LABORATORY EVALUATION OF BLEEDING DIATHESIS IN MEDICAL ICU PATIENTS

Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfillment of the regulations

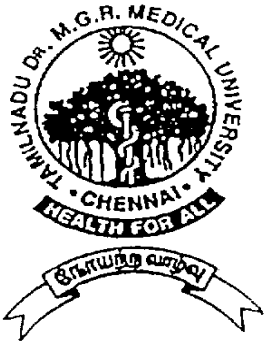
For the award of the degree of

M.D. GENERAL MEDICINE (BRANCH - I)

INSTITUTE OF INTERNAL MEDICINE

MADRAS MEDICAL COLLEGE

CHENNAI 600 003



THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI

APRIL 2015

CERTIFICATE

This is to certify that the dissertation titled **"LABORATORY EVALUATION OF BLEEDING DIATHESIS IN MEDICAL ICU PATIENTS"** is the bonafide original work of **Dr. M.SATHISH KUMAR** in partial fulfillment of the requirements for M.D. Branch – I (General Medicine) Examination of the Tamilnadu DR. M.G.R Medical University to be held in APRIL 2015. The Period of study was from March 2014 to August 2014.

Prof. S. TITO M.D.
Director & Professor,
Institute of Internal Medicine,
Madras Medical College &
Rajiv Gandhi Government General Hospital,
Chennai 600 003.

Prof. R.PENCHALAIAH M.D
Professor ,
Institute of Internal Medicine,
Madras medical college &
Rajiv Gandhi government general hospital,
Chennai -600003.
(Guide)

Prof. R.VIMALA M.D.
D E A N,
Madras Medical College &
Rajiv Gandhi Government General Hospital,
Chennai 600 003.

DECLARATION

I, **Dr. M.SATHISH KUMAR** solemnly declare that dissertation titled **"LABORATORY EVALUATION OF BLEEDING DIATHESIS IN MEDICAL ICU PATIENTS"** is a bonafide work done by me at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3 during March 2014 to August 2014 under the guidance and supervision of my unit chief

Prof. R. PENCHALAIAH Professor of Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai.

This dissertation is submitted to Tamilnadu Dr. M.G.R Medical University, towards partial fulfillment of requirement for the award of **M.D. Degree (Branch – I) in General Medicine – APRIL 2015.**

Place: Chennai -03
Date:

Dr. M.SATHISH KUMAR
MD General Medicine
Post Graduate,
Institute Of Internal Medicine,
Madras Medical College,
Chennai-03

ACKNOWLEDGEMENT

I owe my thanks to Dean, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3. **Prof R. VIMALA, M.D.,** for allowing me to avail the facilities needed for my dissertation work.

I am grateful to beloved mentor **Prof. S. TITO M.D.**, Director and Professor, Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-03 for permitting me to do the study and for his encouragement.

With extreme gratitude, I express my indebtedness to my beloved Chief and teacher **Prof. R.PENCHALAIAH M.D.,** for his motivation, advice and valuable criticism, which enabled me to complete this work. I express my sincere thanks to **Prof. S. RAGUNANTHANAN M.D**, Professor of toxicology and IMCU in charge and **Prof MARGARET CHELLARAJ M.D, D.M** , Professor of Hematology for allowing me to avail the facilities and guiding me through the study

I am extremely thankful to my Assistant Professors

Dr. S.SIVARAM KANNAN M.D., and **Dr. C.R.SRINIVASAN M.D,** for their guidance and encouragement.

I am also thankful to all my unit colleagues and other post graduates in our institute for helping me in this study and my sincere thanks to all the patients and their families who were co-operative during the course of this study.

CONTENTS

LABORATORY EVALUATION OF BLEEDING DIATHESIS IN MEDICAL ICU PATIENTS

Sathish Kumar.M[1], Penchalaiah.R[2], Margaret Chellaraj[3]

ABSTRACT

INTRODUCTION: Bleeding diathesis is a very common occurrence in critically ill patients. The cause is usually multifactorial.

AIMS and OBJECTIVES: To study about the incidence and the type of bleeding diathesis occurring in critically ill patients in the medical ICU.

To analyse and tabulate the common aetiologies of coagulopathy occurring in medical ICU patients.

MATERIALS and METHODS: 50 patients admitted in medical ICU were selected irrespective of the presence of clinical bleeding and patient underwent the questionnaire and the following investigations namely prothrombin time (PT), activated partial thromboplastin time (aPTT), Platelet count, D dimer and Fibrinogen.

1 Post graduate in Internal Medicine, Institute of Internal Medicine, RGGGH
2 Professor of Medicine, Institute of Internal Medicine, RGGGH
3 Professor of Hematology, Dept of Hematology, RGGGH

RESULTS: Out of 50 patients 26 patients had coagulation abnormality. Any drop in platelet count or prolongation of PT, a PTT was considered coagulation abnormality. 23 patients out of 50 had thrombocytopenia with majority of patients having drop between 80,000 and 1 lakh cells per cu.mm. 3 patients had prolonged PT and 10 patients had prolonged aPTT. 1 Patient had DIC who was found to have thrombocytopenia, prolonged PT and aPTT. Sepsis was found to be the commonest etiology of coagulopathy and thrombocytopenia was the commonest coagulation abnormality in our study. Renal failure, liver failure and antithrombotic drugs were the other major causes.

CONCLUSION: A rationale approach must be developed in treating critical care patients with abnormal coagulation. Too much aggressive transfusions can do more harm than good. A good clinical judgement along with updated knowledge is required to treat such patients.

KEY WORDS: coagulopathy, disseminated intravascular coagulation (DIC), Prothrombin time (PT), activated partial Thromboplastin time (aPTT), sepsis

INTRODUCTION

Bleeding diathesis is common in critically ill patients. Patients may have clinical bleeding or only laboratory abnormalities in hemostatic tests. Thrombocytopenia, prolongation of PT or aPTT or both, low fibrinogen and increased fibrin degradation products are the expected abnormalities. The mortality is higher in ICU patients with bleeding tendency. These abnormalities can be independent predictors of survival[1].

Unnecessary transfusion at some clinical situations can do more harm to the critically ill patient. Use of anticoagulants to prevent deep venous thrombosis has also increased the risk of bleeding. There is also concern regarding the risk of bleeding when performing invasive procedures in these patients.

Some causes of thrombocytopenia like thrombotic thrombocytopenic purpura should be recognized promptly as they can life threatening and also amenable to treatment if identified early.

There is a recent trend to follow restrictive strategy in blood transfusion which has shown that mortality is improved compared to liberal strategy[2]. Now there is an increase in awareness of harmful effects of massive transfusion.

Our study aims at determining the incidence and types of bleeding diathesis that commonly occur in our medical ICU. Patients are screened for bleeding diathesis by the following tests namely platelet count & peripheral smear, PT, aPTT, D-dimer and Fibrinogen irrespective of the presence of clinical bleeding. The incidence and the type of abnormality in the hemostatic tests and the underlying probable causes for the bleeding tendency are to be identified in this study.

AIMS & OBJECTIVES

AIMS & OBJECTIVES

1. To study about the incidence and the type of bleeding diathesis occurring in critically ill patients in the medical ICU.
2. To analyze and tabulate the common etiologies of coagulopathy occurring in medical ICU patients.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

NORMAL COAGULATION CASCADE :

Coagulation of blood requires a cascade of reactions which ultimately converts fibrinogen to fibrin. The clotting factors along with calcium and phospholipids are involved in fibrin formation. Two pathways namely intrinsic and extrinsic exist which leads to a final common pathway that results in clotting of blood[3].

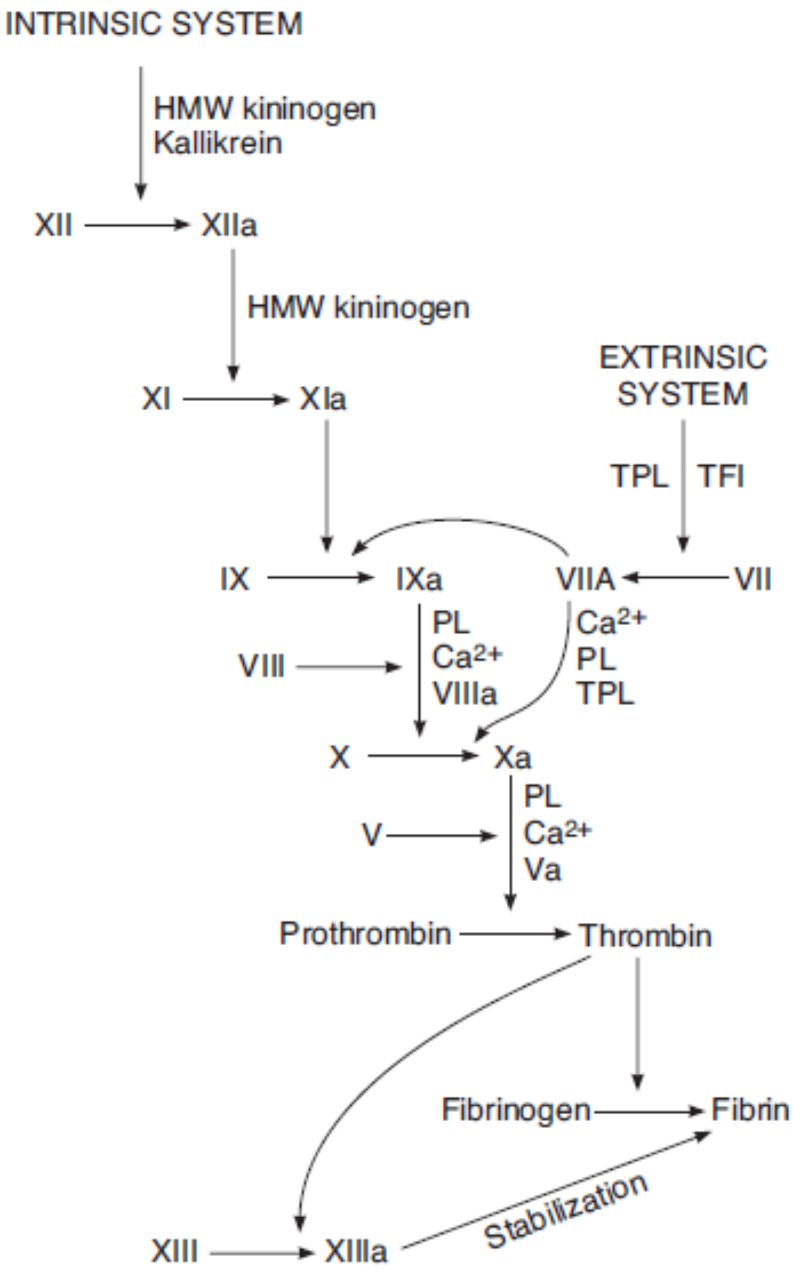
In intrinsic system, high molecular weight kininogen and kallikrein activates factor XII which activates factor XI which further activates factor IX. Activated factor IX along with factor VIII forms a complex which activates factor X. Xa along with factor V, phospholipids and calcium converts prothrombin to thrombin.

