**Mean of PLT count, Platelet indices (PDW,MPV, PCT) Fibrinogen level,PTT and PT in patient according to gender :

| Parameters/normal value | Males | Females | P.value |
|---|---|---|---|
| **PLT count(150-450)** | 527 | 407 | 0.001 |
| **PDW(10-17)** | 18 | 17 | 0.15 |
| **MPV (7-11.5)** | 15.8 | 15.6 | 0.27 |
| **PCT (0.2-0.36)** | 0.6 | 0.5 | 0.005 |
| **Fibrinogen level (150-400)** | 487 | 488 | 0.91 |
| **PTT (26-36)** | 34.4 | 34.0 | 0.51 |
| **PT (11-16)** | 12.0 | 11.0 | 0.51 |

**Table(4-4):**revealed that the mean of platelet count , platelet indices (PDW, MPV, PCT) fibrinogen level ,PTT and PT according to male were (527, 18, 15.8, 0.6, 487, 34.4, 12) respectively, and for female were (407, 17.0, 15.6, 0.5, 488, 34.0,11.0) respectively. When compared the mean of these parameters between gender only two parameters have significant variation which were platelet count and PCT p.value (0.001,0.005)respectively ,but the others parameters; platelet indices (PDW,MPV, PCT) Fibrinogen level,PTT and PT were insignificant variation P.value (0.15,0.27,0.91,0.51,0.51) respectively.

**Table(4-5):**Mean of platelet count , platelet indices(PDW,MPV,PCT) fibrinogen level , APTT and PT in patients according to age groups :

| Parameters/normal value | 40-49 | 50-59 | ≥ 60 |
|---|---|---|---|
| **PLT count(150-450)** | 542 | 509 | 474 |
| **PDW (10-17)** | 17.7 | 17.5 | 17.5 |
| **MPV(7-11.5)** | 15.7 | 15.8 | 15.7 |
| **PCT (0.2-0.36)** | 0.58 | 0.56 | 0.54 |
| **Fibrinogen level (150-400)** | 481 | 491 | 488 |
| **PTT (26-36)** | 34.6 | 34.4 | 34.2 |
| **PT (11-16)** | 11.6 | 11.5 | 11.8 |

**Table(4-5):** noticed that the means of platelet count , platelet indices (PDW, MPV, PCT) fibrinogen level, PTT and PT were not affected according to age groups .

**Table(4-6):**Means of platelet count,platelet indices (PDW,MPV, PCT), Fibrinogen level,PTT and PT in patients according to the duration of disease:

| **Parameters/normal value** | **1-5** | **6-10** | **> 10** |
|---|---|---|---|
| **PLT count (150-450)** | 508 | 473 | 534 |
| **PDW (10-17)** | 17.9 | 17.2 | 17.8 |
| **MPV(7-11.5)** | 15.4 | 15.8 | 15.7 |
| **PCT (0.2-0.36)** | 0.56 | 0.56 | 0.54 |
| **Fibrinogen level (150-400)** | 486.0 | 483.0 | 495.0 |
| **PTT(26-36)** | 34.6 | 34.0 | 34.5 |
| **PT (11-16)** | 11.6 | 11.8 | 11.5 |

**Table(4-6):**notice that the means of platelet count, platelet indices (PDW, MPV, PCT) fibrinogen level ,PTT and PT have no significant variation according to duration of cardiovascular diseases.

**Table(4-7):**Means of platelet count,platelet indices(PDW,MPV,PCT) Fibrinogen level,PTTand PT according to patients who under treatment and patients was not under treatment :

| Parameters/normal value | Yes | No | P.value |
|---|---|---|---|
| **PLT count (150 – 450)** | 417 | 487 | 0.002 |
| **PDW(10-17)** | 17.0 | 18.0 | 0.190 |
| **MPV (7-11.5)** | 16.0 | 15.7 | 0.394 |
| **PCT (0.2 – 0.36)** | 0.59 | 0.55 | 0.159 |
| **Fibrinogen level (150 – 400)** | 477.0 | 487.0 | 0.523 |
| **PTT (26 – 36)** | 35.0 | 34.0 | 0.543 |
| **PT (11- 16)** | 11.9 | 11.7 | 0.878 |

**Table(4-7):**noticedthat the mean of platelet count,platelet indices (PDW,MPV,PCT), Fibrinogen level,PTT and PT for patients under cardiovascular medication were (417, 17.0, 16.0, 0.59, 477.0, 35.0, 11.9) respectively and the mean for patients not under treatment were (487, 18.0, 15.7, 0.55, 487.0, 34.0, 11.7) respectively.When compared the mean of these parameters between patients under cardiovascular medication and patients doesn't take medication, found that only one parameter have significant variation was platelet count P.value (0.002), but the other parametershavenosignificantvariationP.value(0.190,0.394,0.159,0.523,0.543, 0.878) respectively.

# Chapter Five

**Discussion**

**Conclusion**

**Recommondation**

## 5-1Discussion

Cardiovascular disorders always considered as a rich area for scientific research as heart issues affect systemically all human bio vital organs, Platelet count and coagulation profile is very important for diagnosis and monitoring or follow up of cardiovascular disorder.

The present study focused to assess platelet count, platelet indices, fibrinogen levels, Prothrombine time and partial Prothrombine time among Sudanese patients with cardiovascular disorders.

In table (4-1) show distribuation of patients according to sex was found male 271 patients (75%) , while female 89 patients (25 %).

