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Measurement of Prothrombin Time,Activated Partial Thromboplstin Time and Platelet Count among Gastrointestinal Bleeding Patients in Khartoum State

قياس زمني البروثرومبين والثرومبوبلاستين الجزئي النشط وعدد الصفائح الدموية لدى مرضى النزف المعوي في ولاية الخرطوم

A Dissertation Submitted for Partial Fulfillment of the Requirements for M.Sc. Degree in Medical Laboratory Science (Hematology and Immunohematology)

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الآيـــــــة

بسم الله الرحمن الرحيم

يَٰٓأَيُّهَا ٱلَّذِينَ ءَامَنُوٓاْ إِذَا قِيلَ لَكُمۡ تَفَسَّحُواْ فِي ٱلۡمَجَٰلِسِ فَٱفۡسَحُواْ يَفۡسَحِ
ٱللَّهُ لَكُمۡۖ وَإِذَا قِيلَ ٱنشُزُواْ فَٱنشُزُواْ يَرۡفَعِ ٱللَّهُ ٱلَّذِينَ ءَامَنُواْ
مِنكُمۡ وَٱلَّذِينَ أُوتُواْ ٱلۡعِلۡمَ دَرَجَٰتٖۚ وَٱللَّهُ بِمَا تَعۡمَلُونَ خَبِيرٞ ١١

صدق الله العظيم

سورة المجادلة الاية (11)

Dedication

To the Candle of My Life (My Mother)

To My Father

To My Sisters and My Brothers

To All of My Family

To My Colleagues and Friends

I Dedicate This Work

Acknowledgments

All my thanks are in the name of ALLAH, the most Gracious and the most Merciful. In this instance, I extend my thanks, deep sincere gratitude and honest appreciation to my supervisor **Dr. Kawthar Abdalgaleil Mohammed Salih** Department of Hematology and Immunohematology, Sudan University of Science and Technology, for her kindness, good guidance, valuable direction that has kept me on the track.I express my deep thanks to all of my colleagues and friends for their help, encouragement, support and for all the joyful moments we have had during this time. My thanks are also extended to **Mohammed Salih Idress Center** for GIT bleeding, Ibn Sina Hospital and all staff members of Hematology Department-SUST. I feel indebted to many people who participated and helped me in this work.

Abstract

Gastrointestinal bleeding or hemorrhage describes every form of hemorrhage (loss of blood) in the digestive tract from the mouth to the anus. Measurement of coagulation parameters is necessary to assess for continued bleeding.Abnormalities should be corrected rapidly. The study descriptive (Case Control) aimed to measurement coagulation profiles and Platelet count in gastrointestinal bleeding patients (GIB).The study conducted through the period from March 2020 to Nov 2020, in Mohammed Salih Idres Center for gastrointestinal bleeding in Ibn Sina Hospital in Khartoum State.

The study population compromise two groups of adults in different age for both sex (66 males and 34 females) in age range from (20-85 years old). Two hundred subject were recruited for this study, hundred patients with acute gastrointestinal bleeding and hundred healthy volunteers as control group. The data was collected using laboratory investigation to obtain coagulation profile and platelet count results. Data collected using structured questionnaire which include general information and an verbal consent was obtained. Five ml of venous bloods were collected from all participants 2.5ml was added to trisodium citrate anticoagulant and 2.5ml was added in EDTA anticoagulant containers. The data analyzed by SPSS version 20.

The data showed that about 66% of GIB patients were males and 34% were female. The Distribution of GIB patients according to age show that the mean age were 53±16.06 years The clinical manifestation of patients distributed as 49% with esophageal varices, 22% with Duodenal ulcer , 15% with gastritis and 14% with portal hypertension. The present study revealed significantly (*P.V* 0.000) lower PLT value in GIB patients compared with normal control. The PT,INR and APTT values were significally (*P.V* 0.000)and(*P.V* 0.000) higher in GIB patients compared to the normal control respectively, According to the causes of bleeding PT,INR and PLT count were significant increase in all causes has been studied *P.value* (0.007)(0.001)(0.00) respectively and there was no significant change on APTT *P. value* (0.563).

The study concluded that the gastrointestinal bleeding patients may be at risk of thrombocytopenia, hemophilia and hypercoagulable state. Also the study proved the GIB have the quite similar effect in patients regardless of gender, age and history of bleeding although the males were more frequently affected by disease.

المستخلص

قياس معلمات التخثر ضروري لتقييم النزيف المستمر. يجب تصحيح العيوب بسرعة هدفت هذة الدراسة الوصفية (المقطعية) إلى قياس ملامح التخثر وعدد الصفائح الدموية في مرضى النزيف المعدي المعوي (GIB) ، أجريت الدراسة خلال الفترة من مارس 2020 إلى نوفمبر 2020 ، في مركز محمد صالح إدريس للنزيف المعدي المعوي بمستشفى ابن سينا بولاية الخرطوم.يشكل مجتمع الدراسة مجموعتين من البالغين في أعمار مختلفة لكلا الجنسين (66 ذكر و 34 أنثى) في الفئة العمرية من (20-85 سنة). تم تجنيد مائتي شخص لهذه الدراسة ، مائة مريض يعانون من نزيف معدي معوي حاد ومئة من المتطوعين الأصحاء كمجموعة ضابطة. تم جمع البيانات باستخدام الاستقصاء المخبري للحصول على ملف التخثر ونتائج تعداد الصفائح الدموية ، كما تم جمع البيانات باستخدام استبيان منظم يتضمن معلومات عامة وموافقة شفهية ، وتم جمع خمسة مل من الدم الوريدي من جميع المشاركين ، وأضيف 2.5 مل إلى سترات ثلاثي الصوديوم. وتمت إضافة 2.5 مل في حاويات EDTA المضادة للتخثر. تم تحليل البيانات بواسطة الإصدار 20 من SPSS.

تشير البيانات إلى أن حوالي 66٪ من مرضى النزف المعوي كانوا من الذكور و 34٪ من الإناث ، ويظهر توزيع مرضى النزف المعوي حسب العمر أن متوسط العمر كان 53 ± 16.06 سنة ، وتوزعت المظاهر السريرية للمرضى بنسبة 49٪ مع دوالي المريء ، 22 ٪ مصابين بقرحة الاثني عشر ، 15٪ مصابون بالتهاب المعدة و 14٪ يعانون من ارتفاع ضغط الدم البابي. كشفت الدراسة الحالية عن انخفاض معنوي (P.V 0.000) في قيمة PLT في مرضى GIB مقارنة مع السيطرة العادية. كانت قيم PT و INR و APTT أعلى بشكل ملحوظ (PV 0.000) و (PV 0.000) في مرضى GIB مقارنة بالتحكم الطبيعي على التوالي ، وفقًا لأسباب النزيف ، تم دراسة PT و INR و PLT زيادة كبيرة في جميع الأسبابP.value (0.007) (0.001) (0.00) على التوالي ولم يكن هناك تغيير معنوي على قيمة APTT (0.563) .

خلصت الدراسة إلى أن مرضى النزيف المعدي المعوي قد يكونون معرضين لخطر الإصابة بنقص الصفيحات والهيموفيليا وحالة فرط التخثر. كما أثبتت الدراسة أن تأثير GIB مماثل تمامًا على المرضى بغض النظر عن الجنس والعمر وتاريخ النزيف على الرغم من أن الذكور كانوا أكثر عرضة للإصابة بالمرض.

List of contents

List of Tables

List of Figures

List of Abbreviations

ADP	Adinosin Di Phosphate
AEVB	Acute Esophageal Varices Bleeding
ALGIB	Acute Lower Gastro Intestinal Bleeding
APC	Activated Protein C
APTT	Activated Partial Thromboplastin Time
AT	Anti Thrombin
ATP	Adinosin Tri Phosphate
CBC	Complete Blood Count
DC	Direct Current
DIC	Disseminated Intravascular Coagulapathy
EDRF	Endothelium Dervied Relaxing Factor
EDTA	Ethylene Diamine Tetra Acetic acid
GAVE	Gastric Antral Vascular Ectasia
GE	Gastro Esophageal
GI	Gastro Intestinal
GIT	Gastro Intestinal Tract
GP1b	Glycoprotein 1b
HIV	Human Immunodeficiency Virus
HMWK	High Molecular Weight Kininogen
IBD	Inflammatory Bowel Disease
INR	International Normalization Ratio

LGIB	Lower Gastro Intestinal Bleeding
NO	Nitric Oxide
NSIDs	Non Steroid Anti Inflammatory Drugs
OR	Odd Ratio
PAI-1	Plasminogen Activator Inhibitor-1
PGI2	Prostaglandin
PLg	Plasminogen
PLT	Platelet
PMN	Poly Morpho Nuclear
Pn	Plasmin
Pn- A2-AP	Plasmin-Alpha2-Anti Plasmin
PPP	Platelet Poor Plasma
PT	Prothrombin Time
PUD	Peptic Ulcer Diseases
SPSS	Statistical Package for Social Science
SSRI	Selective Serotonine Reuptake Inhibitor
TAFI	Thrombin Activatable Fibrinolytic Inhibitor
TF	Tissue Factor
TFPI	Tissue Factor Pathway Inhibitor
tPA	tissue Plasminogen Activator
TXA2	Thromboxane A2
UC	Ulcerative Colitis
UGIB	Upper Gastro Intestinal Bleeding

UPA	Urokinase Plasminogen Activator
VWF	Von Willebrand Factor
A2-AP	Alpha2- Anti Plasmin
A2-MG	Alpha2- Macro Globulin

CHAPTER ONE

Introduction

CHAPTER I

1.1Introduction

Gastrointestinal bleeding or hemorrhage describes every form of hemorrhage (loss of blood) in the digestive tract from the mouth to the anus. It is a symptom of digestive problems rather than a disease itself. The degree of bleeding can range from nearly undetectable to acute, massive ,life threatening bleeding (Mansoor, 2012) Gastrointestinal bleeding has diverse causes but medical history , patients symptoms and as well as physical examination usually help to distinguish the main causes (Ghosh *et al*., 2002).

Acute lower gastrointestinal bleeding refers to blood loss from the gastrointestinal tract of recent onset, emanating from a location distal to the ligament of Treitz, resulting in instability of vital signs, anemia, and/or need for blood transfusion onset. Also is that occurring from the colon ,rectum ,or anus (Ghassemi and Jensen, 2013).Common causes for lower gastrointestinal hemorrhage include colonic diverticula, angiodysplasia, ischemic colitis, and inflammatory bowel disease. Hemorrhage may also come from intestinal tumors or malignancies. Unusual causes of bleeding include non-steroidal anti-inflammatory drugs (NSAIDS), related non-specific colitis, Meckel's diverticulum, and a norectal diseases (Beck *et al*., 2007)

Upper gastrointestinal bleeding (or haemorrhage) is that originating proximal to the ligament of Treitz; in practice from the oesophagus, stomach and duodenum *(Bhuket et al*., 2018).Most commonly due to peptic ulcer.In area with high prevalence of cirrhosis, bleeding from esophagesl and gastric varices is common,Mallory-weiss tears,gastric and duodenal neoplasm and vascular abnormality are less common (Xavier and Thomas, 2013).

Upper Gastrointestinal bleeding can present in several forms, depending on the rate of blood loss: microscopic blood loss presents as iron-deficiency anemia or hemoccult-positive stools; hematemesis is vomiting of fresh blood; "coffee ground" emesis is vomiting of altered black blood

(Manning-Dimmitt *et al*., 2005).If the bleeding from lower gastro intestinal tract found in the form of melena , a black ,sticky ,tarry and foul smelling stool and as hematochezia (fresh ,bright red blood passed from the rectum) (Carlson, 2007).That mal-absorption syndromes and other chronic gastrointestinal disorders may give rise to vitamin K deficiency. Vitamin K

deficiency may lead to impairment in production of many coagulation factors (V,VII, IX, X) and consequently impaired coagulation mechanism and hence GI bleeding (Ngo *et al*., 2011). The platelet count is important, because immune-mediated thrombocytopenia is a common cause of moderate to severe GI hemorrhage (Boysen, 2015).Clot based test (PT and APTT) use to evaluate bleeding tendency among this patient with GI bleed (Li *et al*., 2015).

1.2 Rationale

Gastrointestinal bleeding is one of the most serious health problem in Sudan and around the world and also lead to morbidity and mortality. Previous study showed that the mortality in those who had oesphgal varices was 3.8% and those who had peptic ulcer 0.4 (Salih *et al*., 2009).

GI bleeding, may be associated with almost any type of hemorrhagic diathesis particularly associated with anticoagulant therapy, hereditary hemorrhagic telangiectasia, thrombocytopenia, von will bran's disease, pseudoxanthoma elasticum and uremia (Ghassemi and Jensen, 2013).

For all these abnormal cases the possible causes may include impaired platelet function, malformation in blood vessels and decreased platelets count (Ghassemi and Jensen, 2013).

In Sudan El Magzoub and colleagues found that the mean PT and APTT were significantly higher among the test group patients with gastrointestinal bleeding than the control group patients .Also, the mean platelets count was significantly low among test group patients as compared with the control group (Magzoub *et al*., 2018).

1.3 Objectives

1.3.1 General Objective

-To measure coagulation profile and platelet count among Sudanese Gastrointestinal Bleeding patients in Khartoum State.

1.3.2 Specific Objectives

-To measure PT, INR, APPT levels and Platelet count among patients with gastrointestinal bleeding.

-To compare PT, INR, APTT levels and Platelet count between patients with gastrointestinal bleeding and healthy control group.

-To study the effect of possible risk factors such as gender, age, causes of bleeding and history of bleeding on study parameters.