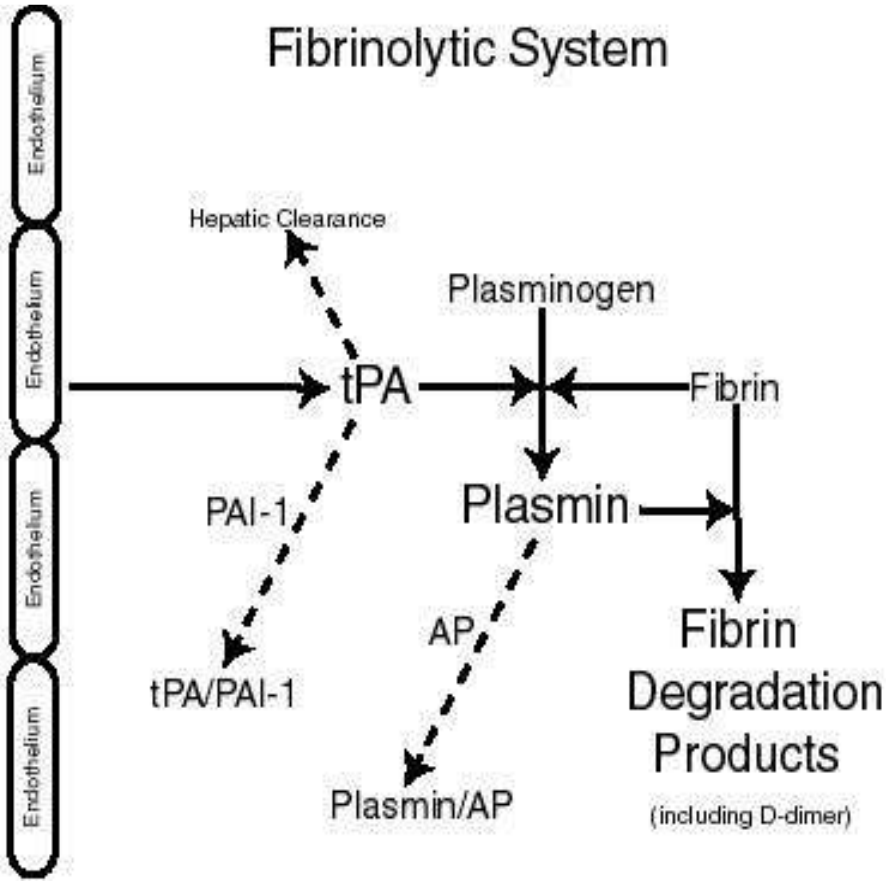
The extrinsic system involves activation of tissue thromboplastin factor which activates factor VII. VIIa activates IX and X finally joining the common pathway. The thrombin is a serine protease which catalyzes fibrinogen to fibrin[4]. Fibrin meshwork initially a loose network gets stabilized by factor XIII (Hageman factor) in the presence of calcium.

CHECKPOINTS IN COAGULATION CASCADE

- There are checkpoints for coagulation cascade which will prevent excess clot formation and also inappropriate clot formation.
- Tissue factor pathway inhibitor inhibits the extrinsic system of the coagulation cascade.
- Tissue plasminogen factor activates plasminogen to plasmin[5].
- Plasmin lyses fibrin and fibrinogen and form Fibrin Degradation Products (FDP) that inhibit thrombin.
- Antithrombin III is a protease that inhibits clotting factor activities thereby preventing clot formation. Thrombomodulin forms a complex with thrombin and activates Protein C. Protein C inactivates factor V and VIII thereby limiting clot formation[6].

Fig 1: COAGULATION CASCADE




Fibrinolytic System
Endothelium
Endothelium
Endothelium
Endothelium
Hepatic Clearance
Plasminogen
tPA
Fibrin
PAI-1
Plasmin
AP
tPA/PAI-1
Fibrin
Degradation
Products
(including D-dimer)
Plasmin/AP

DISORDERS OF HEMOSTASIS IN CRITICALLY ILL MEDICAL ICU PATIENTS

Coagulation abnormalities are very common in critically ill patients. History and clinical examination plays a major role in assessing such patients. Then comes the laboratory screening tests for hemostasis. All the lab values must be interpreted according to the clinical scenario.

For eg. decompensated chronic liver disease and Disseminated intravascular coagulation can produce same pattern of coagulopathy yet the prognosis are very different. There are many causes for derangement of coagulation in critically ill patients and the underlying disorder may require specific treatment. Hence it is vital to identify the coagulation abnormality.

The site of bleeding and its severity should be assessed first. The bleeding can be major, minor or fatal. The bleeding may follow a invasive procedure. Generally coagulation abnormalities develop after 48 hours of admission to ICU.

Coagulopathies can be clinical or subclinical (only laboratory derangement without clinical bleeding). Aggressive transfusions can lead to its own serious consequences like TRALI (Transfusion related lung injury)[7]. Drug history of the ICU patient is very important as the patient may be getting multiple medications which can cause coagulation abnormalities

BASIC SCREENING TESTS :

The commonly used screening tests are PT, aPTT and the platelet count. D dimer and fibrinogen are measured if the clinical situation demands.

aPTT:

aPTT measures the time needed to generate fibrin from beginning of the intrinsic pathway.

Technique:

Citrated plasma, phospholipid and an activating agent like kaolin are added together and incubated at room temperature. Then calcium is added and the time necessary for clumping of kaolin is noted[8]. Normally it is less than 25 to 35 seconds.

Abnormality:

This test is abnormal in factor deficiencies that are involved in both intrinsic and common pathways of coagulation cascade. If the factors are less than 30 percentage then aPTT is prolonged.

Mixing study:

Mixing study is usually done in prolonged aPTT to distinguish from factor deficiency and presence of inhibitors. Patient sample is mixed with normal plasma in ratio of 1:1 and the test is repeated[9]. If the aPTT is

corrected, there is factor deficiency. If it is prolonged it suggests presence of inhibitor like lupus anticoagulants, paraproteins etc.

Clinical significance:

It's a good screening test for factor deficiencies like factor VIII, IX, XII. These factors may be congenitally absent .Acquired causes include liver dysfunction and vitamin K deficiency. The presence of inhibitors like heparin, antithrombin III, lupus anticoagulant can prolong aPTT. Hence aPTT can be used to monitor heparin activity.

PT:

The time needed to generate fibrin after activation of extrinsic pathway and common pathway is measured by PT.

Technique:

Citrated plasma and thromboplastin are incubated at room temperature. Calcium is added and fibrin filaments are observed[10]. The normal value can vary from lab to lab. Generally it is between 12 to 15 seconds

Clinical significance:

Inherited deficiency of factor VII is rare. Acquired causes are usually the end stage liver disease and warfarin therapy. INR (International

Normalized Ratio) allows comparison between laboratories due to different thromboplastin usage.

Fig 2 : COAGULATION FACTOR ACTIVITY TESTED IN APTT IN RED AND PT IN GREEN.

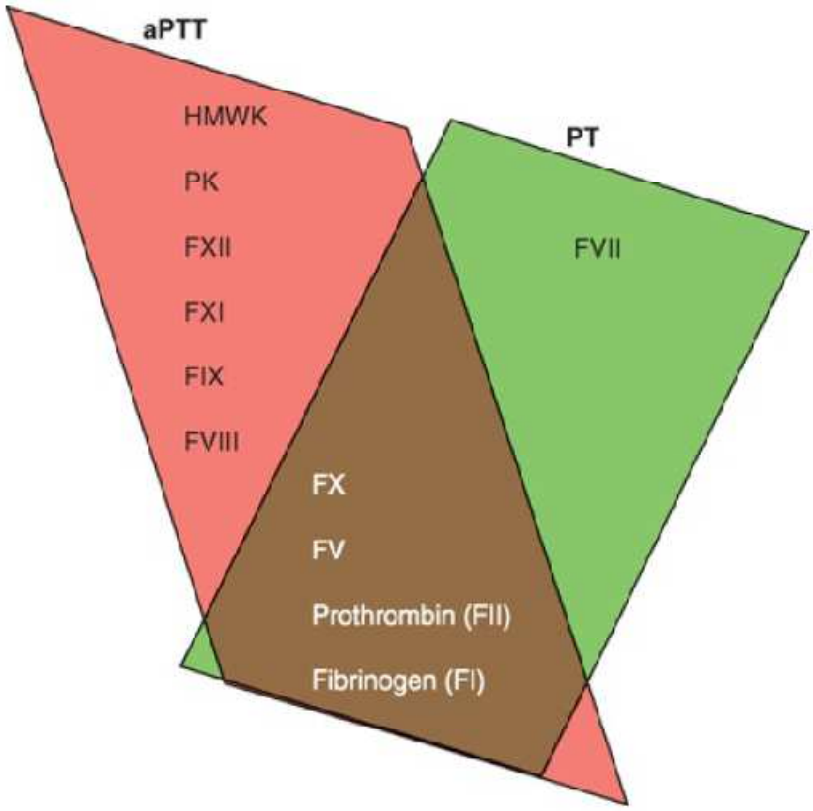


Fig 3 : ABNORMAL COAGULATION PARAMETERS

Test result	Cause
PT prolonged, aPTT normal	Factor VII deficiency
	Mild vitamin K deficiency
	Mild liver insufficiency
	Low doses of vitamin K antagonists
PT normal, aPTT prolonged	Factor VIII, IX, or XI deficiency
	Use of unfractionated heparin
	Inhibiting antibody and/or anti-phoepholipid antibody
	Factor XII or prekallikrein deficiency (no relevance for *in vivo* coagulation)
Both PT and aPTT prolonged	Factor X, V, II or fibrinogen deficiency
	Severe vitamin K deficiency
	Use of vitamin K antagonists
	Global clotting factor deficiency
	Synthesis: liver failure
	Loss: massive bleeding
	Consumption: DIC

Other tests :

Thrombin time and Reptilase time measure fibrinogen conversion to fibrin and are prolonged when there is low fibrinogen as in inherited or acquired dysfibrinogenemia. The thrombin time is affected by heparin but not the reptilase time. Anti Xa assay is used to monitor heparin or low molecular weight heparin activity.

Assessment of platelets quality and quantity:

Platelet count : Automated cell counter provides the platelet count based on size. If there is clumping the machine may take it as an RBC. Always thrombocytopenia must be confirmed by examining the peripheral smear. Bleeding time is a crude technique which do not predict bleeding risk accurately[11]. Von willebrand factor assay and platelet aggregometry are further studies than can measure platelet dependent coagulation.

Fibrinogen quantity:

Fibrinogen plays an important role in coagulation cascade. Hyperfibrinogenemia is usually implicated in chronic inflammation and atherogenesis which may cause a thrombotic state[12] . Normal value lie between 150 to 450 mg/dl.

Hypofibrinogenemia occurs in DIC, liver disease, massive transfusion (dilutional coagulopathy) and inherited disease. Hyperfibrinogenemia occurs in pregnancy, acute phase reactant and female sex.

D-Dimer :

The latex particles are coated with mouse anti-human D-dimer monoclonal antibodies. Test samples containing D-dimers when mixed with the latex particle suspension make the particles agglutinate.

The D-dimer levels are <0.5 ug/ml (expressed in FEU). The D-dimer level increases during pregnancy. It also rises with age (>70 yr). Rheumatoid factor can give false positive D- dimer. Liver disease and DIC can have increased FDP. In clinical practice, parallel measurements of FDP and D-dimer are useful for more accurate estimation of hyperfibrinolytic states[13].

D dimer is also positive in conditions like deep venous thrombosis, sepsis and pulmonary embolism. Lipemia can also interfere with D dimer measurement.

D dimer result should be interpreted along with PT, aPTT and platelet count. It is one of the FDP that is specific for fibrinolysis. 0.5 microgram /ml of D dimer suggests 1 microgram / ml of fibrinogen is cleaved.

COMMON BLEEDING DIATHESIS IN MEDICAL ICU PATIENTS

Thrombocytopenia :

It is the most common coagulation abnormality that occurs in critically ill patients. Thrombocytopenia can be due to decreased production or increased destruction or sequestration. Incidence varies from 20 to 60 % depending upon the cut off value[14].