While in table (4-2) revealed distribuation of patients according to age Were divided 3groups (40-49) years 82 patients (22.8%) ,(50-59) years 83 patients (23.1%) and ( > 60 ) years 195 patients (54.1%).

The study show that the means of platelet count and platelet indices (PDW,MPV,PCT), fibrinogenlevel, APTT and PT were (497.47,17.564, 15.716,0.5586,486.93,34.32,11.711) actually in table (4-3), when compared with normal range (150-450x$10^9$/L), (10-17), (7-11.5), (0.2-0.36), (150-400) ,(26-36) and (11-16) respectively,were significant variation with p.value (0.000).

The study revealed that the mean of platelet count and PCT were higher in male than female with P.value (0.001,0.005) respectively, but for the other platelet indices (PDW, MPV), fibrinogen level, PT and APTT the mean was insignificant between the gender P.value (0.153, 0.272, 0.909, 0.514, 0.510) respectively actually in table (4-4), when compared with other study revealed agreement higher platelet counts are associated with less favorable cardiovascular risk profiles, although mean platelet volume associations were weaker, increased platelet count across FHS cohorts was consistently Some associations with platelet count appeared gender-dependent[52] ,but

disagreement in both gender , male was higher fibrinogen levels associated with smoking and cessation of smoking with lower levels, while evidence that plasma fibrinogen is associated with excess risk of coronary heart disease in femaleespecially at a younger age because plasma fibrinogen levels are related to several major lifestyle and physical characteristics[52] and agreement PT and aPTT were no correlation between gender[51] .

In the present study when compared according to means of age groups notice platelet count high in group (40-49) years more than other groups ,PDW ,MPV,PCT, APTT and PT no significant variation between groups ,while fibrinogen level high in group (50-49) years more than other groups.

Comparison with other study revealed demonstrate that age has a significant effect on platelet translocation behaviour on VWF, effects of age on platelet function are more profound in women than in men, related to the potential influence of sex hormones such as testosterone and estrogen ,while regarding PT and APTT according to age found the mean were (14.73 sec) and (31.65 sec) agreement to the present results [53].the present study according to duration of diseases revlead the platelet count high in group >10 years more than other groups , PDW ,MPV,PCT, APTT and PT no significant variation between groups, while fibrinogen level high in group >10 years more than other groups.

The mean of platelet count in this study was significantly higher in patients under treatment comparing to patients were not; with P.value (0.002) but for the other platelet indices (PDW, MPV, PCT), fibrinogen level, APTT and PT the means were insignificant comparing P.value (0.190, 0.394, 0.159, 0.523, 0.543, 0.87) respectively,when comparing with study done by **Chirinos JA, Castrellon A and etal Digoxin use is associated with increased platelet and endothelial cell activation in patients with nonvalvular atrial fibrillation**, patients who were taking digoxin did not demonstrate any

significant differences in clinical or echocardiographic characteristics compared with patients not taking digoxin[53]

## 5-2:Conclusion:-

1.Platelet count, platelet indices(PDW,MPV,PCT), fibrinogen level, APTT and PT were significant variation according to normal range (497.0,17.6,15.6,0.56,486.9,34.3,11.7) respectively with p.value (0.000).

2. According to gender (Male/Female) were the platelet count and PCT were (527,407), (0.56,0.52) respectively, were significant with p.value (0.001,0.005) respectively.

3. Platelet count according to treatment and not were (417,487) respectively with significant variation with p.value (0.002).

4. Platelet count,platelet indices(PDW,MPV,PCT),fibrinogen level, APTT and PT were significant variation according to age and duration of cardiovascular diseases were no significant variation .

**5-3:Recommendation:-**

1.More laboratory tests to know the relationship between blood platelets and heart diseases, especially specific diseases.

2.To minimize the effect of heart disease and it treatment on blood , the following precaution and recommended :

3. Patient with heart disease should be treated early and put on regular treatment until recovery.

4. Patient with heart disease should be given antiplatelet therapy to avoid abnormal platelet aggregation and maintain normal blood picture .

5. Follow up of patient is very important so as to detect any change in blood picture as early as possible .

6. Sample size should be increased to obtain more accurate result .

# Chapter Six

**References**

**Appendixes**

## 6-1References

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**Appendix:**

**Questionnaire about:- Evaluation of Haemostatic Changes in Patients with Haert Diseases in Shendi locality :-**

1. Patient No. : ☐
2. Sex : a) male ☐ b) female ☐
3. Age : 40-49 years ☐ 50-59 years ☐ >60 years ☐
4. Marital status : married ☐ single ☐
5. Specific diagnosis : …….
6. Duration of disease : ……
7. Patient on drugs : No. ☐ Yes ☐

   type of drug ? ……..……..

   ……

   ……

8. investigations :

a. CBC (specific coagulation platelets count) :

   ……..

b. PDW:

   ……

   ……

c. MPV :

   ……

   ……

d. PCT :

   ……

   ……..……..

e. Fibrinogen level :

   ……..

f. PTT :

……

……

g. PT :

……

……

Consent from…… I agree to the withdrawal of the samples after

……

……

Signature ……...……

**List of normal rang:**

| Test | Normal rang |
|---|---|
| Platelet count | 150-450/L |
| Meanplatelet volume(MPV) | 7-11.5 Mg/dl |
| Distributionwidith(PDW) | 10-17% |
| Platelet-Crit | 0.2-0.36% |
| Fibrinogen | 150-400 Mg/dl |
| Prothrombine time | 11-16 seconds |
| Partialprothrombine time | 26-36 seconds |