CHAPTER TWO

Literature Review

CHAPTER II

2.1 literature review

2.1.1 Overview of Hemostasis

Hemostasis is a complex process that ensures the maintenance of blood flow under normal physiological conditions and prevents major blood loss following vascular injury. The process is tightly regulated to prevent pathological thrombosis. Normal hemostasis relies on the delicate balance of prothrombotic and anticoagulant processes, where five components play a significant role in maintaining the hemostasis, these include: endothelial cells; platelets which are key to platelet plug
formation; coagulation factors that are essential to formation of insolublefibrin clot; coagulation inhibitors; and fibrinolysis (Turgeon, 2012).
Functionally, several process are involved in hemostasis following injury to a small blood vessel:

Blood vessel spam, Formation of platelet plug, Contact among damaged blood vessel , blood platelet, and coagulation protein, Development of a blood clot around the injury, and Fibrinolytic removal of excess hemostatic material to restablish vascular integrity (Zaidi and Green, 2019).

2.1.1.1Function of Hemostasis

a) Maintain blood in a fluid state while it remains circulating within the vascular system.
b) Arrest the bleeding at the site of injury or blood loss by formation of hemostatic plug.
c) Limit this process to the vicinity of damage.
d) Ensure the eventual removal of the plug when healing is complete.

Normal physiology thus constitutes a delicate balance between these conflicting tendencies and deficiency or exaggeration of any one may lead to either thrombosis or hemorrhage (Mann and Zaiden’s, 2005).

2.1.2 Component of hemostasis

2.1.2.1The blood vessel

2.1.2.1.1 General structure of blood vessel

Blood vessel wall has three layer, the intima consist of endothelium and sub endothelium connective tissue and it separated from media by the elastic lamina interna.Endothelial cells form a continuous monolayer lining all blood vessels. The structure and function of endothelial cells vary according to their location in the vascular tree, but in their resting state they share three important characteristics : they are non- thrombogenic ,they play an active role in supplying nutrients to the sub endothelial structures, and act as barrier to cells ,macromolecules and particulate matter circulating in the blood stream. Permeability of endothelium may vary under different conditions to allow various molecule and cells to pass (Hajjar *et al*., 2001).

2.1.2.1.2 Functions of Blood Vessels in Hemostasis

After an injury, the damaged vessels initiate hemostasis. Their first response to injury is constriction or narrowing of the lumen of the arterioles to minimize the flow of blood into the wound area and the escape of blood from the wound site. Vasoconstriction also brings the hemostatic components of the blood (the platelets and the plasma proteins) closer to the vessel wall, facilitating their interactions. Vasoconstriction occurs immediately and lasts a short time. The mechanism of vasoconstriction is complex. It is caused in part by neurogenic factors and in part by several regulatory substances that interact with receptors on the surface of cells of the blood vessel wall. These include serotonin and thromboxane A2 (TXA2), both products of activated platelets, and endothelin-1 produced by endothelial cells. In contrast, healthy intact endothelial cells synthesize and secrete prostaglandin PGI2, also called *prostacyclin*, and nitric oxide (NO), also called endothelium derived relaxing factor (EDRF). Both counteract vasoconstriction by causing vasodilation of the arterioles. Both also inhibit activation and recruitment of platelets (Hajjar *et al*., 2001).

2.1.2.2 Platelet

2.1.2.2.1 Platelet production and structure

Platelets are made in the bone marrow. Huge cell known as megakaryocytes (derived from hematopoietic stem cells) are the precursor to platelets: one megakaryocyte can produce 2,000 platelets. The platelets circulates in the blood for 7-10 days. Platelets either circulate

freely or are sequestered in the spleen.at any given time one-third of the platelet of the platelets are located in the spleen (DeLoughery, 2004).

Platelets are a nucleate .A network of interconnected channels, the open canalicular system extends from the inside of the platelet to the outside environment and may function to allow the rapid release of the constituents of platelet granules. Mitochondria produce ATP and may also participate in the regulation of the platelet activation response (Shaz and Hillyer, 2013).

Platelets contain three types of granules, which release their contents upon activation. Platelets contain lysosomes, although the significance of this organelle is not clear. The most numerous type of granule is the alpha granule, which contains proteins that provide the surface of platelet adhesion. For example, vWF, fibrinogen and vitronectin are matrix proteins contained within the alpha granule that may contribute to thrombus formation and stabilization (Ashraf and Saba, 2014).

2.1.2.2.2 Primary hemostasis

Primary hemostasis results from complex interactions between platelets, Vessel wall and adhesive proteins leading to the formation of initial 'platelet plug'. The formation of the platelet plug involves a series of steps (Palta *et al*., 2014).

2.1.2.2.2.1 Platelet adhesion

After vascular injury vWF acts as a bridge between endothelial collagen and Platelet surface receptors GpIb and promotes platelet adhesion. The platelet glycoprotein complex I (GP-Ib) is the principal receptor for vWF (Heemskerk *et al*., 2002).

2.1.2.2.2.2 Platelet secretion

After adhesion, degranulation from both types of granules takes place with the release of various factors. Release of calcium occurs here. Calcium binds to the phospholipids that appear secondary to the platelet activation and provides a surface for assembly of various coagulation factors (Palta *et al*., 2014).

2.1.2.2.2.3 Platelet aggregation

Thromboxane A2 produced by activated platelets provide stimulus for further platelet aggregation. TxA2 along with ADP enlarge this platelet aggregate leading to the formation of the platelet plug, which seals off vascular injury temporarily. ADP binding also causes a conformational change in GpIIb/IIIa receptors presents on the platelet surface causing deposition of fibrinogen. Thrombin generation also catalyses the conversion of this

fibrinogen to fibrin which adds to the stability of the platelet plug and is now known as secondary hemostasis (Andrews and Berndt, 2004).

Prostacyclin inhibits platelet aggregation (platelet anti-aggregating effect) and the balance between TxA2 and prostacyclin leads to localized platelet aggregation thus preventing extension of the clot thereby maintaining the vessel lumen patency (Palta *et al.*, 2014*)*.

2.1.2.2.3 Secondary hemostasis

Secondary hemostasis consists of the cascade of coagulation serine proteases That culminates in cleavage of soluble fibrinogen by thrombin, Thrombin cleavage generates insoluble fibrin that forms a cross-linked fibrin mesh at the site of an injury. Fibrin generation occurs simultaneously to platelet aggregation It has been traditionally classified into intrinsic and extrinsic pathways, both of which converge on factor X activation (Furie, 2009).

2.1.2.3 The Coagulation System

A number of coagulation proteins (factors) participate in coagulation reactions, which ultimately lead to the formation of a fibrin clot. According to the International System of Nomenclature, coagulation factors are designated by Roman numerals (I to XIII).Coagulation proteins can be divided into following categories: (1)Fibrinogen (F I); (2) Serine proteases: (a) Vitamin K-dependent Factors—II, VII, IX, X, (b) Contact factors—XI, XII, high molecular weight kininogen, prekallikrein; (3) Cofactors— V, VIII, tissue factor (F III); and (4) Transglutaminase: F XIII(Kawthalkar, 2013)

2.1.2.3.1 The Coagulation Factor

Group of plasma protein substance (factor1-X111) contained in plasma, which act in consequent to bring about blood coagulation (Gomez and McVey, 2015).

Table(2.1) factors and related substances (Gomez and McVey, 2015).

Number and/ or name	Function
I fibrinogen	Form clot (fibrin)
II prothrombin	Activates, I, V, VIII, XIII, Protein C and platelet.
III tissue thromboplastin	Unassigned
IV calcium	Cofactor.
V proaccelerin	Co factor of X.
VI	Unassigned –old name of factor Va.
VII stable factor	Actives IX ,X.
VIII (anti-hemophilic factor)	Cofactor of IX.
IX (Christmas factor)	Activates X.
X(Stuart-power factor)	ActivatesII .
XI(Plasma thromboplastin antecedent)	Activates XII, IX, and prekallikrein .
XII(Hageman factor)	Activates prekallikrein and fibrinolysis.
XIII(fibrin –stabilizing factor)	Cross links fibrin.
VWF	Binds VIII, mediates platelet adhesion.
Prekallikrein	Activates XII and prekallikrein; cleaves HMWK.
HMWK	Support reciprocal activation of XII, XI, and prekallikrein.

2.1.2.3.2 Classification of Coagulation Factor

2.1.2.3.2.1 Fibrinogen Group

Consists of factors I, V, VIII, and XIII. These factors are consumed during the process of coagulation. Factors V and VIII are known to decrease during blood storage in vitro. These factors are known to increase during pregnancy, in the presence of conditions of inflammation, and subsequent to the use of oral contraceptive drugs (Turgeon, 2012).

2.1.2.3.2.2 The Vitamin K Dependent Factors

Consists of factors II, VII, IX, and X. All these factors are dependent on vitamin K during their synthesis. Vitamin K is available to the body through dietary sources and

intestinal bacterial production.This group is inhibited by warfarin.This group is considered to be stable and remains well preserved in stored plasma(Turgeon, 2012).

2.1.2.3.2.3 The Contact Group

Consists of factors XI, XII, prekallikrein (Fletcher factor), and HMWK (Fitzgerald factor). These factors are involved in the intrinsic coagulation pathway. They are moderately stable and are not consumed during coagulation (Turgeon, 2012).

2.1.2.3.3 Common Characteristics of Coagulation Factor

Proteins that are clotting factors have four characteristics in common. These characteristics are as follows:

A deficiency of the factor generally produces a bleeding tendency disorder with the exception of factor XII, prekallikrein (Fletcher factor), and high– molecular weight kininogen (HMWK; Fitzgerald factor),The physical and chemical characteristics of the factor are known ,The synthesis of the factor is independent of other proteins, and The factor can be assayed in the laboratory (Furie, 2009).

2.1.2.3.4 Coagulation Cascade

The coagulation cascade involves the marked amplification of procoagulant proteins from relatively few initiation substances by the sequential activation of enzyme precursors (zymogens) to active enzymes. These are usually serine protease enzymes (Hall, 2015).

The result is the rapid and marked generation of thrombin, which converts soluble fibrinogen into the insoluble fibrin. Fibrin enmeshes platelet aggregates and converts the unstable platelet plug into a stable fibrin clot. Traditionally, the coagulation pathway was classified into extrinsic, intrinsic and common pathways. This classical model still remains useful in interpreting in vitro coagulation screening tests (i.e. prothrombin time [PT], activated partial thromboplastin time[APTT]) (Zaidi and Green, 2019).

2.1.2.3.4.1Extrinsic Clotting Cascade

It is considered as the first step in plasma mediated hemostasis. It is activated by TF, which is expressed in the subendothelial tissue. Under normal physiological conditions, normal vascular endothelium minimizes contact between TF and plasma procoagulants, but vascular insult

expose TF which binds with factor VIIa and calcium to promote the conversion of factor X to Xa (Owens and Mackman, 2010).

2.1.2.3.4.1.2 Intrinsic Clotting Cascade

It is a parallel pathway for thrombin activation by factor XII. It begins with factor XII, HMW kininogen, prekallekerin and factor XI (contact family) which results in activation of factor XI. Activated factor XI further activates factor IX, which then acts with its cofactor (factor VIII) to form tenasecomplex on a phospholipid surface to activate factor X (Hall, 2015).

2.1.2.3.4.1.3 Common Pathway

Activated factor X along with its cofactor (factor V), tissue phospholipids, platelet phospholipids and calcium forms the prothrombinase complex which converts prothrombin to thrombin. This thrombin further cleaves circulating fibrinogen to insoluble fibrin and activates factor XIII, which covalently crosslinks fibrin polymers incorporated in the platelet plug. This creates a fibrin network which stabilizes the clot and forms a definitive secondary hemostatic plug (Kumar *et al*., 2014).

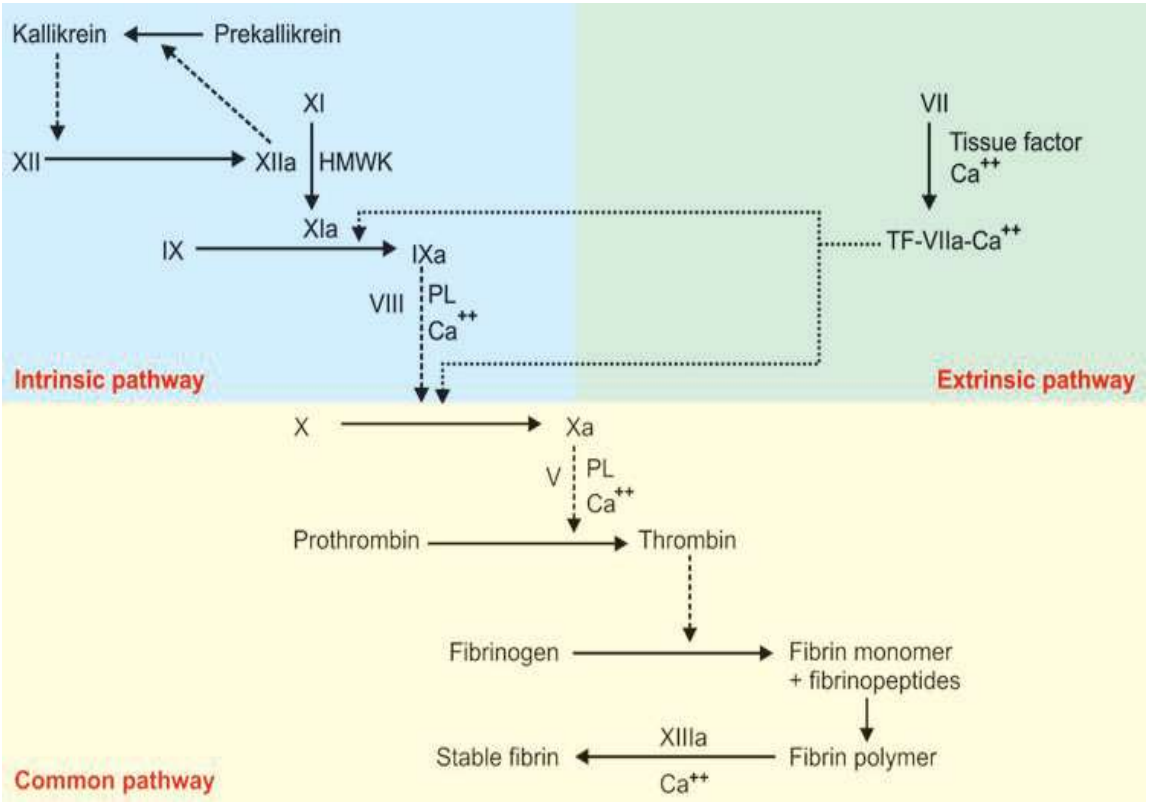


Figure (2.1) Scheme of blood coagulation. Solid arrows indicate transformation. Broken lines indicate action (Kawthalkar, 2013).