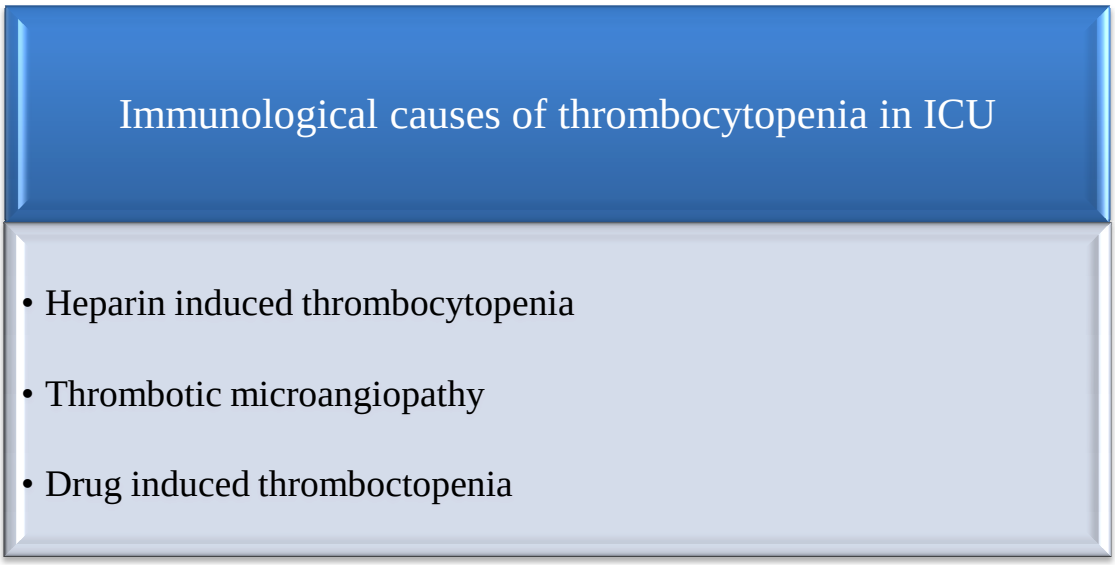
Platelets are the first line of defense when endothelium is breached. Highest incidence occurs in cases of sepsis. Usual cut off value is less than 1,50,000 cells/cu.mm. But in critically ill patients thrombocytopenia can defined as count less than 1,00,000 cells/cu.mm. Etiology is usually multifactorial in critically ill patients[15].

First and foremost problem is spurious thrombocytopenia which should be ruled out before evaluating any patient with thrombocytopenia. EDTA antibodies can cause clumping and hence we may get a low count. Such sample should be repeated with citrate anticoagulant. Always confirm thrombocytopenia by looking at the peripheral smear.

ICU patients with thrombocytopenia have poor prognosis when compared with patients who have normal platelet counts. It is not necessary to treat all patients with thrombocytopenia. At the same time we should not miss serious conditions like heparin induced thrombocytopenia and thrombotic microangiopathy. Each condition needs different treatment modalities.

Current studies state that if patient is hemostatically stable and has thrombocytopenia, platelet transfusion can be withheld till the count drops less than 10,000 cells/cu.mm. If the patient is actively bleeding platelet count should be maintained above 50,000cells/cu.mm. For neurosurgical procedures count should be maintained above 1,00,000 cells/cu.mm.

Immunological causes : 3 major causes are heparin induced thrombocytopenia, thrombotic microangiopathy and drug induced.



HIT is a life threatening complication and the incidence is around 2 to 3 %. Heparin forms complex with platelet factor 4 antibody which binds and activates platelets thereby causing thrombosis and thrombocytopenia. Thrombosis can be arterial, venous or both[16] .Platelets start to fall after five days of heparin. Platelet count starts to improve after 4 to 14 days of discontinuation of heparin.

Patient who are supposed to receive heparin should have a baseline platelet count. Incidence of HIT is higher in surgical than medical patients. Standard assays for HIT are Serotonin Release Assay (SRA) and The Heparin Induced Platelet Activation Assay (HIPA) [17].

Manifestations of HIT
• Pulmonary embolism • Deep vein thrombosis • Arterial thrombosis, acute coronary syndrome, Stroke • Peripheral arterial disease • Adrenal haemorrhage • Venous limb gangrene

Diagnosis of HIT is not straight forward. It is a clinico pathologic diagnosis along with test positive for PF4 antibodies.

Four factors helpful in diagnosis of HIT
• The degree of thrombocytopenia • The timing of the platelet fall • Presence of thrombosis • Presence of other causes of thrombocytopenia

4 ‘T’ assessment of HIT

Category	2 Point	1 Point	0 Point
Thrombocytopenia	- > 50% fall or - Nadir 20-100 x10 / L	- 30-50% fall - Nadir 10-19 x 10 /L	- < 30% fall - Nadir < 10 x 10 / L
Timing of platelet fall	- 5-10 days - ≤ 1 day if recent - History of exposure within past 30 days	- > 10 days - ≤ day with P/H heparin 31-100 days	- ≤ 1 day with no past history of heparin
Presence of thrombosis or other rare specific sequelae	Proven thrombosis Skin Necrosis Ac systemic reaction after IV heparin bolus	Progressive / silent thrombosis Erythrematous lesions	None
Presence of other causes of thrombocytopenia	None	Possible	Definitive

Possibility of HIT	Total Points
High	6-8
Intermediate	4-6
Low	0-3

When to suspect?

If the platelet count falls by thirty percent or more and if the patient has new episodes of thrombosis or skin lesion between 4 and 14 days of heparin administration HIT should be suspected and patient should be clinically assessed.

Difference between type 1 and type 2 HIT

	Type I	Type II
Frequency	10-20%	2-3%
Nadir Platelet/cmm	1,00,000	50,000
Timing of onset	1-3 days	5-10days
Antibody mediated	None	HIT antibody (IgG-HeparinPF4)
Bleeding	NIL	Rare
Thrombosis	NIL	30-50%
Treatment	NIL	Stop Heparin and use nonheparin anticoagulants
Danger to life	None	Serious complications endanger life

Management of HIT:

- Stop all heparin including low molecular weight and anti Xa.
- Do not give platelet transfusion.
- Use direct thrombin inhibitors like argatroban, lepirudin and add warfarin when platelet count is above 1lakh cells/cu.mm and also when adequate INR is obtained.

DRUG INDUCED THROMOCYTOPENIA

The problem in diagnosing DITP is we often mistake it as immune thrombocytopenic purpura and also patient may not reveal that he/she is taking herbal medicines which would have been the actual etiology.

Pathogenesis :

DITP can cause life threatening bleeding tendency and many times it goes unrecognized. The drug dependent antibodies are formed only in the presence of sensitizing drugs. The drug binds platelet epitope on one side and drug dependent antibody on other side thus creating a sandwich. Therefore there is thrombocytopenia and hence the bleeding tendency. Moreover the platelets improve when the drug is glycoprotein 2b/3a or Ib[18].

DITP should be suspected when there is unusual occurrence of thrombocytopenia and also when a patient presents with recurrent thrombocytopenia often recovering well in between. Commonest mistake is diagnosing such people as immune thrombocytopenic purpura.

CRITERIA FOR DIAGNOSING DITP

1. Drug administration preceded thrombocytopenia; recovery from thrombocytopenia complete and sustained after drug discontinued
2. Other drugs administered prior to thrombocytopenia were continued or reintroduced after discontinuation of the suspected drug
3. Other etiologies of thrombocytopenia excluded
4. Re-exposure to the drug resulted in recurrent thrombocytopenia

Levels of evidence

1. Definite: all 4 criteria met
2. Probable: Criteria 1-3 met
3. Possible: Criterion 1 met
4. Unlikely: Criterion 1 not met

DITP (common drugs)

- Vancomycin, Rifampin
- Diclofenac
- Ranitidine
- Abciximab, eptifibatide
- Carbamazepine
- Hydrochlrothiazide, methyl dopa

Log on to the following website for DITP database www.ouhsc.edu/platelets Drug dependent antibodies assay are not specific and are not available widely[19]. Hence the diagnosis is based on clinical circumstances.

Management:

- Stop the suspected drug that caused thrombocytopenia
- If clinical bleeding occurs maintain platelet count more than fifty thousand cells/cu.mm
- Drug dependent antibodies can persist lifelong hence patient should avoid the drug indefinitely
- Corticosteroids should be stopped when DITP is confirmed[20].

As a physician we should report the experience to the FDA adverse event reporting system. It will also help to construct the database for the future.

DITP should be suspected whenever there is an unusual occurrence of thrombocytopenia. In ICU it is even more difficult to diagnose as the etiology can be multifactorial. The management can be as simple as stopping the offending drug or beverage or herb.

THROMBOTIC MICROANGIOPATHIES (TMA)

TMA is a group of disorders characterized by microvascular thrombosis.

TMA includes acquired Thrombotic Thrombocytopenic purpura (TTP), congenital TTP, Hemolytic uremic syndrome and secondary thrombotic angiopathy.

The first case was reported by Eli Moschowitz in a sixteen year old girl who presented with fever, anemia, albuminuria. She subsequently died and on post mortem her renal vessels showed hyaline thrombi. TMA preferably affects central nervous system and kidneys.

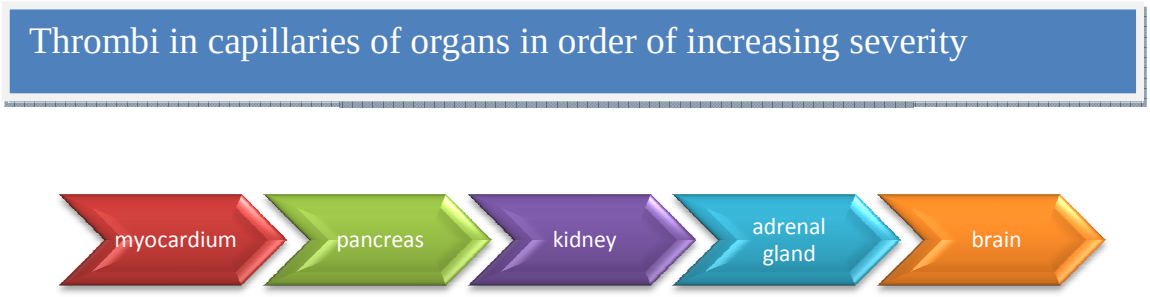
Hemolytic Uremic syndrome (HUS) was identified in children who developed renal failure following a diarrheal illness. But HUS patients recovered well and didn't have the same course of TTP[21].

TTP pentad includes renal failure, microangiopathic hemolytic anemia, CNS involvement, fever and thrombocytopenia. TTP was largely described in females in the age group 10 to 39 years.

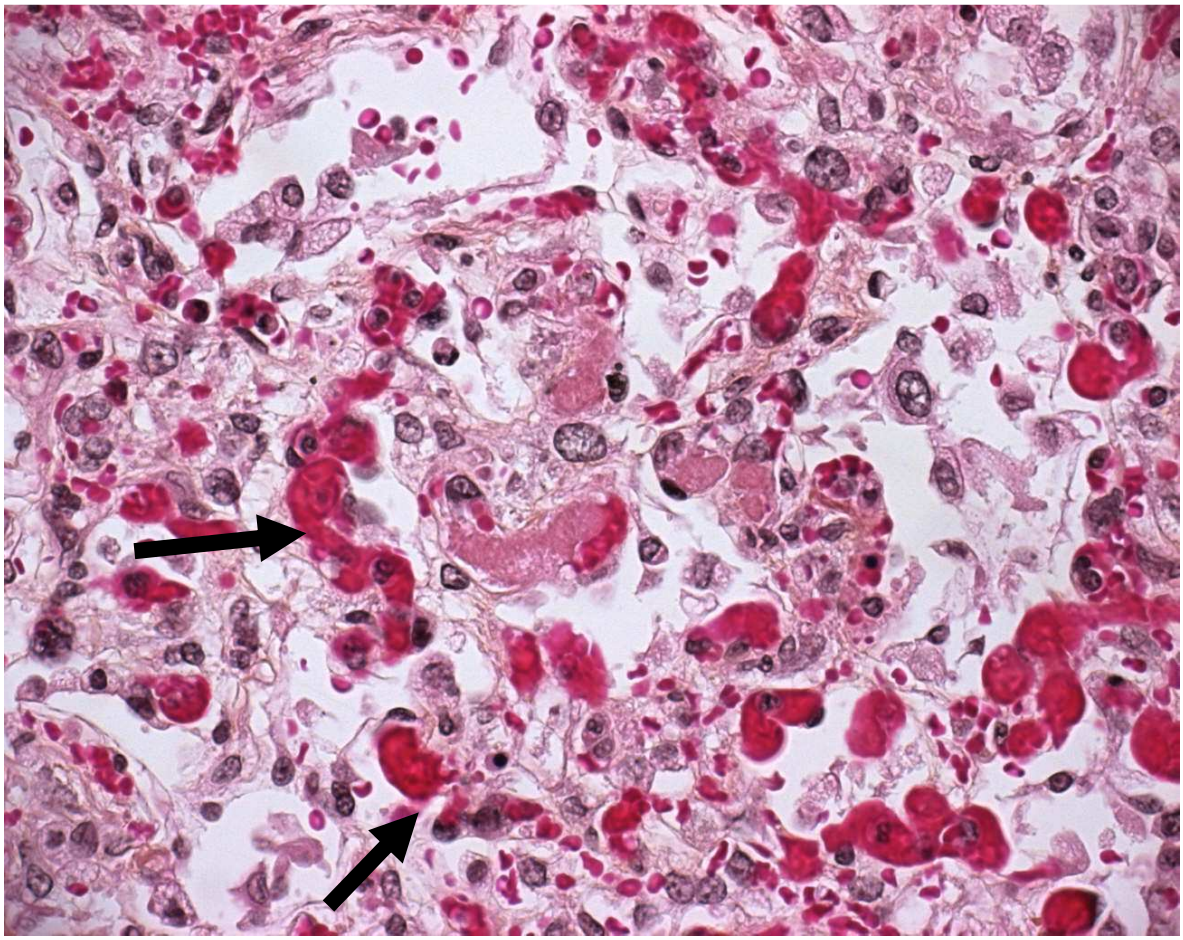
Pathogenesis:

ADAMTS13 is a metalloprotease that is necessary to cleave Von Willebrand factor (VWF). Large VWF multimers promotes intravascular platelet aggregation and microvascular thrombosis[22]. IgG autoantibodies against ADAMTS13 in these patients prevent the depolymerase activity. Plasma exchange is known to supply the enzyme which forms the basis of treatment.

SEVERE SEPSIS HAS FOUND TO DECREASE ADAMTS13 LEVELS



RENAL MICROVASCULATURE SHOWING INTRAVASCULAR THROMBI



Liver and lungs are relatively spared. Any organ can be involved.

Incidence of TTP is common in age groups 30 to 50 years. Male to female ratio is 1:2. Obesity , heredity and African ancestry are risk factors for TTP.

Clinical presentation:

Onset can be acute or insidious. CNS involvement includes headache, seizures, hemiparesis, lethargy, confusion, coma and other focal deficits.

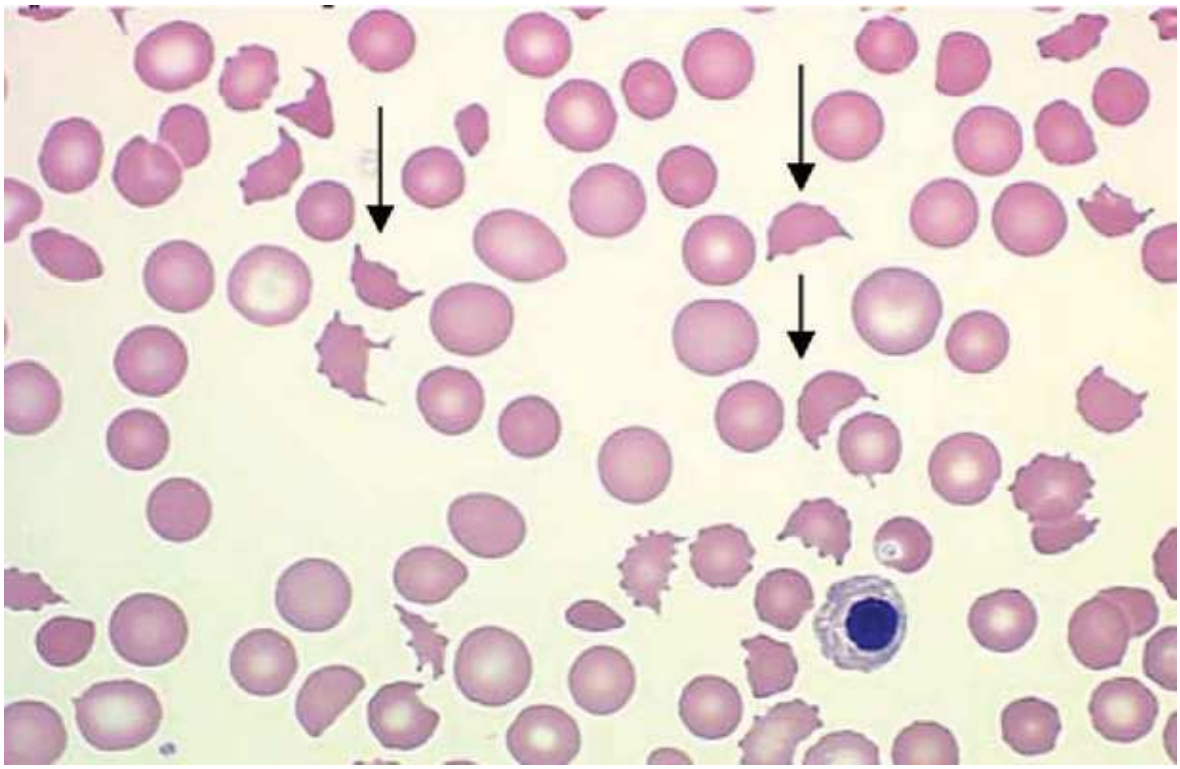
Bleeding tendencies include petechiae and purpura. Organ bleeding can occur.

Acute renal failure occurs in 1/3rd of cases. 1/3rd will present with hemolytic anemia. Pancreatitis, heart failure and myocardial infarction can occur. 1/5th can have hepatosplenomegaly.

Laboratory evaluation :

Anemia of hemoglobin <5 g/dl is seen in 1/3rd of cases. LDH values are increased with usual value around 1200 IU/ml. serum haptoglobin is reduced. Direct coombs test is negative in most of the cases. Peripheral smear shows schistocytes apart from thrombocytopenia. Platelet count is around 20,000 cells/cu.mm in half the patients. ADAMTS13 activity can be measured in citrated plasma[23].

Peripheral smear in TTP showing schistocytes



Differential diagnosis

- Congenital TTP (Upshaw-Schulman Syndrome)
- TTP With acquired ADAMTS13 deficiency
- Secondary thrombotic microangiopathy
- Tissue transplant associated
- Cancer (erythroleukemia, metastatic carcinoma)
- Pregnancy associated (HELLP, eclampsia)
- Autoimmune disorders (SLE, APLA)
- Drugs (ticlopidine)
- Hemolytic uremic syndrome

PLAN OF MANAGEMENT

- Glucocorticoids (prednisone 2 mg/kg per day)
- Plasma exchange 1.5 volumes /day
- Plasma infusion 15–30 mL/kg if plasma exchange is delayed more than 12 hours.
- After platelet count exceeds 50,000/L, give aspirin 80 mg/day and routine thromboprophylaxis (e.g., low-molecular-weight heparin)
- Continue until complete response for 3 days (platelets >150,000/L, LDH normal), then decrease plasma exchange to every other day for two more treatments and stop.
- If response is durable, taper steroids

MONITORING IN TTP

- Monitoring:Neurologic status,Hemoglobin and platelet count , Blood film for schistocytes , LDH , Serum electrolytes, calcium, blood urea nitrogen (BUN), creatinine, ECG, cardiac enzymes
- Common complications: Cardiac arrhythmias, infarction , Catheter-associated bleeding or thrombosis ,Citrate toxicity (hypocalcemia, alkalosis) and Minor allergic reactions to plasma

SEPSIS RELATED COAGULOPATHY

Sepsis related coagulopathy can vary from mild laboratory abnormality in the coagulation parameters to Disseminated Intravascular coagulation (DIC) [24]. There is a complex interplay between hemostatic mechanisms that can either lead to a bleeding tendency or can also present with thrombosis. Development of DIC is a poor outcome predictor of sepsis.

How coagulation system is activated in DIC due to sepsis?

The tissue factor dependent pathway is the trigger for activation of coagulation pathway . The pro inflammatory cytokines exaggerated by monocytes and macrophages upregulate the tissue factor thus leading to activation of coagulation system.

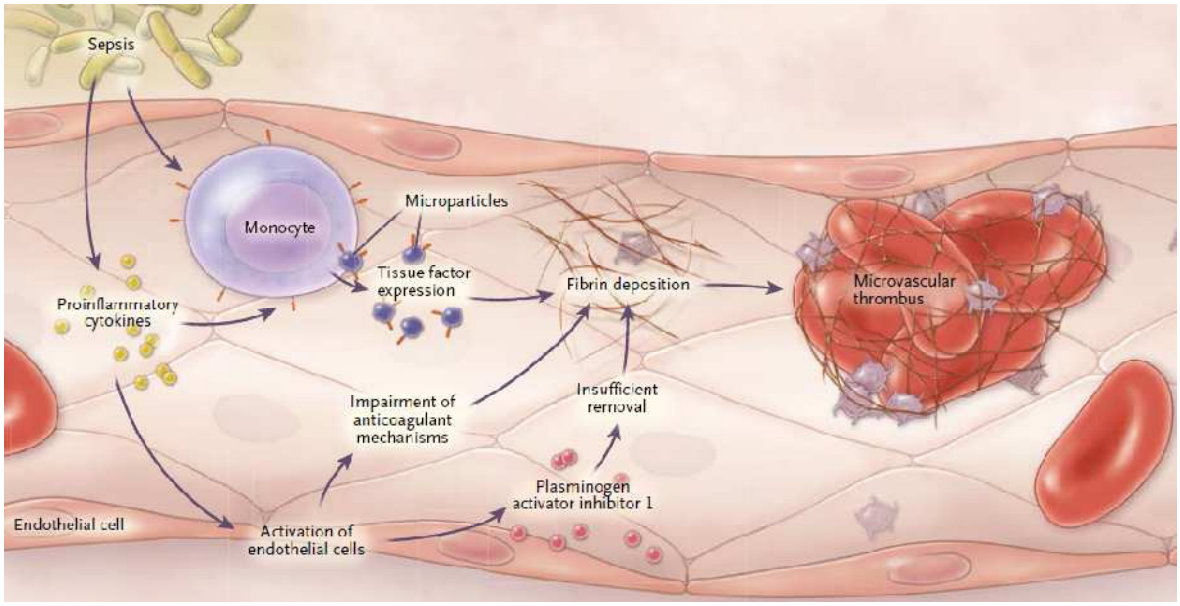


Figure showing activation of coagulation system in sepsis DIC

Dysfunctional anticoagulant pathway	Dysfunctional fibrinolytic system	Platelet activation
• Lower levels of anti thrombin III • Lower levels of protein C and S	• Release of plasminogen activator inhibitor type 1 causing a procoagulant situation	• Platelet are activated directly by endotoxins • Activated platelets provide scaffold for the assembly of coagulation complexes

Treatment for sepsis induced Coagulopathy:

Fresh frozen plasma (FFP) :

FFP is usually indicated in septic patients with active bleeding. No role of prophylaxis[25]

Factor concentrates and fibrinogen:

It is usually indicated in septic patients with active bleeding and specific coagulation factor deficiencies. No role of prophylaxis.

Platelets :

Platelets should be transfused in patients with platelet count of less than fifty thousand cells/ cu.mm with active bleeding. If the patient is not bleeding then a threshold of upto 10 to 20 $*10^3$ can be allowed before transfusion.

Vitamin K :

Vitamin K can be given parenterally 10 mg for 3 days in cases of relative deficiency.

Heparin :

If the patient has less risk of bleeding it can be used in purpura fulminans and as a prophylaxis for deep venous thrombosis (DVT).

Protein C concentrate has been tried in pediatric population. Results awaited.

Antithrombin:

In case of severe deficiency antithrombin is given. It is not recommended for Prophylaxis.

Management of sepsis related coagulopathy should consider combination therapies targeting inhibition of Tissue Factor activated coagulation in combined with restoration of anticoagulant pathways, as well as cytokines removal.

LIVER DISEASE AND COAGULOPATHY

Decompensated chronic liver disease is usually thought as a hemorrhagic coagulopathy. These patients generally have abnormal coagulation tests. If PT is prolonged more than 3 seconds from control certain procedures like liver biopsy or surgery cannot be performed.