2.1.2.4 Inhibitors of Coaggulation

It is fundamental that clot formation is regulated and localized to the site of injury, so that arterial or venous thrombosis are prevented. Hence, a crucial element to a balanced hemostasis is played by the naturally occurring inhibitors to coagulation, which include tissue factor pathway inhibitor (TFPI), heparin cofactor II, antithrombin (AT), and protein C and protein Activation TFPI is the principle regulator of the thrombin generation initiation phase (i.e. inhibits FXa, FVIIa and TF), whereas AT attenuates thrombin activity and its generation (inhibits FIIa, FXa, FIXa, and FXIa) (Gomez and McVey, 2015) .TFPI is synthesized in endothelial cells and is mostly stored in platelets A small amount is in free circulation in the plasma. Plasma concentrations of TFPI are greatly increased with heparin. Heparins bind to antithrombin and potentiates its action by 1000- to 4000-fold. Protein C and protein S are both serine protease enzymes, whose activation is essential for inhibition of FVa and FVIIIa. The protein C/S pathway is activated by thrombin which binds to thrombomodulin (an endothelial cell surface receptor), and activate protein C e this in turn will inactivate FVa and FVIIIa. Protein S is a cofactor to activated protein C (APC), potentiating its action. Almost all currently available anticoagulant drugs will inhibit either FXa or FIIa (Zaidi and Green, 2019).

2.1.2.5 Fibrinolysis

The role of the fibrinolytic system is to dissolve blood clots during the process of wound healing and to prevent blood clots in healthy blood vessels. The fibrinolytic system is composed primarily of three serine proteases that are present as zymogens (i.e., proenzymes) in the blood. Plasmin cleaves and breaks down fibrin. Plasmin is generated from the zymogen plasminogen by the proteases tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA).tPA and plasminogen come together on the surface of a fibrin clot, to which they both bind (Lijnen and Collen, 2009).

tPA then activates plasminogen, which subsequently cleaves fibrin. PA activates plasminogen in the presence of the uPA receptor, which is found on various cell types All three of these serine proteases are downregulated by serpins that are present in blood. Alpha-2-antiplasmin inhibits plasmin, and plasminogen activator inhibitors 1 and 2 inhibit tPA and uPA (Rau *et al*., 2007) .

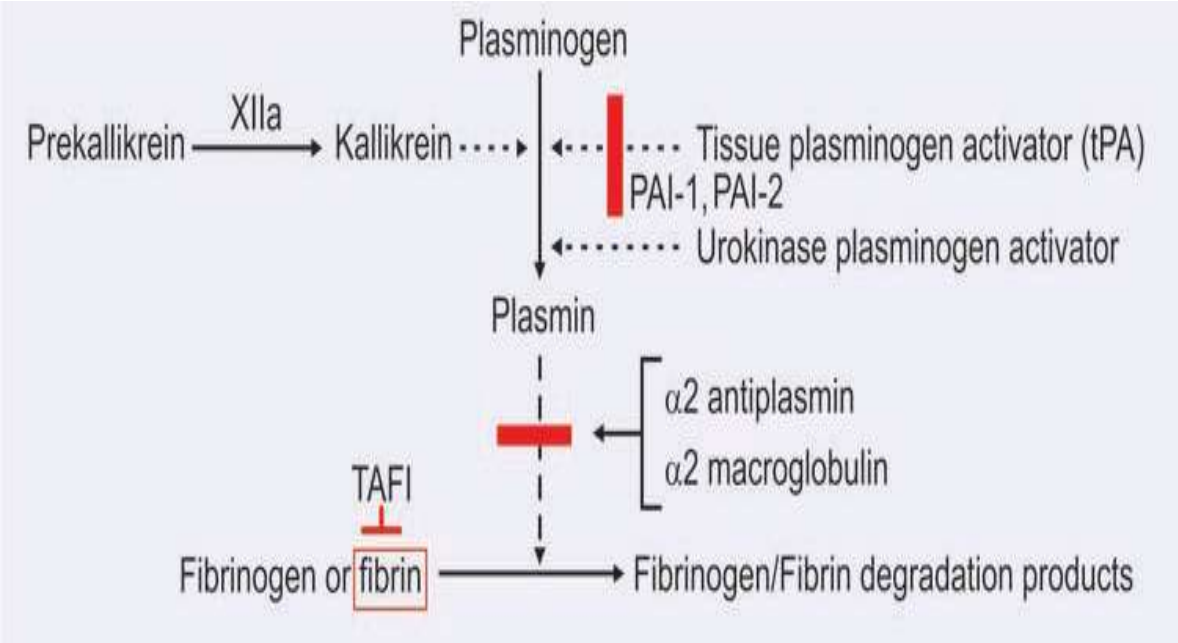
2.1.2.5.1Inhibitor of Fibrinolysis

Endothelial cells synthesize fibrinolytic inhibitors. PAI-1 is the major inhibitor of tPA in plasma. PAI-1 belongs to the family of serpins. In addition to endothelial cells, liver, megakaryocytes, and monocytes can synthesize PAI-1. In plasma, there is a molar excess of

PAI-1 compared to tPA, and the expression of PAI-1 is also highly regulated. The expression of PAI-1 is stimulated by inflammation, hormones, and cytokines. PAI-1 is also present in the subendothelial matrix, where it may function to inhibit degradation of the matrix. Both plasma and subendothelial PAI-1 form a complex with vitronectin, a major cell adhesion protein (Monroe and Hoffman, 2014).

Thrombin activatable fibrinolytic inhibitor (TAFI) is an enzyme (carboxypeptidase) described as an inhibitor to fibrinolysis; it can be regarded as a link between coagulation and fibrinolysis. It is decreased in hemophilia, in liver cirrhosis, and in DIC, and increased in APC resistance (Egberg and Blombäck, 2014).

α2-Antiplasmin (α2-AP), or α2-plasmin inhibitor, a 63-kDa serpin, is the primary physiologic inhibitor of Pn, circulating at a concentration of about1 μM (70 μg/mL).It forms a very stable inactive Pn–α2-AP complex, it can be covalently cross-linked to fibrin, making it more resistant to lysis,and it can competitively inhibit Plg interactions with fibrin due to the presence of exposed lysine residues (Weisel and Litvinov, 2014).**α**2-Macroglobulin (α2-MG) with a molecular weight of 725 kDa is found in circulation at a concentration of about 3 μM (2.5 mg/mL) and can bind to different proteases and their complexes with inhibitors. Under certain conditions Pnand Plg activators may react with α2-MG followed by relatively slow inhibition of their activity. Cell- and fibrin-bound Pn is protected from α2-MG(Weisel and Litvinov, 2014).



Figure(2.2) The fibrinolytic system(Kawthalkar, 2013).

2.1.2.6 Coagulation in GIT Bleeding

Coagulation disorders associated with GI hemorrhage include rodenticide toxicity, disseminated intravascular coagulation, coagulation factor deficiencies(factor XII and prekallikrein deficiency),and thrombocytopenia Thrombocytopenia is the most common coagulation disorder resulting in GI hemorrhage and should not be overlooked. Vascular anomalies, because of the high incidence of varices, are a common cause of GI hemorrhage in humans. In contrast, only a few cases of vascular anomaly have been reported in the veterinary literature. It should be considered when more common causes of GI hemorrhage have been ruled out The coagulation profile may identify coagulopathies such as rodenticide intoxication or clotting factor deficiencies. It also may detect prolonged bleeding times that are not the direct cause of GI hemorrhage (Boysen, 2015)

2.2 GIT Anatomy

The gastrointestinal tract is essentially a tube that extends from the mouth to the anus.It has generally the same structure throughout. There is a hollow portion of the tube known as the lumen, a muscular layer in the middle, and a layer of epithelial cells. These layers are responsible for maintaining the mucosal integrity of the tract (Holster *et al*., 2011).

2.2.1The Upper GIT

The teeth, tongue, salivary glands, and mouth are the uppermost organs of the alimentary canal where food is masticated, mixed with saliva, and swallowed (Scanlon and Sanders, 2007).

Also Include The oropharynx and esophagus convey dietary contents and oral secretions from the back of the oral cavity to the stomach. The stomach serves a number of important physiologic functions: accepting and storing food, mixing food with secretions, digesting food, and delivering food to the small intestine in timed increments The fundus, body, and antrum comprise the three anatomic areas of the stomach. In terms of motility, the upper half accepts food from the esophagus, and the lower half mixes and delivers food to the small intestine (Preston and Wilson, 2018).

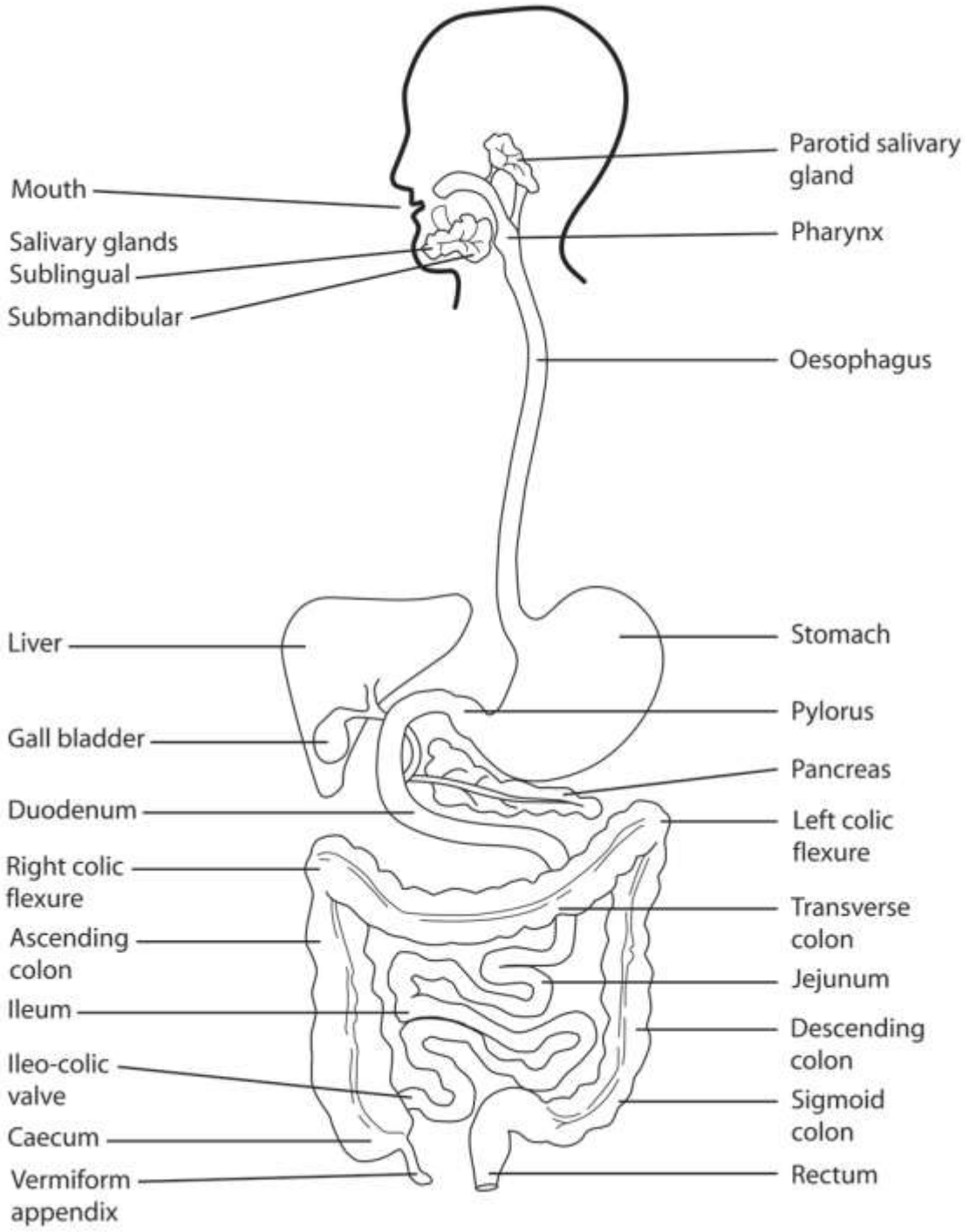
2.2.2 The Lower GIT

The small intestine is the longest section of the GI tract, at about 6 m. It is divided into three functional segments: duodenum (first 0.3 m), jejunum (next 2.3 m), and ileum (final 3.4 m). The majority of macronutrient, vitamin, and mineral absorption occurs in the small intestine. Absorption of the nutrients liberated by the digestive process is facilitated by the increase in epithelial surface area by villi (10-fold) and microvilli (20-fold) (Scanlon and

Sanders, 2007). Large intestine The large intestine comprises the cecum; ascending, transverse, descending, and sigmoid colon; rectum; and anus The large intestine plays a lesser role in digestion compared to the small intestine but is intricately involved in ion and water absorption (Preston and Wilson, 2018).

2.2.3 Accessory Organs

The pancreas, gallbladder, and liver serve as accessory organs for the intestines, providing specialized secretions to digest carbohydrates, proteins, and lipids in the small intestine. Pancreatic secretions are highly regulated by neural and hormonal means both in anticipation of eating and in response to food in the gastrointestinal (GI) tract. Hepatobiliary secretions are steadily produced but then stored in the gallbladder for regulated secretion into the small intestine. Once digested and absorbed, most nutrients travel via the portal circulation to the liver to either be extracted and processed or to pass through to the systemic circulation (Preston and Wilson, 2018).