COAGULATION SYSTEM :

Coagulation system in liver disease is complex. It is a dynamic process of hemostasis. There is decreased production of factors II, V, VI, IX, X, XI, XIII, fibrinogen, protein C, protein S and vitamin K. Hence there is a decrease in both pro coagulant and anticoagulant proteins. It is also a hyperfibrinolytic state. Increased FDP and thrombocytopenia occur. Test results may be suggestive of a bleeding tendency. The hemostatic balance can be tipped off either way by precipitating factors like renal failure, infections etc[26].

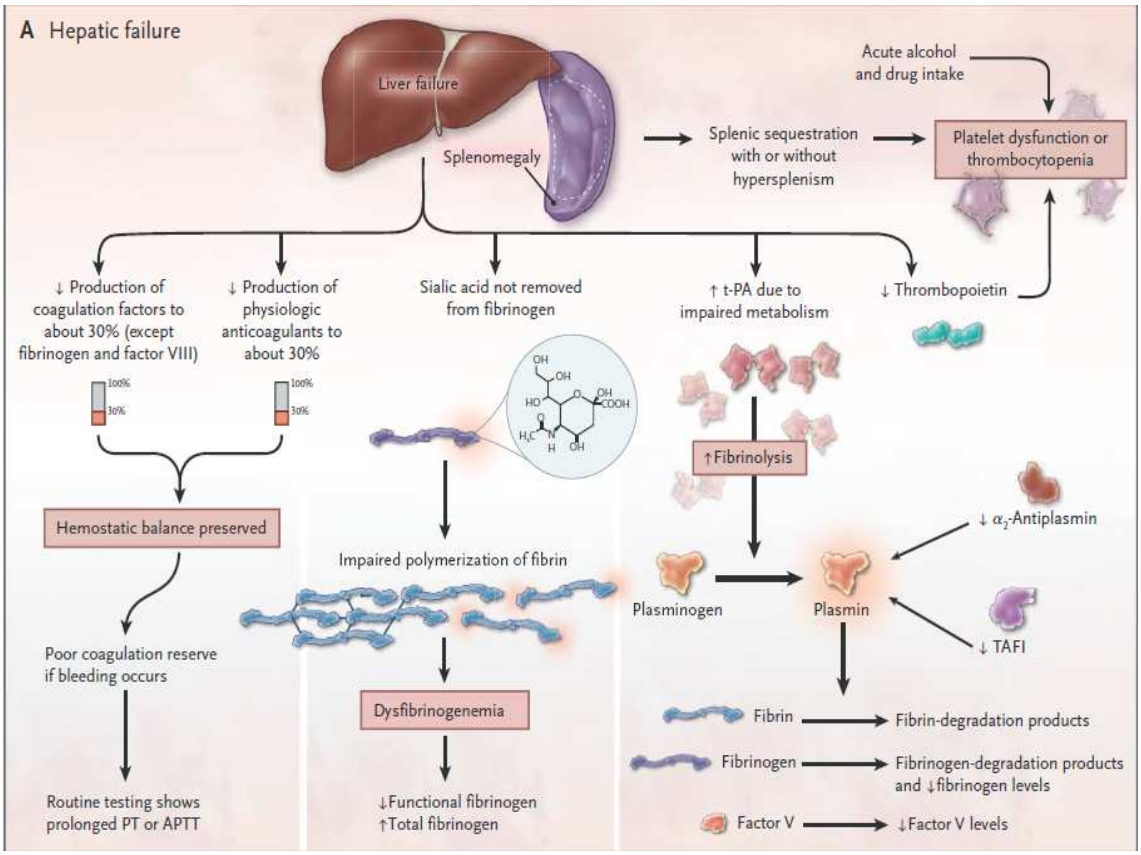


Figure showing the coagulation abnormalities in liver disease

THROMBOCYTOPENIA IN LIVER DISEASE:

Thrombocytopenia can be due to myelosuppression (Hepatitis c virus infection, thrombopoeitin deficiency, ethanol direct toxicity, low grade DIC auto antibodies, folate deficiency), platelet sequestration.

TEST FOR ASSESSING CAOGULOPATHY IN DCLD:

INR liver , thromboelastogram , thrombin generation time are more accurate in assessing global hemostasis rather than the conventional tests. But still PT is used in Child Pugh scoring and INR is used in MELD scoring[27].

MANAGEMENT :

10 mg parenteral vitamin K can given for 3 days for DCLD patients routinely. FFP should not be given routinely to DCLD patients who have abnormal coagulation parameters in the absence of clinical bleeding.

Hazards of unnecessary transfusion include Transfusion Related Lung Injury (TRALI), volume overload, increase in portal hypertension and risk of allergic reactions.

Table showing management options in coagulopathy due to liver disease

Therapy	Usage	Comment
RBC transfusion	Bleeding patients	Target Hb 7 to 8g/dl
Vitamin K	Every patient	May not be useful if patient has no deficiency
Fresh frozen plasma	doubtful in bleeding patients	May be used in bleeding patients when volume expansion is not an issue
Platelets	Count less than 50,000	Limited data
Cryoprecipitate	In patients who bleed	Limited data
Prothrombin complex concentrate	In patients who bleed	Limited data
Desmopressin	In patients who bleed	Efficacy unproved
Aprotinin, tranexamic acid, and epsilon amino caprioic acid	Patients with hypofibrinogenemia Fibrinogen less than 100mg/dL	Can induce thrombosis
Recombinant factor VII	In placing ICP devices, bleeding after surgery, massive variceal bleed	Can induce thrombosis

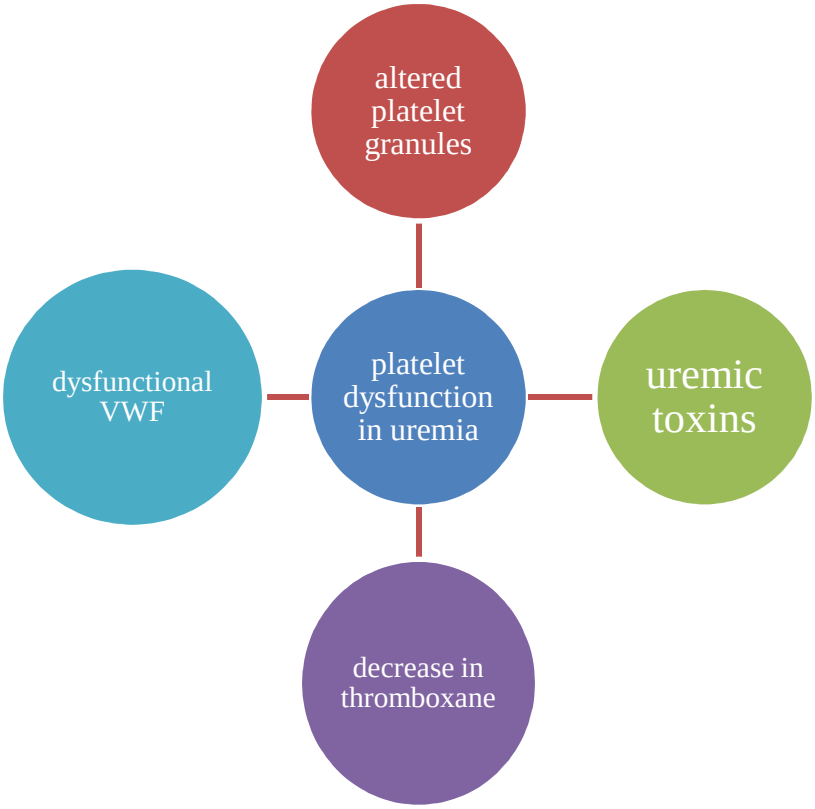
To conclude , hemostasis in patients with DCLD is a complex issue with opposing forces which are in dynamic equilibrium and are affected by external factors like infection and renal failure. Currently, available tests for hemostasis have a poor predictability for bleeding or thrombosis in patients with DCLD. New tests like Thromboelastogram , thrombin tests may give a better idea but need prospective studies. But still conventional tests like PT, INR are in use for evaluating the severity of the disease[28].

The role of specific interventions like antifibrinolytics, platelet transfusion and recombinant factors, anticoagulant usage need to be defined clearly.

Note : The INR liver is PT calibrated using plasma from patients with DCLD instead of vitamin K antagonists like acitrom and may resolve variability of INR in these patients.

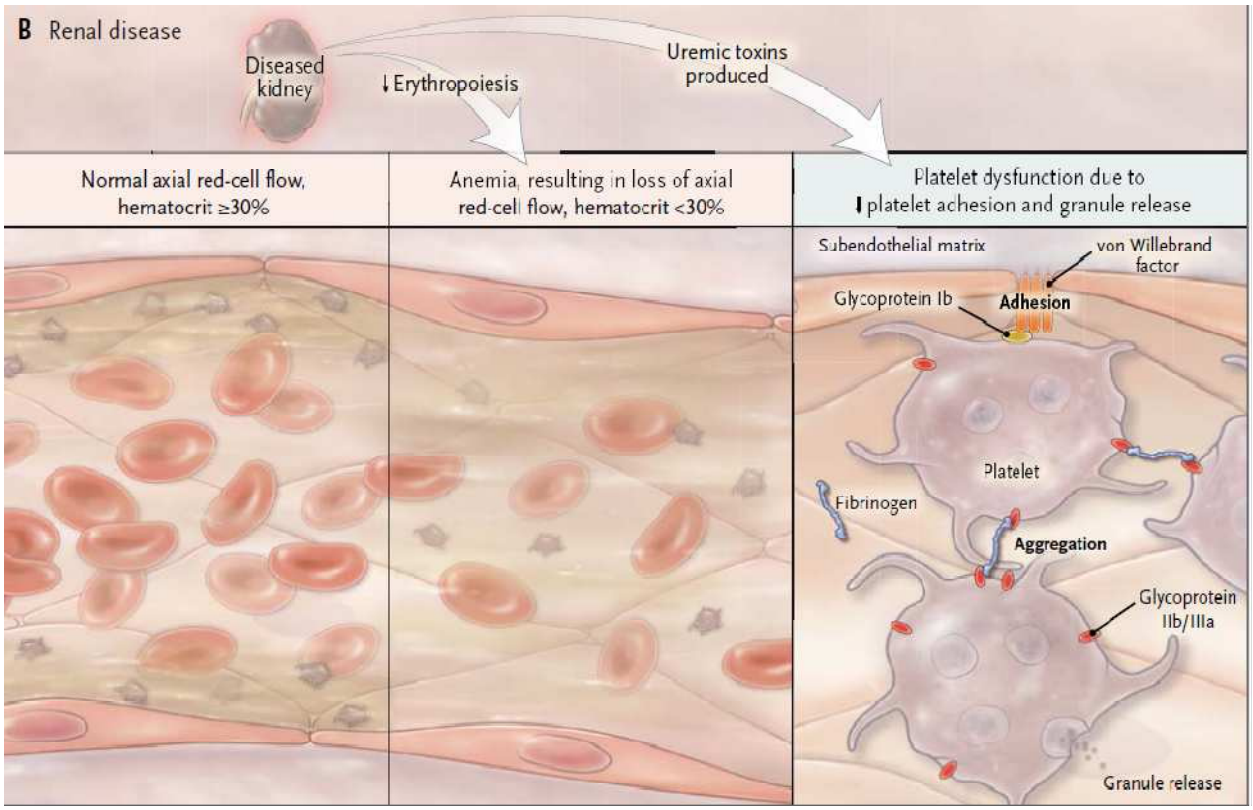
COAGULOPATHY IN RENAL DISEASE

Usual clinical manifestations would be epistaxis, petechiae and bleeding from local site.



Peritoneal dialysis, conjugated estrogen, desmopressin, erythropoietin are all useful for improving bleeding time

UREMIA AND ITS EFFECTS ON PLATELETS



In anemia when the hematocrit falls below 30 there is loss of laminar flow (where the RBC will be in central portion and platelets along the endothelium normally).

Now the platelets are no longer easily available to the endothelium for formation of platelet plug. Hence there is prolongation of bleeding time.

Estrogens decrease synthesis of L-arginine, which is a precursor of NO, resulting in decreased production of cyclic GMP as well as an increased production of thromboxane A2, and ADP which is crucial for the formation of platelet plugs.

They may also decrease protein S and antithrombin and enhance factor VII.

The dose of conjugated estrogens necessary to improve bleeding time and clinical bleeding in uremia is 0.6 mg/kg i.v during 30 minutes O.D for 5 consecutive days

COMMON ANTITHROMBOTIC DRUGS USED IN ICU

ASPIRIN:

It is an antiplatelet drug that irreversibly inhibit cyclooxygenase enzyme. Its effect can persist up to days even though the half life is 20 mins. Platelet transfusion is the procedure for immediate reversal [29].

CLOPIDOGREL:

It is a $P2Y_{12}$ antagonist that is metabolized by the liver and has a half life of six to fifteen hours. Platelet transfusion is the procedure for immediate reversal.

UNFRACTIONATED HEPARIN:

It has indirect anti Xa and anti IIa effect. It also increases the action of antithrombin by a factor of 10,000. Its half life is forty five to ninety minutes. Protamine at a dose of 1 mg neutralizes 100 units of unfractionated heparin.

LOW MOLECULAR WEIGHT HEPARIN:

Action is same as unfractionated heparin but mainly Xa effect. It is cleared by the kidneys and half life is around 4 hours. Protamine neutralizes sixty percent of its effect. In case of life threatening bleeding use recombinant factor VII.

DANAPAROID:

A heparinoid with a ratio of anti Xa to anti IIa of >20. It is excreted by the kidneys. No specific antidote available . Half life is 24 hours.

FONDAPARINUX:

It is a synthetic pentasaccharide with indirect anti Xa effect. It is eliminated by kidneys and has a half life of 17 to 20 hours. No specific antidote available

BIVALIRUDIN:

It has direct antithrombin effect and commonly used in interventional cardiac procedures. It is short acting (24 min). No specific antidote available.

ARGATROBAN:

It is a direct thrombin inhibitor which has a half life of 44 min and is metabolized by the liver. No specific antidote available.

VITAMIN K ANTAGONISTS (VKA):

It reduces functional levels of vit K dependent clotting factors (2,7,9,10). It is metabolized by the liver. Antidotes are vit K parenteral and prothrombin complex concentrates. If prothrombin complex concentrates are not available use FFP.

DABIGATRAN:

It is a direct thrombin inhibitor and excreted by the kidneys. Half life is around 13 hours. No specific antidote available. In case of life threatening bleeding use recombinant factor VII.

RIVAROXABAN, APIXABAN, EDOXABAN:

These are direct anti Xa inhibitors. Undergoes both hepatic and renal metabolism. No specific antidote available.

DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

Definition :

Disseminated intravascular coagulation (DIC) is a clinic pathologic syndrome in which extensive intravascular coagulation occurs as a result of exposure or production of procoagulants inadequately balanced by natural anticoagulant mechanisms and intrinsic fibrinolysis.

Disturbance of the endothelium in the microcirculation along with inflammatory cells and release of inflammatory cytokines play a key role in the mechanism of DIC.

Diffuse multiple organ bleeding, hemorrhagic necrosis, and thrombus in large and medium blood vessels and microthrombi in small blood vessels are common findings at post mortem.

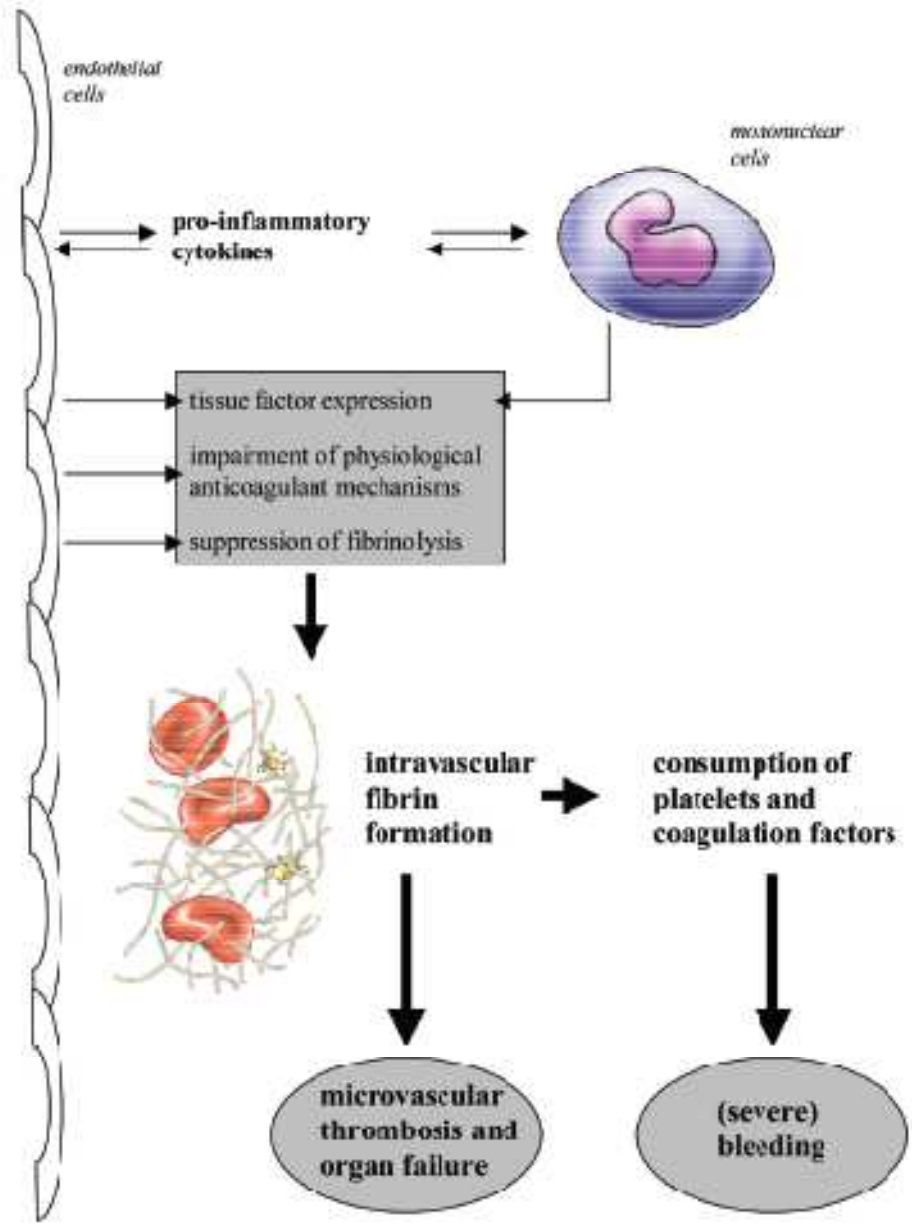


Figure showing activation of coagulation in DIC

Clinical conditions that complicate DIC

- Malignancy
- Trauma
- Sepsis
- Obstetric complications (Abruptio placentae, HELLP syndrome)
- Transfusion reactions

ORGAN DYSFUNCTION ASSOCIATED WITH DIC	
Adrenals	Hemorrhagic necrosis
CNS	Coma, convulsions
GIT	Bleeding, intestinal ischemia
Lungs	ARDS
Liver	Hepatic failure, jaundice
Renal	AKI, acute cortical necrosis
CVS	Shock, infarction
Skin	Purpura, bleeding from injury sites

LABORATORY FINDINGS IN DIC

Test	Abnormality
Platelet count	Decreased
Prothrombin time	Prolonged
aPTT	Prolonged
Fibrin degradation products	Elevated
Protease inhibitors (e.g., protein C, AT, protein S)	Decreased

DIC SCORING SYSTEM

Definition of the scoring system for disseminated intravascular coagulation (DIC) as suggested by the International Society of Thrombosis and Haemostasis (5)

Points	0	1	2	3
Platelet, count/nL	>100	≥50	<50	
D-dimer, μg/mL	≤1.0		1.0–5.0	>5.0
Fibrinogen, g/L	>1.0	≤1.0		
Prothrombin index, %	>70	40–70	<40	

The score ranges from 0 to 8 points. A scoring system for DIC of ≥5 points is compatible with overt DIC.

Purpura Fulminans:

Purpura fulminans is a severe, lethal form of DIC in which vast areas of the skin over the extremities and buttocks undergo hemorrhagic necrosis. The disease affects children predominantly and occasionally adults[30].

Diffuse microthrombi in small blood vessels and necrosis are present in biopsies of skin lesions. Onset can be within 2 to 4 weeks of a mild infection like scarlet fever, or rubella, or can occur during an acute infection in patients with acquired or hereditary thrombophilias affecting the protein C pathway.

Patients affected by purpura fulminans are sick with fever, hypotension, and bleeding from multiple sites and they usually have typical laboratory abnormalities of DIC.

MANAGEMENT OF DIC

First and foremost thing in DIC is to treat underlying disorder. For example in sepsis antibiotics must be directed against the organisms responsible for sepsis Intensive support of vital functions is needed.

Adequate Volume replacement and correction of low perfusion state, acidosis, and oxygenation may improve blood flow and oxygen delivery to the circulation.

Organ support measures like hemodialysis in AKI and ventilator for respiratory failure are necessary if the patient develops multi organ failure. Vitals, renal and liver function must be monitored periodically.

BLOOD COMPONENT THERAPY:

The past concept that transfusion can worsen DIC is outdated. Now it is rational to give platelet transfusion, cryoprecipitate, Fresh Frozen plasma or prothrombin complex concentrate in a patient who is actively bleeding.

Role of heparin in DIC is still controversial. Anti fibrinolytics like tranexamic acid has increased the risk of thrombosis and hence they are not recommended routinely [31].

Antithrombin III has been beneficial in small clinical trials but not yet approved for usage. Recombinant Activated Protein C (APC) has been licensed in many countries for its usage in sepsis with organ failure. Most frequent side effect of APC is bleeding.

MEDICAL MANAGEMENT OF BLEEDING IN THE CRITICALLY ILL

Points to note:

1. Dilutional anemia can occur if there is a massive transfusion . Hence it is better to follow restrictive strategy.
2. Hypothermia impairs coagulation. There is a 33% reduction in clotting factor activity at temperatures less than 33 degree celcius.
3. Acidemia can reduce activity of factor II and VII as well as depress platelet function

DESMOPRESSIN:

Synthetic analogue of anti diuretic hormone. It releases VWF from endothelial storage sites. Dosage is 0.3 microgram/kg. It lacks vasoconstrictive activity[32]. Transient headache, flushing can occur.

FRESH FROZEN PLASMA:

FFP is prepared by centrifugation method and then treated with a solvent to inactivate lipid coated viruses like hepatitis C, B. Average volume of FFP 1 unit is equal to 200 ml. Risk of TRALI is less with solvent treated FFP

FFP is used to replace clotting factor deficiencies either single or multiple factors. FFP is also used in TTP for plasma exchange. Clotting factors must reduce by 30% to cause clinical bleeding. Four units of FFP will increase the clotting factors by 10 %.

CRYOPRECIPITATE:

The following components are the major constituents in cryoprecipitate

1. Factors VIII and XIII
2. VWF
3. Fibronectin
4. Fibrinogen

1 unit contains 70 IU/ml of factor VIII and 140 mf of fibrinogen. Recommended if the bleeding is due to hypofibrinogenemia and for hemophilia if factor VIII not available. ABO compatibility is not essential.

FIBRINOGEN:

Minimum fibrinogen level required for hemostasis is 0.75 g per litre. Commercial fibrinogen preparations are not available in most of the countries.

CRYOSUPERNATANT:

Supernatant plasma separated during cryoprecipitate preparation. It has VWF, factor XIII and fibronection. It is low in fibrinogen and factor VIII.

PLATELETS:

Platelet transfusions are indicated to maintain desired platelet count according to the clinical setting. For e.g CNS surgeries require minimum platelet count of 1 lakh cell/cu.mm.

One single donor platelet is equal to 4 to 6 random pooled donors. Platelet concentrates are slightly acidic and volume varies from 150-300 ml.