Figuer (2.3) Component organs and accessory organs of the gastrointestinal tract. Reproduced with permission from (Smith and Watson, 2008).

2.3 Normal GIT Physiology

The unique physiological processes that take place in the digestive system are digestion, absorption, secretion, motility and excretion. Digestion is the process whereby large food molecules are broken down to smaller ones. Food is ingested as large pieces of matter containing substances such as protein and starch which are unable to cross the cell membranes of the gut epithelium. Before these complex molecules can be utilized they are degraded to smaller molecules, such as glucose and amino acids, which can be absorbed from the gastrointestinal system into the bloodstream. The mixture of ingested material and secretions in the gastrointestinal tract contains water, minerals and vitamins as well as fats, carbohydrates and proteins (Holster *et al*., 2011)

The products of digestion, other small dissolved molecules, ions and water are transported across the epithelial cell membranes, mainly in the small intestine. This is the process of absorption. The transported molecules enter the blood or lymph for circulation to the tissues. This process is central to the digestive system, and the other physiological processes of the gastrointestinal tract, such as elimination, subserve it. Food which is ingested travels along the gastrointestinal tract to the appropriate sites for mixing, digestion and absorption to occur (Beck *et al*., 2007).

Most of the gastrointestinal tract is lined by two layers of smooth muscle; contraction of this muscle mixes the contents of the lumen and moves them through the tract. Motility in the digestive system is under neural and hormonal control. Exocrine glands secrete enzymes, ions, water, mucins and other substances into the digestive tract. The glands are situated within the gastrointestinal tract, in the walls of the stomach, small intestine and large intestine, or outside it in the case of salivary glands, pancreas and liver. Secretion in all regions of the gastrointestinal tract is controlled by nerves and hormones (Scanlon and Sanders, 2007).

2.4 GIT Functions

The digestive and absorptive functions of the gastrointestinal tract (OIT) include chewing of food and mixing it with saliva (mastication and salivation), swallowing, and its movement through esophagus and stomach, where digestion begins, to the small intestine (the site of further digestion And absorption). From the small intestine the food mass moves into the large intestine and into the rectum where undigested matter and feces are expelled (Duthie and Gardner, 2006).

There are three main functions of the gastrointestinal tract:

• Transportation

• Digestion

• Absorption of food

The mucosal integrity of the gastrointestinal tract and the functioning of its accessory organs are vital in maintaining the health of your patient Digestion is the chemical breakdown of ingested foods into absorbable molecules. The digestive enzymes are secreted in salivary, gastric, and pancreatic juices as well as the mucosa of the small intestine. Absorption is the movement of nutrients, water and electrolytes from the lumen of the intestine into the blood system(Scanlon and Sanders, 2007).

2.5 GIT Bleeding

Gastrointestinal bleeding (also called a " GI bleed") happens when the gastrointestinal tract is injured or irritated. Bleeding may come from a tear or ulcer along the gastrointestinal tract, abnormal blood vessels, or a cancer of the intestines or stomach. The gastrointestinal tract has 2 parts: upper and lower. The upper gastrointestinal tract includes the esophagus (the tube from the mouth to the stomach), stomach and first part of the small intestine. The lower gastrointestinal tract includes much of the small intestine, large intestine (bowels), rectum and anus .Gastrointestinal bleeding can present in several forms, depending on the rate of blood loss: microscopic blood loss presents as iron-deficiency anemia or hemoccult-positive stools; hematemesis is vomiting of fresh blood; "coffee-ground" emesis is vomiting of altered black blood; melena is black tarry stools; hemochezia is the passing of red blood via the rectum (usually from the lower gastrointestinal tract, but sometimes from a briskly bleeding upper gastrointestinal source) (Manning-Dimmitt *et al*., 2005).

2.5.1 Types of GIT Bleeding

Gastrointestinal bleeding can be divided into arising from the upper or lower gastrointestinal tract. Upper gastrointestinal bleeding (UGIB) is more common with reported incidence ranging from 48–168 cases per 100 000 adults per year Lower gastrointestinal bleeding has an annual UK incidence of 20–30 cases per 100 000 (Jairath and Stanworth, 2012).

2.5.2 Acute Upper GIT Bleeding

Upper GI bleeding (UGIB) is defined as bleeding emanating proximal

to the ligament of Treitz: from the esophagus, stomach, and duodenum (Lee and Laberge, 2004)

2.5.2.1 Common Causes of Upper GIT Bleeding

The causes of UGIB are many and are different according to the geographical area. The commonest cause of UGIB in the United States is peptic ulcer disease which accounts for more than 50 percent of the causes, this is followed by gastric erosion, and variceal bleeding .In the United Kingdom the commonest cause of again is peptic ulcer causing 30 to 50 percent of all causes of UGIB, but interestingly no cause was identified no in 24%of the cases. Here in Sudan, which is a tropical country, however,bleeding due to esophageal varices is the commonest cause (Van Leerdam, 2008).

2.5.2.1.1 Varcial cause

2.5.2.1.1.1 Peptic ulcer diseases (PUD)

A peptic ulcer is an erosion in a segment of the GI mucosa, typically in the stomach (gastric ulcer) or the first few centimeters of the duodenum (duodenal ulcer), that penetrates through the muscular is mucosae Etiologies underlying peptic ulcer disease include Helicobacter pylori (H. pylori) infection, use of aspirin and no steroidal anti-inflammatory drugs(NSAIDs), rare disorders such as gastrinoma (Zollinger-Ellison syndrome), and opportunistic infections, particularly in immunosuppressed patients (Bolduc and Peura, 2003).

H. pylori infection is present in 50 to 70% of patients with duodenal ulcers and in 30 to 50% of patients with gastric ulcers. If H. pylori is eradicated, only 10% of patients have recurrence of peptic ulcer disease, compared with 70% recurrence in patients treated with acid suppression alone.NSAIDs now account for > 50% of peptic ulcers. Cigarette smoking is a risk factor for the development of ulcers and their complications. Also, smoking impairs ulcer healing and increases the incidence of recurrence(Jairath and Stanworth, 2012)

A family history exists in 50 to 60% of children with duodenal ulcer Symptoms depend on ulcer location and patient age; many patients, particularly elderly patients, have few or no symptoms. Pain is most common, often localized to the epigastrium and relieved by food or antacids. The pain is described as burning or gnawing, or sometimes as a sensation of hunger. The course is usually chronic and recurrent. Only about half of patients present with the characteristic pattern of symptoms (Bolduc and Peura, 2003).

Gastric ulcer symptoms often do not follow a consistent pattern (e.g., eating sometimes exacerbates rather than relieves pain). This is especially true for pyloric channel ulcers, which are often associated with symptoms of obstruction (e.g. , bloating, nausea, vomiting) caused by edema and scarring (Greenson, 2015).

Duodenal ulcers tend to cause more consistent pain. Pain is absent when the patient awakens but appears in midmorning and is relieved by food but recurs 2 to 3 h after a meal. Pain that awakens a patient at night is common and is highly suggestive of duodenal ulcer. In neonates, perforation and hemorrhage may be the first manifestation of duodenal ulcer. Hemorrhage may also be the first recognized sign in later infancy and early childhood, although repeated vomiting or evidence of abdominal pain may be a (Greenson, 2015).

2.5.2.1.2 Esophageal varices

Esophageal varices are the second most common cause of UGIB, accounting for 5% to 14% of cases. These patients have portal hypertension and many also present with underlying alcoholic liver disease or hepatitis-induced cirrhosis. Although more than 50% of variceal bleeding stops spontaneously, up to 80% of patients will either continue to bleed or re-bleed within the first 6-months. As with peptic ulcers, vasopressin and octreotide are used as pharmacological treatment options. When pharmacologic therapy fails, endoscopic band ligation or sclerotherapy is the treatment of choice (Lee and Laberge, 2004).

2.5.1.2 Non-variceal causes of UGIB

2.5.1.2.1Erosive

An erosion is a breach of the epithelial surface that does not extend beyond the muscular is mucosa and has a diameter _5mm. Erosions can occur throughout the gastrointestinal tract. Causes of upper gastrointestinal erosions can be divided into direct toxic: Mucosal erosions caused by direct toxic effects of drugs are more frequently seen since aging populations are naturally burdened with chronic diseases and polypharmacy(Van Leerdam, 2008).

Non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin are considered the main cause of erosive disease in Western patients.NSAIDs can produce a spectrum of mucosal damage. Intramucosal petechial hemorrhage can occur within two hours of initial ingestion. Superficial and hemorrhagic erosions, gastroduodenitis and ulceration may develop with continued exposure (Holster *et al*., 2011).

Other notorious mucosal damage causing drugs are selective serotonin reuptake inhibitors (SSRIs), and corticosteroids. Both classes of drugs are associated with peptic ulcer bleeds as well as non-ulcer, non-variceal bleeds. Mechanic: A common cause of mechanical erosive disease is hiatal hernia. Larger hiatal hernia can give rise to development of linear erosions and ulcers or so-called Cameron lesions within the stomach at the impression of the diaphragm (Bolduc and Peura, 2003)

They predominantly occur along the smaller curvature, and their exact etiology is unknown. They most likely occur as a result of the combination of chronic mechanical

trauma (e.g. rubbing of the mucosal folds at the level of the diaphragm during respiratory excursions) and acid injury. Local ischemia has been suggested to contribute to this process, H. pylori does not appear to play a role (Bolduc and Peura, 2003).

Cameron lesions are found in about 5% of the patients with hiatal hernia undergoing upper endoscopy, two thirds of these patients have multiple lesions .Their prevalence rises with the size of the hernia. They have been reported to occur in 10–20% of patients with a hernia _5 cm usually they are seen accidentally, although they may cause acute or chronic gastrointestinal bleeding and iron deficiency anemia. Cameron lesions were found in 24% of those anemic patients. Since then, Cameron lesions have been associated with chronic bleeding leading to anemia, but also with acute bleeding. Cameron lesions are a well-known cause of missed diagnoses in patients with upper GI bleeding undergoing endoscopy (Palmer, 2002).

Patients with larger hiatal hernia and signs of anemia or bleeding should therefore be adequately inspected including endoscopy in retroversion to optimize the inspection of the hernia and inflammatory etiology Erosive esophago-gastro-duodenitis, an acute or chronic inflammation of the lining of the esophagus, stomach and/or duodenum, has many possible causes. Acute causes are associated with excessive alcohol consumption and the use of drugs(Greenson, 2015).

Chronic causes include gastro-esophageal reflux disease and H. pylori infection .Infection with H. pylori causes chronic inflammation of the gastric mucosa, which may slowly progress via atrophic gastritis, intestinal metaplasia, and dysplasia to gastric adenocarcinoma (Greenson, 2015)

2.5.1.2.2 Gastritis

Gastritis is inflammation of the gastric mucosa caused by any of several conditions, including infection (Helicobacter pylori), drugs (NSAIDs, alcohol), stress, and autoimmune phenomena (atrophic gastritis). Many cases are asymptomatic, but dyspepsia and GI bleeding sometimes occur. Treatment is directed at the cause but often includes acid suppression and, for Helicobacter pylori infection, antibiotics(Xavier and Thomas, 2013).

Acute gastritis is characterized by PMN infiltration of the mucosa of the antrum and body chronic gastritis implies some degree of atrophy (with loss of function of the mucosa) or metaplasia. It predominantly involves the antrum (with subsequent loss of G cells and decreased gastrin secretion) or the corpus (with loss of oxyntic glands, leading to reduced acid, pepsin, and intrinsic factor) (Xavier and Thomas, 2013).

2.5.1.2.3 Esophagitis

The main presenting features are odynophagia, dysphagia and retrosternal chest pain. While noninfectious conditions such as gastro esophageal reflux disease and pill esophagitis are the most common causes in immunocompetent hosts, infections of the esophagus are common in the immunocompromised. In patients with HIV infection, the most common cause is esophageal candidiasis (Palmer, 2002).

While the presence of oropharyngeal candidiasis can be a clue to esophageal infection, its absence does not rule it out. Diagnosis can be made by endoscopy, which reveals white plaques on the esophageal mucosa; biopsy reveals the presence of budding yeasts. An alternative strategy is to undertake a therapeutic trial of a systemic antifungal agent; if the symptoms do not resolve within days, then further investigation is warranted(Hamid,2018).

Cytomegalovirus esophagitis causes similar symptoms, but endoscopy reveals ulcerative lesions. Ulcers are also seen in herpes simplex virus esophagitis, but they tend to have heaped-up borders as opposed to the more shallow lesions of cytomegalovirus; there may or may not be associated oropharyngeal lesions. It is important to note that a number of patients with HIV infection presenting with esophagitis may have simultaneous infection with more than one agent, whereas others will have no infection identified. The latter condition, named idiopathic esophageal ulcer, may respond to steroids(Vicari and Frakes, 2003).

2.5.1.2.4 Mallory – Weiss Tears

Mallory-Weiss tears occur in the distal esophagus near the gastroesophageal (GE) junction as a consequence of retching or vomiting. The tears involve either underlying esophageal venous or arterial plexus. Patients usually present with a history of extensive alcohol intake or portal hypertension

Most tears in patients without portal hypertension heal spontaneously within 48 hours and, therefore, only conservative management is required. Uncommon cases of uncontrollable bleeding or re-bleeding can occur and this problem requires endoscopic injection or thermal therapy, angiography with selective embolization and surgery(Lee and Laberge, 2004).

2.5.1.2.5 Neoplasms

Neoplasms of the upper GI tract is uncommon causes of UGIB (2-5%)A variety of benign and malignant tumors affects the upper GI tract and can cause bleeding However, the volume or rate of bleeding from neoplasms of the upper GI tract usually does not cause a medical emergency and most bleeding is self-limited. The diagnosis is usually made with

endoscopy and the treatment is surgical resection or oncologic chemotherapy and/or radiation(Lee and Laberge, 2004).