Platelets are contraindicated in TTP and HIT. One unit of platelet raises the count by 20,000 cells. Splenic sequestration can produce different results. It is usually given over a period of 30 mins using a standard intravenous set.

ANTIFIBRINOLYTICS:

They act by inhibiting serine proteases like plasmin by reducing conversion of plasminogen to plasmin, preventing plasmin binding, and displacing it from the developing clot.

Aprotinin is more effective when used prophylactically and can decrease the bloodloss during major surgeries associated with massive blood loss ,especially in cardiothoracic surgeries.

Aprotinin is given at dose of 14 mg and is quickly excreted. Therefore continuous infusion should be maintained.

LYSINE ANALOGUES:

Amino caproic acid and tranexamic acid are the lysine analogues that bind to plasminogen as it has five binding sites.

Aminocaproic acid half life is short and given in dose of 5 g i.v loading over 1 hour and then 1 to 2 g every hour till bleeding stops. There is lesser risk of anaphylaxis.

Tranexamic acid at a dose of 10 mg /kg inhibits fibrinolysis (better than aminocaproic acid) and has been used to reduce bleeding after tonsillectomy, prostate surgery and severe menorrhagia.

COAGULATION FACTOR CONCENTRATES

Coagulation factor concentrates include Factor XIII, and Factor VIIa, prothrombin complexes. They are commonly indicated in trauma, liver disease, and any oral anticoagulant toxicity.

They provide a rapid and easy method of improving Coagulation stability without the hazard of FFP transfusion, volume load, or infections. At a dose of 30 IU/ kg i.v prothrombin complex concentrate reversed coagulation deficiencies completely[33].

Recombinant Factor VIIa is approved for the management of Coagulopathy with inhibitors to factors VIII or IX, but also effective in patients with injury, thrombocytopenia, and oral anticoagulants overdose.

MATERIALS AND METHODS

MATERIALS AND METHODS

The study was conducted in Intensive Medical Care Unit (IMCU), Institute of Internal Medicine, Madras Medical College, Rajiv Gandhi Government General Hospital, Chennai-600003 during the period between March 2014 and August 2014.

The laboratory work was done with the help of the hematology department , MMC & RGGGH .

50 patients were studied who were admitted in IMCU , IIM, RGGGH . a patient is said to have a coagulopathy if he/she has either one or combination of following abnormalities

1. Thrombocytopenia (less than 1 lakh cells/cu.mm)

2. Prolonged PT

3. Prolonged aPTT

INCLUSION CRITERIA:

1. Patients with any medical illness admitted to ICU who do not have primary hematological disease at the time of admission.

2. Patient should have been in ICU for a minimum of 48 hours.

EXCLUSION CRITERIA:

1. Patients who have already known hematological disease
2. Surgical ICU patients (e.g trauma patients)

Patients have their history taken according to the Questionnaire and subjected to clinical examination and investigations.

The following tests of hemostasis are done only once.

1) Platelet count and peripheral smear

2) PT (Prothrombin time)

3) aPTT (activated Partial Thromboplastin Time)

4) Fibrinogen

5) D-dimer

The results were analyzed and tabulated with the help of EPI INFO statistical software.

CONSENT:

Written and informed consent were obtained from all the participants in feasible cases or their attenders

ETHICAL COMMITTEE APPROVAL:

The study was approved by INSTITUTE OF ETHICAL COMMITTEE of MADRAS MEDICAL COLLEGE.

CONFLICT OF INTEREST : None

SPONSORSHIP : None

OBSERVATION AND RESULTS

OBSERVATION AND RESULTS

The results of the study were tabulated and analyzed. The coagulation parameters and their underlying etiology were analyzed . D- dimer and fibrinogen were considered together with other basic parameters like PT, aPTT and platelet count.

D-dimer can be elevated in venous thromboembolism, pregnancy, advanced age, inflammatory conditions, liver disease, malignancy and recent surgery. It is a sensitive but not a specific parameter to consider it separately.

Similarly Fibrinogen is also not a specific marker. It can be elevated in acute myocardial infarction, sepsis, pregnancy, inflammatory disorders and peripheral vascular disease. Low levels of fibrinogen is seen in conditions like end stage liver disease, DIC and afibrinogenemia.

The commonest laboratory abnormality in hemostasis and common critical care diseases that cause deranged coagulation parameters were studied.

The following variable were included in the analysis;

Age, sex, serum creatinine, serum total bilirubin, presence of clinical bleeding, site of bleeding, anticoagulant usage, PT, aPTT, platelet count, peripheral smear, D-dimer and fibrinogen levels .

D- dimer and fibrinogen abnormalities cannot be interpreted independently. PT and aPTT must be considered together to confirm hemostatic abnormality.

RESULTS

The highest number of critical care patients (21) were in the age group 13 to 39 years. There were 18 and 11 patients in the age groups 40 -59 and 60 -89 years respectively. Total number of patients studied were 50. All the patients were admitted in medical ICU.

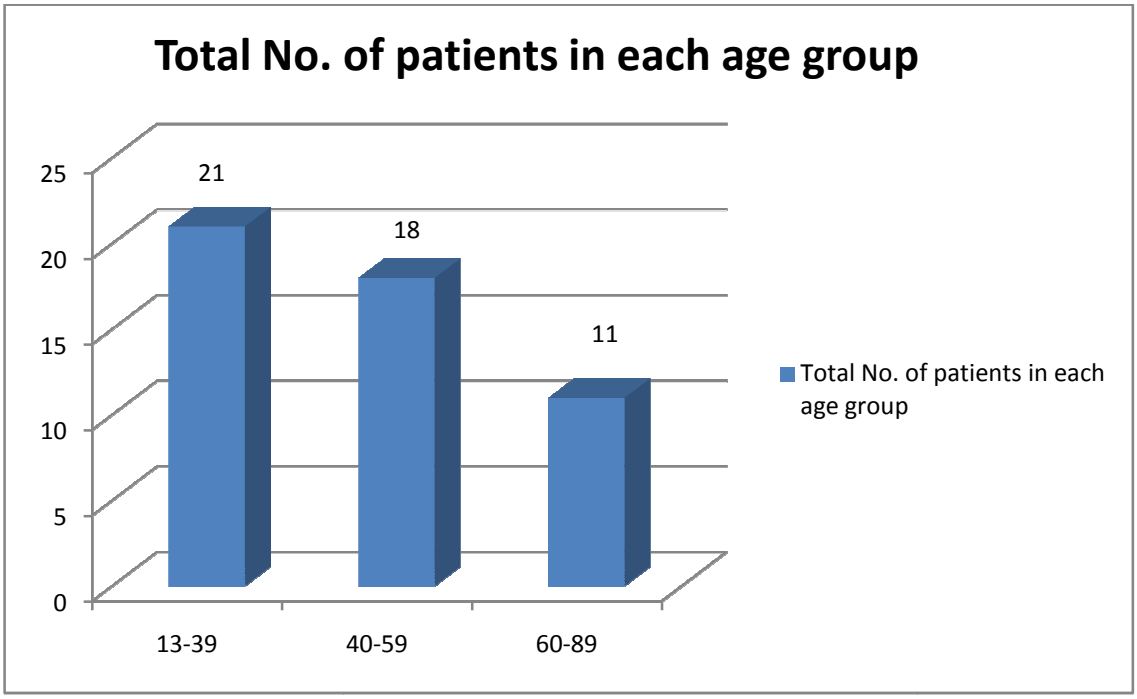


Fig 1: distribution of study population age wise.

AGE (in years)	No. of Patients (n=50)
13-39	21
40-59	18
60-89	4

Table 1: age wise distribution of study population

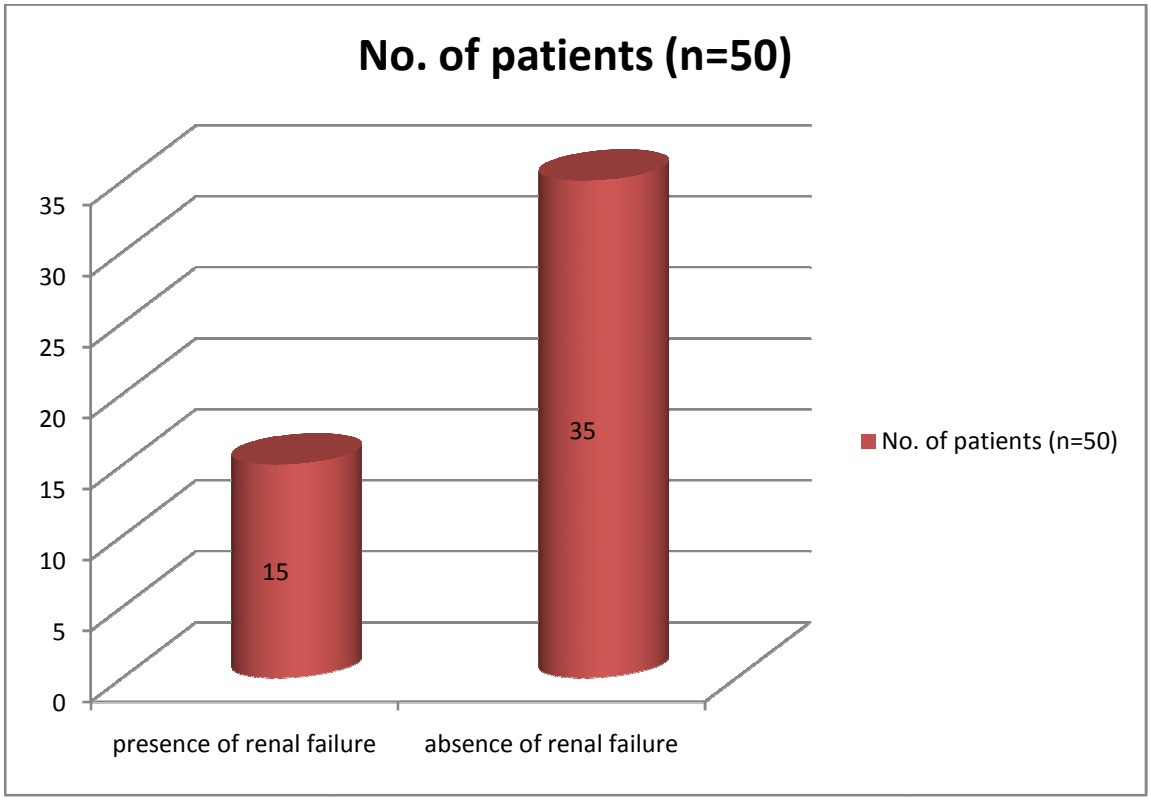


Fig 2: sex wise distribution of study population

Majority of the patients in our study were males (31). Females were 19 in number.

Sex	No of patients(n=50)	Percentage %
Male	31	62
Female	19	38

Table 2: Sex wise distribution of study population

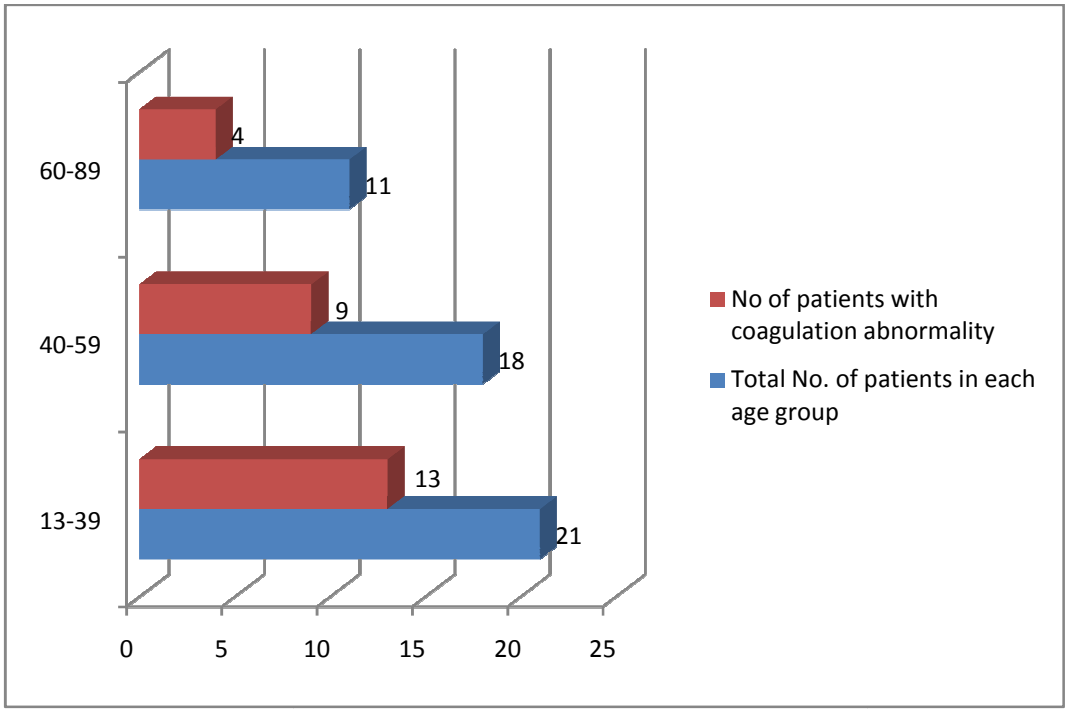


Fig 3: Distribution of patients with coagulation abnormalities in each age group.