2.5.1.2.6 Dieulafoy's lesion

Dieulafoy disease is defined as bleeding from a large aberrant vessel in the mucosa that ruptures by pressure rather than ulcerative erosion. First described by Gallard in 1884 and later by Dieulafoy in 1898, it is also called submucosal arterial malformation or caliber-persistent artery. It is a rare cause of GI bleeding (0.3-7% of acute hemorrhage) and most often occurs in the stomach. Chronic gastric ulcer, alcohol, and NSAID are thought to be precipitating factors (Daley and Granton, 2018).

2.5.1.2.7 Gastric antral vascular ectasia (watermelon stomach)

Gastric antral vascular ectasia (GAVE) is also known as "watermelon stomach," has a characteristic appearance of longitudinal rows of flat and reddish spots. These lesions tend to present more often with occult GI bleeding and iron deficiency anemia.GAVE has been associated with female gender, older age (> 70 years old), and cirrhosis(Fortinsky and Barkun, 2019)

Also associated with several auto-immune diseases (e.g. Sj€ogren's Syndrome, Addison's disease, and systemic sclerosis), renal failure and bone marrow transplantation (53–56). GAVE generally does not respond to treatments which reduce portal pressure (Holster *et al*., 2011).

2.5.3 Acute lower GIT Bleeding

Lower gastrointestinal bleeding (LGIB) is defined as bleeding which originates from a site distal to the ligament of Treitz and is usually suspected when patients present with haematochezia, or maroon stools per rectum, although some researchers defined LGIB as bleeding from a colonic source only and any bleeding from the small bowel has been shown to be a distinct entity LGIB can present as an acute and life-threatening event or as chronic bleeding, which might manifest as iron-deficiency anemia, faecal occult blood or intermittent haematochezia(Fortinsky and Barkun, 2019).

Acute lower gastrointestinal bleeding (ALGIB) is a frequent gastrointestinal cause of hospital admission particularly in the elderly, and its incidence seems to be rising (Arabi *et al*., 2018) .In 15% of cases ALGIB and the incidence increases with age and comorbidity, and the identification of the origin of bleeding may be difficult There are several factors which might contribute to increased mortality like a severe course of bleeding and recurrent bleeding as well as advanced age, comorbidity, intestinal ischemia, and hemodynamic instability (Beck *et al*., 2007).

ALGIB presents a more complex diagnostic and therapeutic challenge than upper gastrointestinal bleeding (UGIB) and it is usually less dramatic than UGIB.Colonoscopy remains the mainstay of diagnosis and therapy for ALGIB. For LGIB lesions which are amenable to endoscopic therapy, the

proper selection of hemostatic tools usually results in a successful outcome The majority of ALGIB cases resolve spontaneously with no adverse outcome (80–85%) and death is uncommon (2– 4%) (Arabi *et al*., 2018).

2.5.3.1 Causes Acute Lower GIT Bleeding

Common causes for lower gastrointestinal hemorrhage include colonic diverticula, angiodysplasia, ischemic colitis, and inflammatory bowel disease. Hemorrhage may also come from intestinal tumors or malignancies. Unusual causes of bleeding include no steroidal anti-inflammatory drugs (NSAIDS), related non-specific colitis, Meckel's diverticulum, and anorectal diseases (Beck *et al*., 2007).

2.5.3.1.1colonic diverticula

The most common cause of life-threatening LGI hemorrhage is a diverticular bleed. Forty percent of LGIB is diverticular in origin, yet bleeding complicates less than 5% of all cases of diverticulosis Diverticulosis is common in the developed world and increases with age – the prevalence of diverticulosis is < 10% in adults under 40 and increases in up to 60% in those aged 80(Vicari and Frakes, 2003).

Despite the fact that 90% of diverticula are in the left colon, at least 60% of bleeding colonic diverticula documented at angiography are proximal to splenic flexure.The exact etiology of diverticular bleeding is not clear. Although it is thought to be a result of an acute rupture of the vasa recta close to the neck of a diverticulum, it is unclear what precipitates the rupture (Vicari and Frakes, 2003).

2.5.3.1.2Angiodysplasia

Angiodysplasiae are ecstatic, dilated, thin-walled vessels in the gastrointestinal tract. They occur mostly in the stomach and less frequently in the small bowel and colon. They account for 5–7% of patients presenting with gastrointestinal bleeding. Often found in patients with advanced age, angiodysplasias are associated with chronic renal failure, hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu Syndrome), chronic mucosal ischemia, and prior radiation therapy (Vicari and Frakes, 2003).

The previous belief that angiodysplasia was related to aortic valve disease has been a subject of hot debate .The diagnosis can be made by visualizing small, punctate, bright red,

vascular mucosal lesions during endoscopy Platelet dysfunction associated with chronic renal failure has been postulated as a cause for recurrent bleeding (Sung *et al.*, 2012).

Endoscopic treatment using thermal coagulation can be successful but the multiplicity and involvement of sites not easily accessible, often in the small bowel, make its management difficult. Estrogen-progesterone treatment has been used to prevent recurrent bleeding from angiodysplasia but efficacy not proven by clinical studies(Sung *et al*., 2012).

2.5.3.1.3 Ischemic colitis

Ischemic colitis is a transient reduction in blood flow to the colon. Necrosis may occur but is usually limited to the mucosa and sub mucosa, only occasionally causing full-thickness necrosis necessitating surgery. Ischemic colitis occurs mainly in older people (> 60) and is thought to be caused by small-vessel atherosclerosis. It can also be a complication of abdominal aortic aneurysm repair Symptoms of ischemic colitis are milder and of slower onset than those of acute mesenteric ischemia and consist of left lower quadrant pain followed by rectal bleeding (Gandhi *et al*.,2007).

2.5.3.1.4 Inflammatory bowel diseases

Idiopathic inflammatory bowel diseases include the chronic crypt destructive colitides, chronic ulcerative colitis, and Crohn's disease. Ulcerative colitis and Crohn's disease differ in natural history, clinical and pathologic associations, effective therapies, and response to treatment (Baumgart and Carding, 2007).

These differences, particularly with regard to recommended surveillance strategies and treatment options, underscore the importance of distinguishing between them. While classic cases can be separated, there may be gross, clinical, and histologic overlap of features not only between ulcerative colitis and Crohn's disease but also with other inflammatory conditions of the colon, resulting in an initial diagnosis of indeterminate colitis initially in up to 20% of cases of idiopathic inflammatory bowel disease (Greenson, 2010)

2.5.3.1.4.1 Ulcerative colitis

Ulcerative colitis is a chronic crypt destructive inflammatory process of unknown cause characterized by a predominantly mucosal-based disease and clinically associated with exacerbations and remissions of bloody diarrhea.

Ulcerative colitis has a slightly higher incidence in males, and occurs at all ages, with the major peak incidence in the age range of 15 to 25 years and a minor peak in the seventh decade of life(Iacobuzio-Donahue and Montgomery, 2011).

There is a familial association, with up to 25% of the patients having another affected family member. Clinically, ulcerative colitis is characterized by recurrent episodes of bloody

diarrhea that can undergo spontaneous or therapy-induced remission. The initial presentation may be indolent in onset or may be severe and acute, presenting with toxic hemorrhagic colitis. The clinical diagnosis is rendered following the exclusion of infectious colitis (Iacobuzio-Donahue and Montgomery, 2011).

2.5.3.1.4.2 Crohn'S Disease

Crohn's disease, also referred to as regional enteritis, granulomatous enterocolitis, and terminal ileitis, is a chronic relapsing and remitting inflammatory disease of unknown cause that is often multifocal and can affect any portion of the gastrointestinal tract. It is typically characterized by foci of glandular destruction, aphthous erosions, and serpiginous ulcers, as well as areas of transmural inflammation, fibrosis, and sometimes granulomas (Greenson, 2010)

Because of its transmural nature, fissures, sinuses, and fistulas may occur. Crohn's disease has a slightly higher incidence in females, and occurs at all ages, with the major peak incidence between 20 and 30 years of age. The initial presentation may be indolent in onset or may be acute and severe (Iacobuzio-Donahue and Montgomery, 2011).

The symptoms are variable but often include cramping pain, typically localized to the right lower quadrant, no bloody diarrhea, as well as fever, malaise, and anorexia. These findings may mimic acute appendicitis. Although the appendix may be involved with Crohn's disease, appendicitis, as a presenting feature, is considered extremely rare. Hemorrhage and hematochezia are uncommon, but chronic blood loss does occur as a result of erosions and ulcers. Patients with upper intestinal disease may present with dyspepsia, weight loss, hypoalbuminemia, and iron deficiency anemia, mimicking gluten- sensitive enteropathy (celiac sprue). Fistulas between organs (enterovaginal, enterovesical, and enterocutaneous) may result in the passage of blood, feces, pus, and air (Mashako *et al*., 2005).

2.5.3.1.5 Meckel's diverticulum

Ileal outpouching due to persistence of the congenital omphalomesenteric or vitelline duct ,most common congenital malformation of GI tract ,mostly asymptomatic Seen in ˜ 1-4% of population Symptomatic usually before age 2 most common cause of GI bleeding in children ,Ectopic gastric or pancreatic mucosa may be seen In 30-50% of cases Acid production from gastric mucosa may cause ulceration and bleeding .Most common congenital malformation of GI tract Persistence of embryologic omphalomesenteric duct (Sagar and Shah, 2006).

2.5.3.1.6 anorectal diseases

Anorectal causes are the commonest causes of chronic, intermittent, bright red rectal bleeding. These include: hemorrhoids, anal fissures, IBD (predominantly UC), radiation proctopathy, solitary rectal ulcer syndrome, neoplasia (adenomas/cancers) (Sung *et al*., 2012)

2.5.3.1.7 Bleeding From Haemorroid

Hemorrhoids are a cause of minor to moderate chronic rectal bleeding. Rarely is emergency surgery required for bleeding hemorrhoids. The exact incidence of this common condition is difficult to estimate as many people are reluctant to seek medical advice for various personal, cultural, and socioeconomic reasons, but epidemiological studies report a prevalence varying from 4.4% in adults in the United States to over 30% in general practice in London .Though rare, significant hemorrhage has been reported and therefore it is mandatory to exclude an obvious source by endoscopy prior to further investigation (Fortinsky and Barkun, 2019).

Detailed anatomic studies have demonstrated that sliding downward of the anal cushions is a likely etiology .The anal cushions are composed of blood vessels, smooth muscle, and elastic connective tissue within the submucosa. Hemorrhoids are associated with straining and irregular bowel habits. Although it is commonly believed that constipation is an important risk factor for the development of hemorrhoids, other studies have suggested that diarrheal disorders are more frequently associated with hemorrhoid disease (Barnett and Quallich, 2003).

2.5.4 Occult of lower GIT bleeding

CCULT gastrointestinal bleeding typically refers to bleeding that is not apparent to the patient. The potential for occult bleeding is emphasized by the finding that for melena to be produced consistently, 150 to 200 ml of blood must be present in the stomach. Moreover, patients with gastro duodenal blood loss of 100 ml per day may have stools that appear normal (Rockey, 1999).

Thus, occult bleeding is usually identified only by tests that detect fecal blood or, if bleeding is sufficient, when it becomes manifest as iron deficiency. Occult gastrointestinal bleeding can also refer to bleeding that is clinically evident but from an obscure source. Obscure gastrointestinal bleeding is the least common form of occult gastrointestinal bleeding but represents a tremendous diagnostic and therapeutic challenge (Morrison *et al*, 2018).

2.5.5 Fecal occult blood

The amount of blood lost from the gastrointestinal tract is normally approximately 0.5 to 1.5 ml per day, an amount that is typically not detected by occult-blood tests. Nonetheless, occult blood is commonly detected in the stool by fecal occult-blood tests when there has been no clinical evidence of bleeding or iron deficiency. In screening studies, 2 to 16 percent of the patients tested had positive tests, although many tests may have been falsely positive (Rockey, 1999).

A variety of fecal occult-blood tests have been designed, primarily to screen for colon cancer. However, they also detect blood from other lesions in the gastrointestinal tract. The likelihood that fecal occult-blood tests will detect gastrointestinal blood is affected by the anatomical level of bleeding, factors relating to the patient such as stool transit time, stool mixing, and intraluminal hemoglobin degradation and the intrinsic features of the bleeding of gastrointestinal tract lesions (e.g., irregular bleeding) (Chiang *et al*,2011).

2.6 Previous Studies

Jing Li compared with the ‘no AUGIB’ group, the ‘AUGIB’ group had similar PLT (99.99689.90 vs.101.47683.03; P¼0.734) and APTT (42.96615.20 vs.43.77611.01; P¼0.219), but significantly higher PT (17.3065.62 vs.16.0364.68; P<0.001) and INR (1.4560.69 vs.1.3160.59; P<0.001). A lower PT was independently associated with the absence of AUGIB (OR¼0.968; 95% CI: 0.942–0.994). Compared with the ‘no AEVB’ group, the ‘AEVB’ group had significantly lower PLT (86.87662.14 vs.101.74683.62; P¼0.004) and APTT (40.9867.9 vs.43.72610.97; P<0.001), but similar PT (16.5363.71 vs.16.0464.68; P¼0.088) and INR (1.3560.41 vs.1.3160.59; P¼0.225). A higher PLT was independently associated with the absence of AEVB (OR¼1.004; 95% CI: 1.002–1.006; P¼0.001)(Li *et al*., 2015).

Ayub and Noor found that total 280 cases reported with chronic liver disease out of which 150 cases were having gastrointestinal bleeding having history of melena and hematemesis. There were 76.7% cases with prolonged prothrombin time. In 88.6% cases APTT was prolonged. 88.6% were having low platelet count less than 1.5×105. There were 58.7% male and 41.3% female cases (Ayub *et al*., 2018).

In Sudan El Magzoub and others found that according to type of disease, the patients investigated were divided into 5 groups: 44 patients (62. 9%) with esophageal varices, 18 patients (25.7%) with peptic ulcer, 5 patients (7.1%) with liver cirrhosis, one patient (1.4 %) with Hepatitis C virus, and 2 patients (2.9%) with other GI bleeding conditions. Also, the predominant cases of GI bleeding was among patients aged 36-67years with median age of 51.6 years. As shown the mean PT (17.66 ± 4.96 seconds) and APTT (43.87 ± 16.80 seconds) were found significantly higher among the test group patients than the control group patients (p = 0.00 for both PT and APTT). Also, the mean platelets count (170.8 ± 126.3x109/L), was significantly low among test group patients as compared with the control group patients (p = 0.00) (Magzoub *et al*., 2018).

CHAPTER THREE

Material and Methods

CHAPTER III

Material and Method

3.1 Study design

This was descriptive matched case control study and hospital based study.

3.2 Study setting and Duration

The study was conduct in Mohammed Salih Edris for Gastrointestinal Bleeding Center in Khartoum State .In period between March 2020 to Nov 2020.

3.3 Study population

Patients with gastrointestinal bleeding who attending bleeding center at Ibn Sina Hospital as case and matched group of samples were collect from healthy individuals as control.

3.4 Sample size

100 samples as case and 100 samples as control.

3.5 Inclusion criteria

Patients with gastrointestinal bleeding from both sex were included and apparently healthy individuals taken as control group

3.6 Exclusion criteria

Any patients and healthy individual under the age 18 years.

Diabetic, hypertensive, smoker patients and any condition associated with coagulation profiles affected were excluded.

3.7 Ethical consideration

The study approved by the Scientific Ethical Committee of Medical Laboratory Science, Sudan University of Science and Technology. Verbal permission was obtained from the bleeding center at Ibn Sina Hospital and also from participants after they had been informed with the objective and benefits of the study .The participants were insure that the collected information was be kept confidential and was not be used for any other purpose than this study.

3.8 Sample collection

Venous blood was collected using sterile disposable plastic syringe after cleaning the vein puncture area with 70% ethanol from each subject, Five ml of venous bloods were collected from all participants 2.5ml was added to trisodium citrate anticoagulant at ratio of 4.5 to 5.0 of (3.2%(0.109M) The sample was centrifuge at 1300 rpm for 15min to obtain platelet poor plasma (ppp) 2.5ml was added in EDTA anticoagulant containers.

3.9 Data collection

Self a administered questionnaire was design to obtain subjects information which help in the study.

3.10 Methodology

3.10.1 Principle of semi –automated coagulation analyzer (Carton MI)

In electromechanical clot detection systems such as the system employed by BBL's time-honored Fibrometer, fibrin strands attach to a moving mechanical electrode (probe), completing an electrical circuit and stopping the interval timer. There is one stationary and one moving probe. During clotting, the moving probe enters and leaves the plasma at regular intervals.

The current between the probes is broken as the moving probe leaves the plasma. When a clot forms, the fibrin strand conducts current between the probes even when the moving probe exits the solution. The current completes a circuit and stops the timer (McGlasson *et al*., 2015).

3.10.2 Prothrombin Time

Is a functional measure of the extrinsic pathway and the common pathway.

3.10.2.1 Principle of ProthrombinTime

In this test, platelet poor plasma from a patient (collected in a blood collection tube containing sodium citrate) is mixed with thromboplastin and calcium and then clotting time is determined at 37C using a variety of methods, including photo optical and electromechanical. Automated coagulation analyzers are commercially available for measuring PT along with other coagulation parameters (Wahed and Dasgupta, 2015).

3.10.2.2 Reagents and material

Commercial pooled normal plasma control. PT reagents, often called thromboplastin or tissue thromboplastin, are prepared from recombinant or affinity-purified *tissue factor* suspended in phospholipids mixed with a buffered 0.025- mol/L solution of calcium chloride (McGlasson *et al*., 2015).

3.10.2.3 Assay procedure

Opened the device, checked the system, put samples and reagent in incubation station, Test identification code entered, removed cuvette to measuring well, sample identification code entered, pipetting the sample in the cuvette and Pipetting the reagent (thromboplastin) and started the timer.

3.10.2.4 Normal range

The general reference interval for the PT is 12–15 seconds (McGlasson *et al*., 2015).

3.10.2.5 Interpretation

The PT can be prolonged because of deficiency of factors VII, X, V, II (prothrombin), and fibrinogen or the presence of an inhibitor. Prolongation of the PT is also seen with proteins induced by vitamin k absence or antagonists or antagonism(McGlasson *et al*., 2015).

3.10.3 Activated partial thromboplastin time

Is a functional measure of the intrinsic pathway as well as the common pathway and can detect hereditary or acquired defects of some coagulation factors. Phospholipid (lacking tissue factor, hence the term partial thromboplastin) and particulate matter (such as kaolin) are added to plasma to generate a clot. Abnormalities in the intrinsic and common pathway will result in prolongation of the APTT (Key *et al*., 2009)

3.10.3.1 Principle of the activated partial thromboplastin time

Patient's platelet poor plasma (citrated plasma, but oxalate can also be used), surface activating agent (silica, kaolin, celite, or ellagic acid), calcium, and platelet substitute (crude phospholipid) are mixed, and then clotting time is determined by using an automated coagulation analyzer (Wahed and Dasgupta, 2015).

3.10.3.2 Reagent and material

Commercial pooled normal plasma control. The PTT reagent contains phospholipid (previously called partial thromboplastin) and a negatively charged particulate activator such as silica, kaolin, ellagic acid, or celite in suspension. The phospholipid, which was historically extracted from rabbit brain, is now produced synthetically (Key *et al*., 2009)

3.10.3.3 Assay procedure

Opened the device. Checked the system, put samples and reagent in incubation station.

Test identification code entered, removed cuvette to measuring well, sample identification code entered, put the sample and activator in cuvette and incubated for 3min.Added the calcium and started the timer.

3.10.3.4 Normal range

The general reference interval for adults is in the range of 25–35 seconds but varies by laboratory (Egberg and Blombäck, 2014).

3.10.3.5 Interpretation

Most prolonged PTTs result from deficiencies of factors XII, XI, IX, and VIII. In patients developing circulating anticoagulants, prolonged PTTs are often the first signs of this complication. Lupus anticoagulants also often cause prolongation of PTT(Egberg and Blombäck, 2014).

3.10.4 Platelet count

A platelet count should always be performed to rule out the possibility of thrombocytopenia as the cause of bleeding symptoms. A low platelet count should be further investigated by a hematologist(Egberg and Blombäck, 2014).

3.10.4.1 Principle of Electronic impedance, or low-voltage direct current (DC) Detection Method:

Blood sample is aspirated, measured to a predetermined volume, diluted at the specified ratio, and then fed into each transducer. The transducer chamber has a minute hole called the aperture. On both side of the aperture, there are the electrodes between which flows direct current. Blood cells suspended in the diluted sample pass through the aperture, causing direct current resistance to change between the electrodes. As direct current resistance changes, the

blood cell size is, detected as electric pulses. Blood cell count is calculated by counting the pulses, and a histogram of blood cell sizes is plotted by determining the pulse sizes. Also analyzing a histogram makes it possible to obtain various analysis data (Li *et al*., 2013).

3.10.4.2 Method test performed

Complete blood count CBC was done using Sysmex Automated Hematology Analyzer KX 21N series SN B 2010.

3.10.4.3 Normal range

The reference interval for platelet counts is 150-400 * 103/mcL (150-400 * 109/L) (Rodak *et al*., 2013).

3.10.4.4 Interpretation

Thrombocytopenia is defined as platelet count below 1,50,000/cmm. Common causes of thrombocytopenia are hematological malignancies, ingestion of certain drugs, disseminated intravascular coagulation, idiopathic thrombocytopenic purpura, connective tissue diseases, megaloblastic anemia, and aplastic anemia. Thrombocytosis (platelet count >4,00,000/cmm) occurs in inflammation, following hemorrhage, and in myeloproliferative disorders(Kawthalkar, 2013).

3.11 Data analysis

The collected data was entered, cheeked and processed by using a computer based statistical program SPSS (Statistical Package for Social Science) Version 20. (Mean±STD, One way a nova test and independent sample T test, P value significant ≤ 0.05).

CHAPTER FOUR

Results

CHAPTER IV

Results

Two hundred volunteers of age as case between 20-85 years were enrolled in this study 100 were gastrointestinal bleeding patients with mean of age 53 ± 16., 66/100 (66%) were males and 34/100(34%) were females. 100 were apparently healthy subjects as control with mean of age 52±16.35,67/100(67%) were male and 33/100 (33%) were female (Table 4.1).

Age grouped into 3 age groups, and age group III (> 60y) high frequent (37%) followed by age group II (40 – 60 y) (34%) , and age group I (<40y) was the lowest (29%) in case compared to control age group II(40-60) high frequent(39%) followed by age group III(> 60y) (35%), and age group I (<40y) was the lowest (26%)(Table 4.2).One way a nova test showed insignificant comparison between age group and PT,INR,APTT and platelet count in both case *P. value* (0.883), (0.558) ,(0.787), (0.915),respectively and control *P. value (*0.866),(0.401),(0.457),(0.545),respectively (Table 4.3).

Mean level of PT was 19.2 ±5.6, 13.5 ± 1.2 in the case group and control group respectively. Statistically there was significant correlation in PT level between case and control group *P.value* (0.00). Mean level of INR was 1.3 ± 0.34, 0.96 ± 0.1 in the case group and control with statistically significant correlation in INR level between case and control group *P.value* (0.00). Mean level of APTT 90± 26.4 in the case group compared with APTT 32.5±4.8 in control subject and there was statistically significant correlation in APTT level between case and control group *P.value* (0.00). Mean level of platelet count 178.7 ± 121.5, 285.9 ± 71.2 in the case group and control group, respectively with statistically significant correlation in platelet count between case and control group *P.value* (0.00) (Table 4.4).

Correlation of PT level with gender in case showed mean level of PT was 19.4 ± 6.3 in male and 18.7 ± 3.8 in female with no statistical significant *P.value* (0.534) while man of PT in control was 13.56±1.24 in male and 13.45±1.27 in female with no statistical significant *P.value* (0.661) Figure (4.1).

Mean level of INR in male and female of the case group was1.40±0.36 and 1.33±0.29, respectively and mean of INR in control group was 0.96±0.10 in male and 0.97 ± 0.09 in female with no statistical correlation between mean level of INR and gender in both case and control group *P.value* (0.292), (0.738), respectively. Figure (4.2).

Mean level of APTT in male and female of the case group was 92.5 ± 28.8 and 87.8 ± 21.21, respectively and mean level of APPT in control group was 32.18±4.49 in male, and 33.16±4.78 in female. There was no statistical correlation between APTT level and gender in both case and control group *P.value* (0.40), (0.348), respectively. Figure (4.3).

Mean level of platelet count in male and female of the case group were 168.59±std and 198.50±std, respectively and mean of PT in control group were 288.78±73.59 in male and 280.15±67.06 in female.There was no statistical correlation between platelet count and gender in both case and control group *P. value* (0.246),(0.572), respectively Figure (4.4).

Study showed that no statistical correlation between PT , INR, APTT levels, and platelet count and age in both case *P. value* (0.214),(0.10),(0.476),(0.074),respectively and control *p. value* (0.564),(0.471),(0.710),(0.344) (figure 4.5,4.6,4.7,4.8).

Mean level of PT in case group under cause of esophageal varies, duodenal ulcer, portal hypertension and Gastritis 20.6±7.14,16.1±1.91,20.7±3.2,17.7±2.33, respectively with statistical significant increase *P. value* (0.007). Mean level of INR in case group under cause of esophageal varies, duodenal ulcer, portal hypertension and Gastritis 1.4±0.38,1.1±0.17,1.4±0.29,1.3±0.26,respectively with statistical significant increase *P. value* (0.001).Also Mean level of APTT in case group under cause of O.V,D.U,PHTN and Gastritis 89.7 ± 29.21,86.1 ±26.12,95.6± 26.03,97.2 ±16.50,respectively with no statistical significant change *P. value* (0.563). Mean level of platelet count in case group under cause of O.V,D.U, PHTN and Gastritis 163.1± 117.8,267.5 ± 99.4,59.8 ± 23.3,210.3 ± 114.1 ,respectively with statistical significant increase *p.value* (0.00) (table 4.5).

Mean PT level in patient first presentation, less than 5 years, 5-10 years and more than 10 years 18.3±3.4,19.8±6.9,21.3±6.07,17.0±0.21,respectively with no statistical correlation between mean level of PT and history of bleeding *P. value* (0.427). Mean INR level in patient first presentation, less than 5 years, 5-10 years and more than 10 years 1.3±0.31, 1.3±0.30, 1.1±0.07, respectively with no statistical correlation between mean level of INR and history of bleeding *P .value* (0.061). Mean APTT level in patient first presentation, less than 5 years, 5-10 years and more than 10 years 93.7 ± 3.4,89.6 ± 24.9,92.8 ± 51.2,57.9 ± 5.51, respectively with no statistical correlation between mean level of APTT and history of bleeding. *P value* (0.217).Mean platelet count in patient first presentation, less than 5 years, 5-10 years and more than 10 years 216.4 ± 148.8,153.8 ± 90.39,143.5 ± 91.31,115.0 ± 77.78,

respectively with no statistical correlation between mean of platelet count and history of bleeding *P value* (0.064) (table 4.6).

Table (4.1): Frequency of gender and mean ±STD of age among study volunteer

Variable	Frequency and Percentage(case)	Frequency and Percentage(control)
Sex		
Male	66/100 (66%)	67/100 (67%)
Female	34/100 (34%)	33/100 (33%)
Mean age ±std	53±16.006	52±16.35
Total	100	100

Table (4.2): Frequency of age group in study volunteer

Age group (years)	Case	Control
<40	29/100 (29%)	26/100 (26%)
40-60	34/100 (34%)	39/100 (39%)
>60	37/100 (37%)	35/100 (37%)
Total	100	100

Table (4.3): Comparison of PT, INR, APTT levels and Platelet with age groups in case group

Age group	Mean ± STD PT	Mean ± STD INR	Mean ± STD APTT	Mean ± STD Platelet count
<40	18.8±3.05	1.3±0.23	94.5±20.53	194.7±139.8
40-60	20.1±4.60	1.5±0.42	91.6±34.19	149.7±113.73
>60	18.6±7.64	1.3±0.30	87.4±22.51	192.7±111.17
P. value	0.498	0.018	0.552	0.233

Table (4.4): Comparison of prothrombin time, international normalization ratio, activated partial thromboplastin time levels and Platelet count between study subjects

Parameters	Case	Control	*P. value*
Mean ± STD PT	19.2 ± 5.6	13.5±1.2	0.00
Mean ± STD INR	1.3± 0.34	0.96±0.10	0.00
Mean ± STD APTT	90 ± 26.4	32.5±4.8	0.00
Mean ± STD Platelet count	178.7±121.5	285.9±71.2	0.00
Total	100	100	-

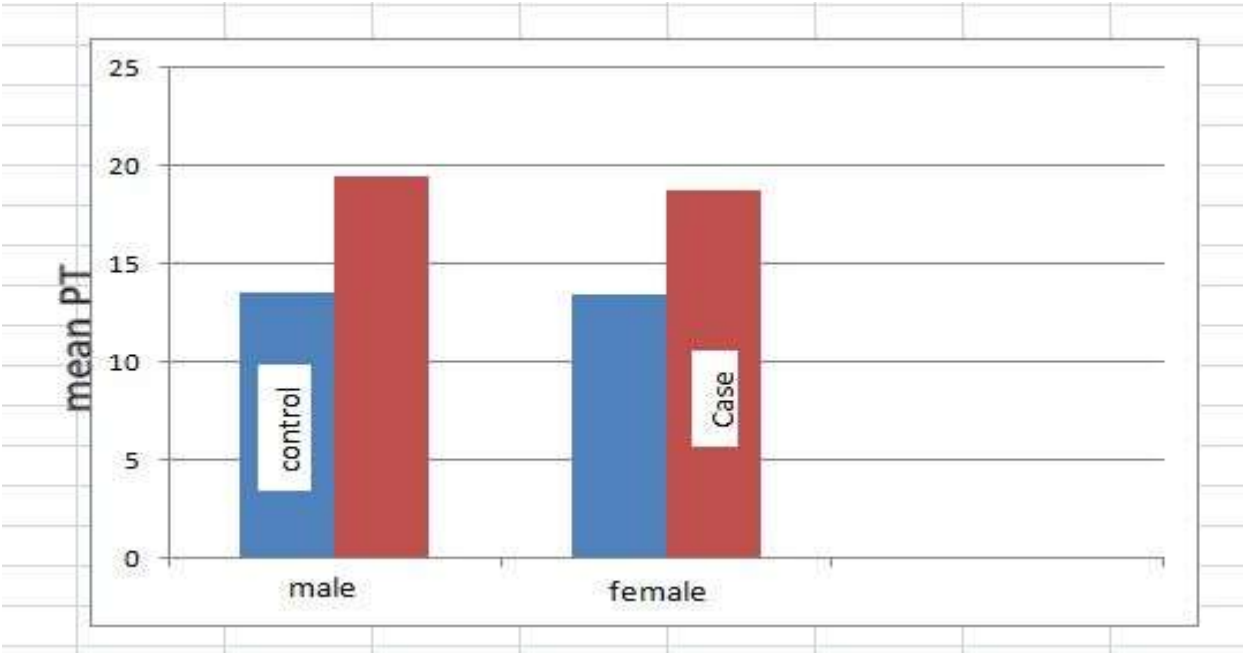


Figure (4.1): Comparison mean level of PT between males and females in case and control group

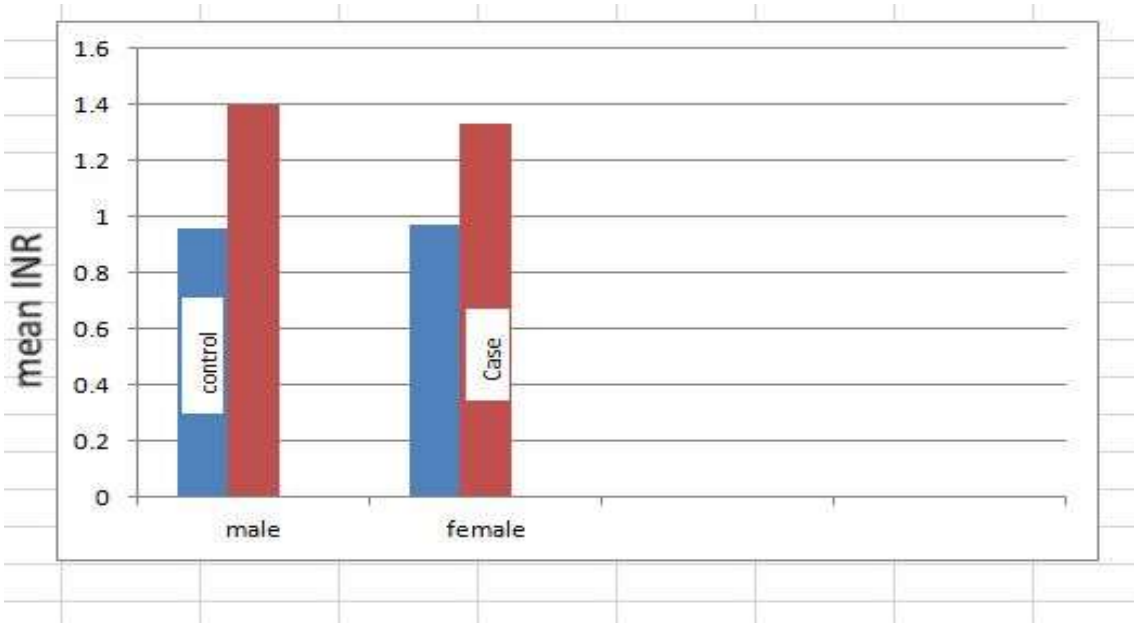


Figure (4.2): Comparison mean level of INR between males and females in case and control group

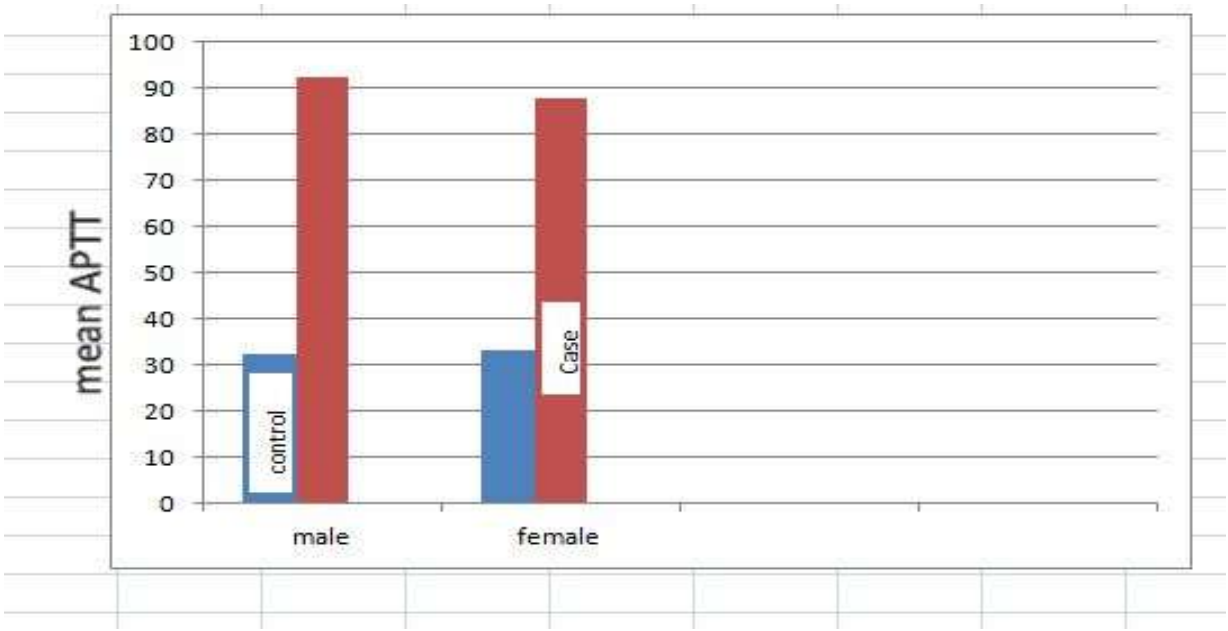


Figure (4.3): Comparison mean level of APTT between males and females in case and control group

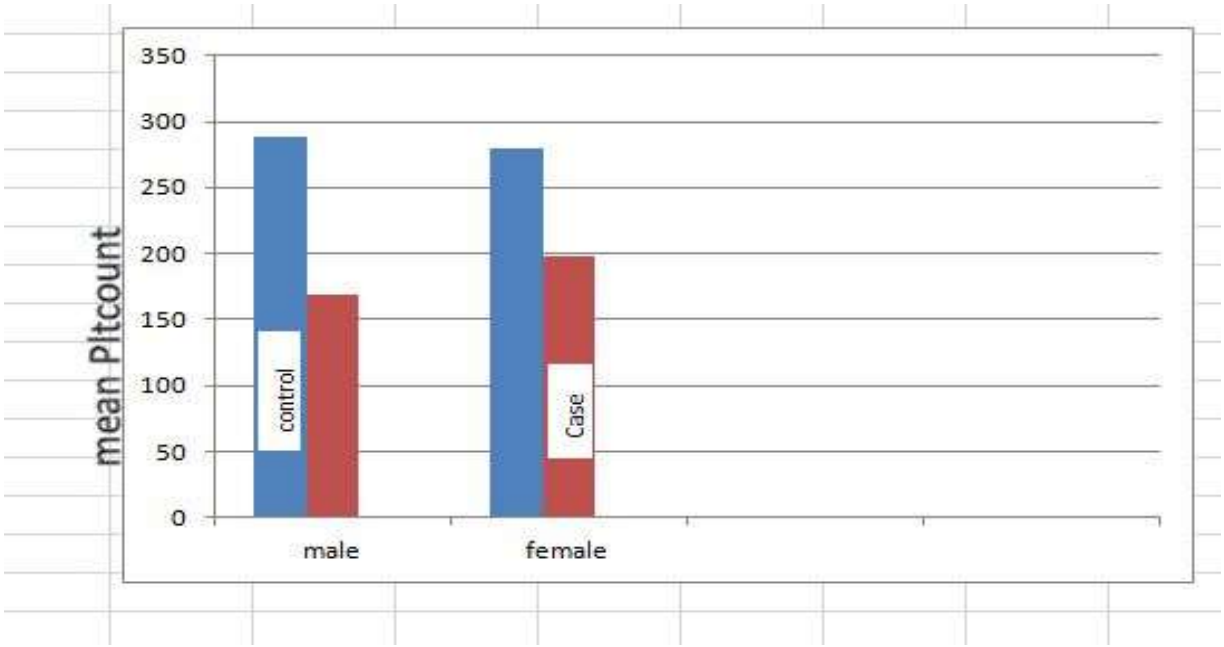
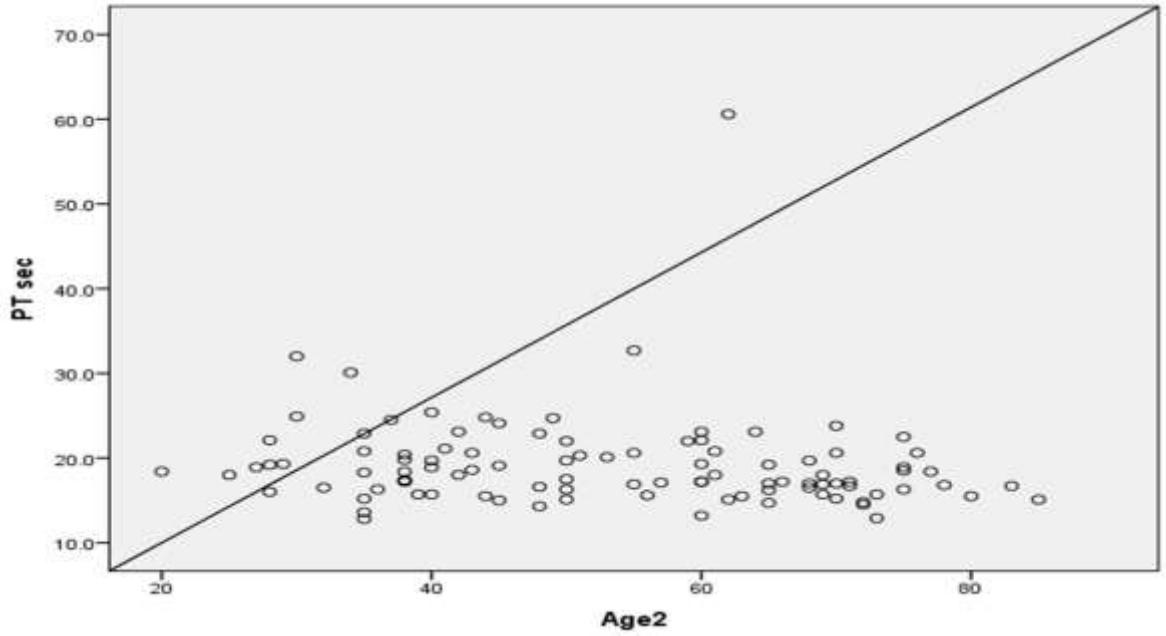
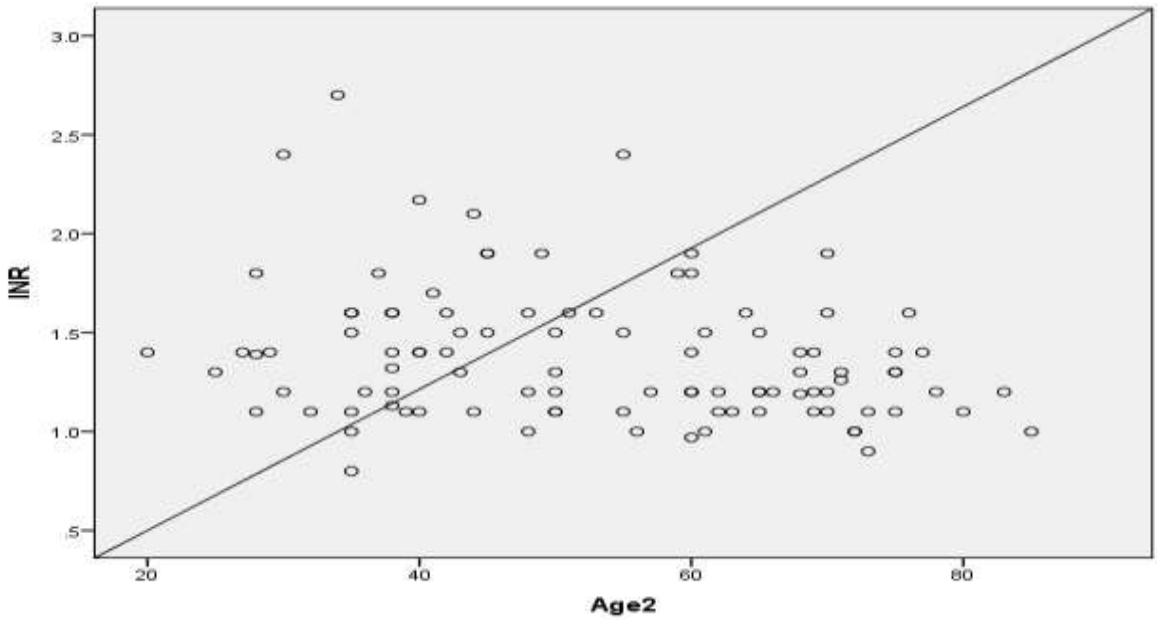


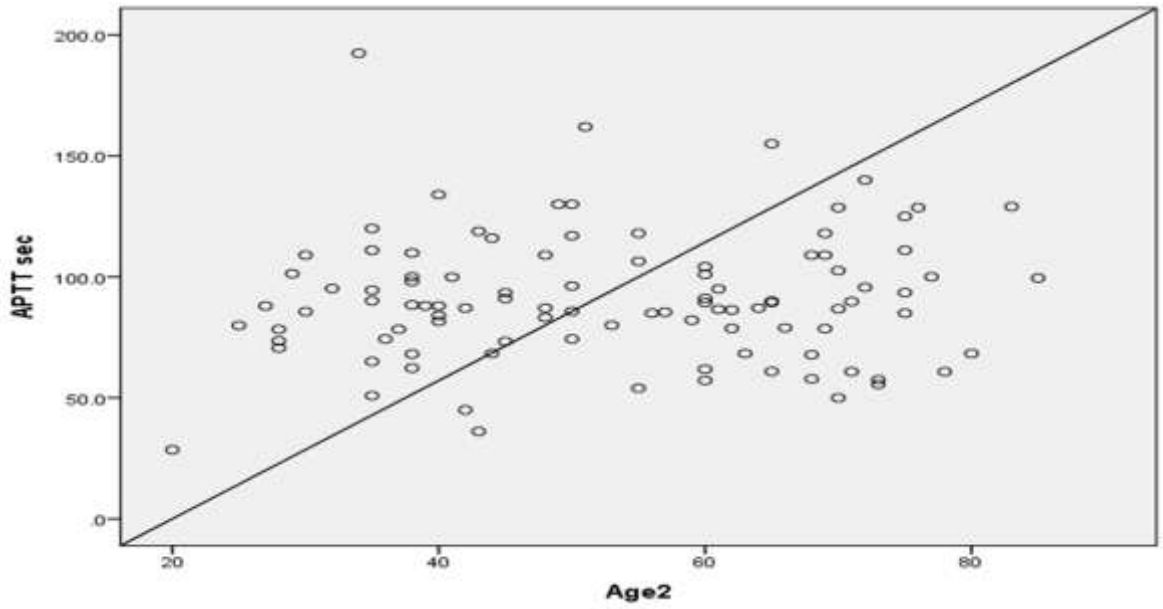
Figure (4.4): Comparison mean level of platelet count between males and females in case and control group



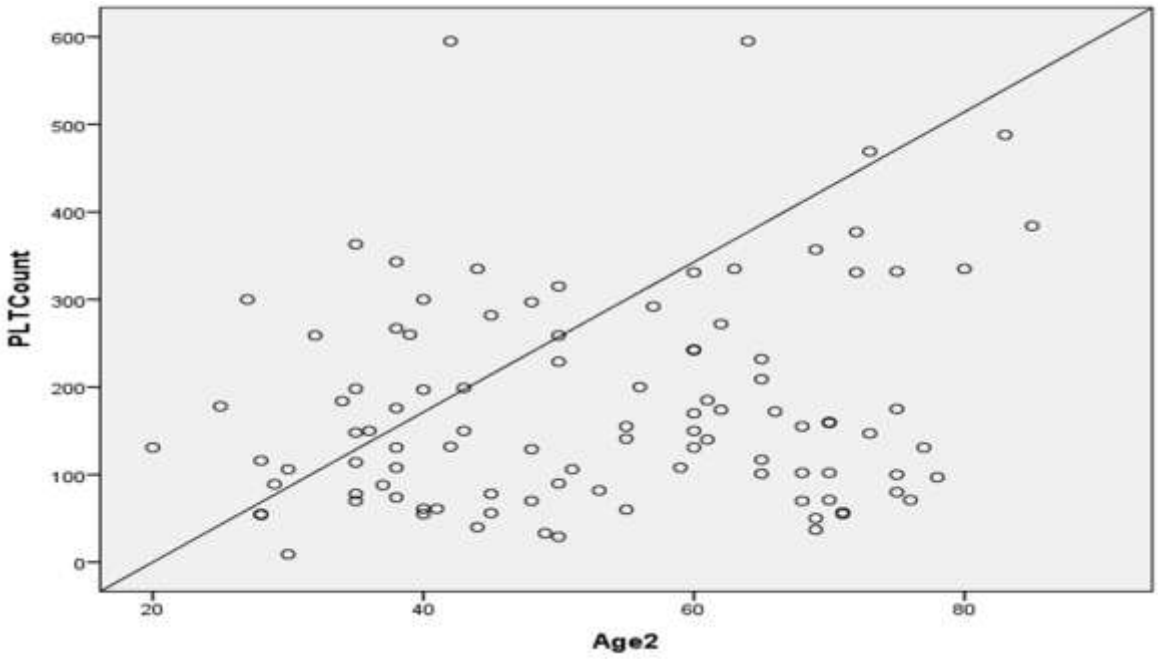
Figure(4.5): Correlation between PT level and age of cases. There was no coreelation between PT and age of cases *P. value* 0.214.



Figure(4.6): Correlation between INR level and age of cases. There was no coreelation between PT and age of cases *P. value* 0.10.



Figure(4.7): Correlation between APTT level and age of cases. There was no coreelation between PT and age of cases *P. value* 0.476.



Figure(4.8): Correlation between platelet count and age of cases.There was no coreelation between PT and age of cases *P. value* 0.07

Table (4.5): Comparison of PT, INR, APTT levels and Platelet with bleeding causes in case group

variable (cause of bleeding)	Mean PT± STD	Mean INR±STD	Mean APTT±STD	Mean Platelet count ±STD	*P. value*
Osephagal varices	20.6±7.14	1.4±0.38	89.7±29.2	163.1±117.8	0.007
Duodenal ulcer	16.1±1.91	1.1±0.17	86.1±26.12	267.5±99.4	0.001
Portal hypertension	20.7±3.2	1.4±0.29	95.6±26.03	59.8±23.3	0.563
Gastritis	17.7±2.33	1.3±0.26	97.2±16.50	210.3±114.1	0.000

Table (4.6): Comparison of PT, INR, APTT levels and Platelet with history of bleeding in case group

History of bleeding	Mean PT± STD	Mean INR±STD	Mean APTT±STD	Mean Platelet count ±STD	*P. value*
First presentation	18.3±3.4	1.3±0.31	93.7±23.7	216.4±148.8	0.427
>5 years	19.8±6.9	1.3±0.30	89.6±24.9	153.8±90.39	0.217
5-10 years	21.3±6.07	1.7±0.65	92.8±51.2	143.5±91.31	0.061
<10 years	17.0±0.21	1.1±0.07	57.9±5.51	115.0±77.78	0.064

CHAPTER FIVE

Discussion, Conclusion and Recommendations

CHAPTER V

Discussion, Conclusion and Recommendations

5.1Discussion

The study investigated the effect of gastrointestinal bleeding on platelet count and some haemostatic parameters (Prothrombin time and Activated Partial Thromboplastin Time) in Sudanese patients with gastrointestinal bleeding with age range from(20-85).The present study indicated the mean of patients with GIB was (53) this observation were supported by previous work in Sudan (Bay *et al*., 2006) who reported the mean valued of GIB in Khartoum State were (44) years. This is also comparable to that reported in north Ireland where mean age of GIB patients was reported to be 59 years (Ravindra *et al*., 2008).In this study Oesphagel Varices were the predominant cause of gastro intestinal bleeding (49%) then Duodenal Ulcer (22%),the Gastritis (15%) and portal hypertension (14%).This observation similar to observation reported in Sudan but in contrast to the fact that peptic ulcer was the mean cause of bleeding as reported in studies under taken in Germany and USA(Hearnshaw *et al*., 2011).

In the present study plasma level of PT, INR, APTT and platelet count were measured in 100 gastrointestinal bleeding patients and in 100 apparently health control. The result reviled that the mean levels of PT,INR,APTT in case group higher than control group and the difference was significant *p.value* (0.00),(0.00),(0.00), respectively and mean platelet count in case group lower than control group and the difference was significant *p.value* (0.00).This result was supported by Ayub show demonstrated that significantly elevated PT,INR,APTT levels in case than control group *p. value* less than 0.05(Ayub,2018).The mean level of PT,INR,APTT and platelet count in the present study was agree with Elsayed and Hassan result which show that PT,INR,APTT levels were significantly increase in case than control *p.value* less than 0.05 and platelet count was significantly decrease in case than control *p.value* less than 0.05 (Elsayed and Hassan, 2013).In the present study there is correlation between mean level of PT,INR,APTT and platelet count and bleeding causes, no statistical significant change on APTT *p.value* (0.563) and there was statistical significant increase on PT,INR and platelet count *p.vlaue* (0.007),(0.001),(0.00),respectively similar result was found by jngli which found correlation between PT,INR,APTT and platelet count and causes of disease who found PT , INR and platelet count were significantly higher in patients with acute gastrointestinal bleeding than in those without *P.value* (0.001), APTT was not

significantly different between the two groups *P value* (0.219) (Li *et al*., 2015). In the present study there is no correlation between the mean level of PT,INR,APTT and platelet count and age in both case and control *p.value* (0.214),(0.10),(0.476),(0.074), respectively this result agree with Aoki and Uchino found no correlation berween them *p.value* more than 0.05. (Aoki and Uchino, 2011). Also similar result accomplished by Tomizawa found no correlation between the mean level of PT,INR,APTT and platelet count and age *p.value* more than 0.05(Tomizawa *et al*., 2016).Also present study show no correlation between the mean level of PT,INR,APTT and platelet count and gender in both case and control group *p. value* (0.534), (0.292), (0.40), (0.246),respectively this result confirmed by Greenspoon and Barkun which found no correlation between mean of PT,INR,APTT and platelet count and gender *p.value* (0.644),(0.392),(0.60),(0.240),respectively (Greenspoon and Barkun, 2010).In the present study also there is no correlation between mean level of PT,INR,APTT and platelet count and history of disease *p.*value (0.427) ,(0.061), (0.217), (0.064), respectively similar result was found by Beck which found no correlation between mean of PT,INR,APTT and platelet count and history of bleeding *p.*value more than 0.05(Beck *et al*., 2007).

5.2 Conclusion

- The study revealed that the PT, INR, APTT had higher value and Platelet count had lower values in patients with gastrointestinal bleeding compared with normal control.

- According to the causes of bleeding PT, INR, platelet count were significant increase in all causes of bleeding and there was no significant change on APTT.

- Gastrointestinal bleeding have the quite similar effect in patients regardless of gender, age and history of bleeding, although the males were more frequently affected by disease.

5.3 Recommendations

1. Complete other coagulation profiles such as fibrinogen level and D-dimer test.
2. For prolongation of Prothrombin Time and Activated Partial Thromboplastin Time factor assay it necessary to determine which factor deficiency.

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APPENDIXES

Appendix (A1)

Hematological analyzer (Sysmex kx21n)

Appendix (A2)

Coagulometer (Carton MI)

Appendix (A3)

Sudan University For Sciences And Technology

Faculty Of Graduate Study

College Of Medical Laboratory Sciences

Department Of Hematology and Immunology

Measurement of PT, INR, APTT and Platelet Count among Gastrointestinal Bleeding Patients in Khartoum State

Research Questionnaire

1/ ID Number…….

2/ Name……..…….

3/ Sex Male ☐ Female ☐

4/ Age……..……

5/ Causes of bleeding …….…….

…….

6/ History of bleeding ……..……...

……..…….

7/ Laboratory investigations

- PT ……..……Sec

- INR …….

- APTT ……..…… Sec

- Platelet count ……..……$^{*}10^{9}$/L