Age (in years)	Total No. of patients in each age group	No of patients with coagulation abnormality	Percentage (%)
13-39	21	13	62
40-59	18	9	50
60-89	11	4	36

Table 3: Distribution of patients with coagulation abnormalities in each age group

Coagulation abnormality is considered as either decrease in platelet count or increase in PT or aPTT in our study. D-dimer and fibrinogen can be elevated non specifically in sepsis and other critical conditions.

Majority of hemostatic abnormalities occurred in the majority group i.e 13- 39 years whereas least % of hemostatic abnormality were observed in elderly age group.

Renal failure is also an important cause of bleeding diathesis in ICU. It can cause platelet dysfunction in the presence of normal platelet count.

Platelet dysfunction due to uremic toxins lead to prolonged bleeding time.

Heparin is also used in CKD patients during hemnodialysis.

Peritoneal dialysis,estrogen , desmopressin have found to improve platelet function.

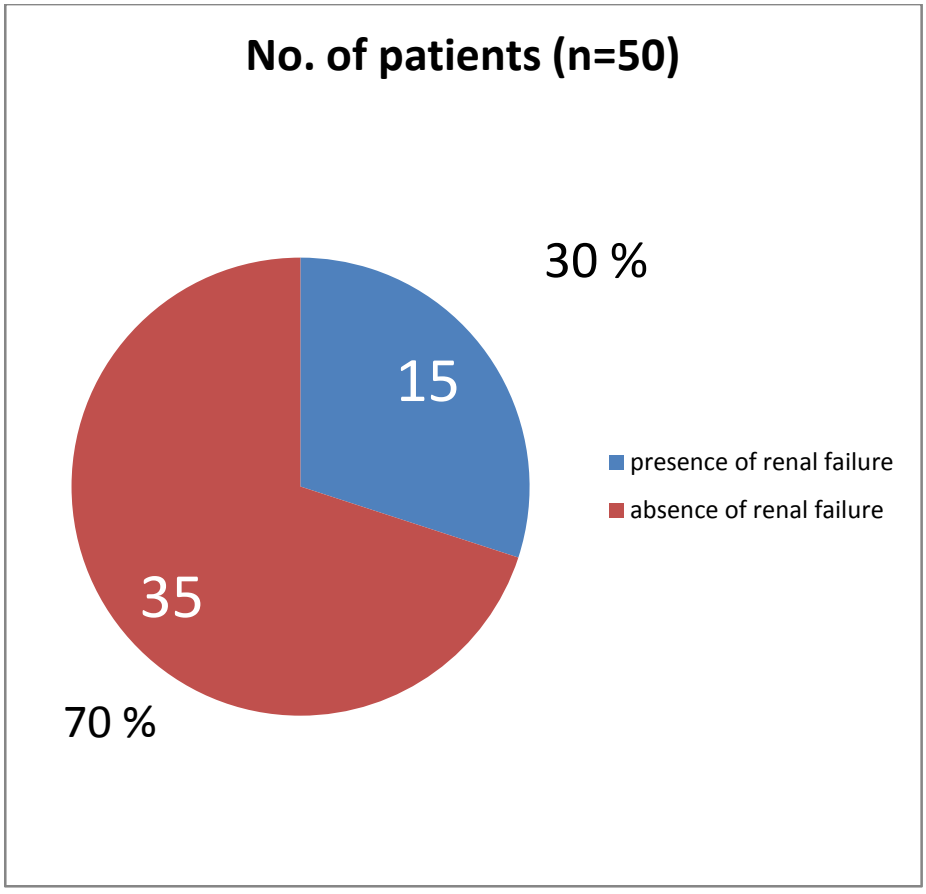


Fig 4: shows number of patients with renal failure in study population

Renal failure	No. of patients (n=50)
presence of renal failure	15
absence of renal failure	35

Table 4: showing the number of patients with renal failure in our study population

Serum creatinine of more than 1.5 was considered as renal failure for the study purpose. 30 percent of ICU patients in our study had renal failure.

The bleeding diathesis can be multifactorial in ICU patients. Uremia is one of the important contributor of the coagulopathy seen in ICU patients.

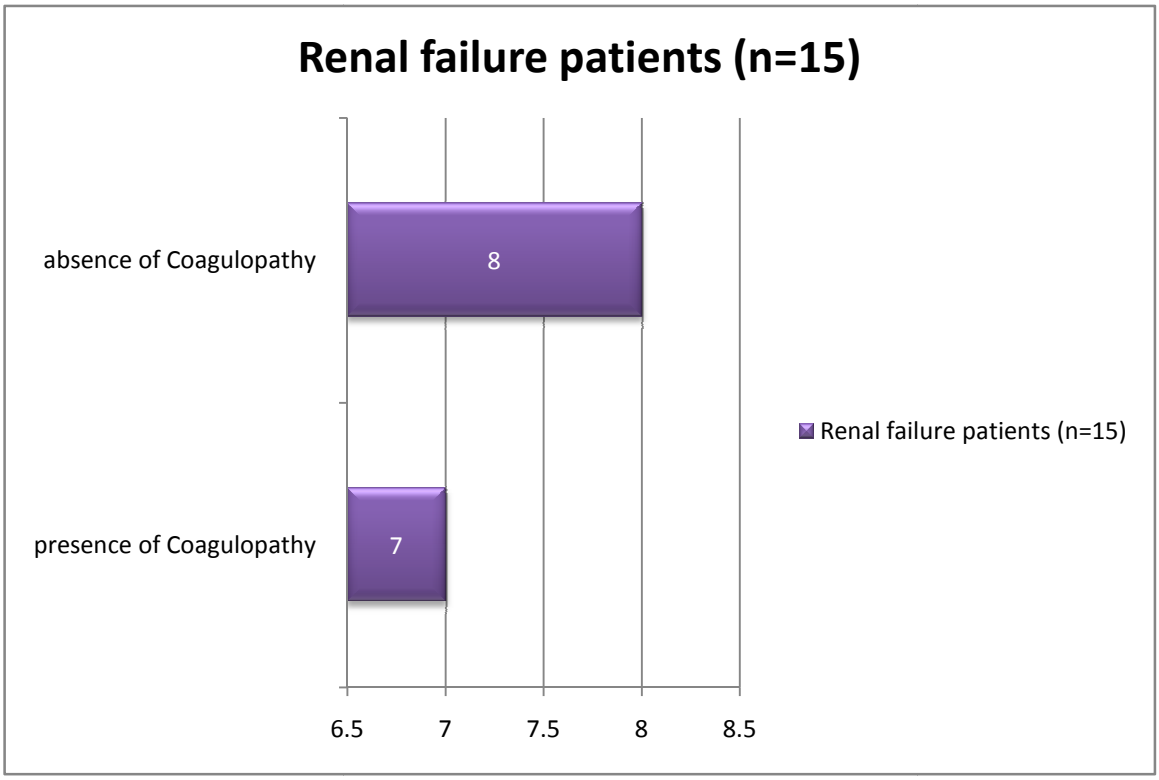


Figure 5: showing the number of patients with renal failure with and without coagulopathy in our study population

Out of 15 patients with renal failure 7 people had abnormal coagulation parameters. Uremia can cause abnormal platelet function without a reduction in platelet count.

Coagulopathy	Renal failure patients (n=15)
presence of Coagulopathy	7
absence of Coagulopathy	8

Table 5: showing the number of patients with renal failure with and without coagulopathy in our study population

Elevated liver parameters	No. of patients (n=50)
presence of Elevated liver parameters	7
Normal LFT	43

Table 6: showing the number of patients with elevated liver parameters in our study population

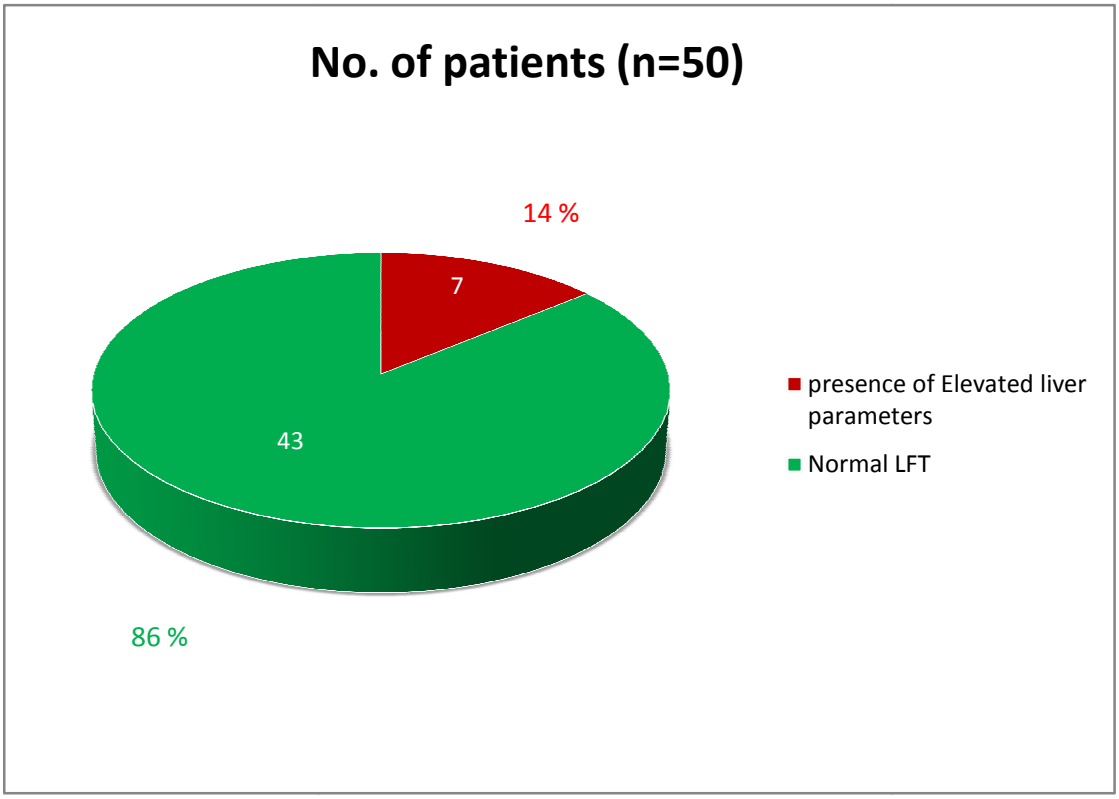


Figure 6: showing the number of patients with elevated liver parameters in our study population

Out of 50 study patients 43 patients had normal liver function test parameters and 7 had deranged LFT. Hemostasis in liver disease is complex as there is reduction in both pro coagulant and anticoagulant proteins. So there is a dynamic balance.

Coagulopathy	patients with deranged LFT (n=7)
presence of Coagulopathy	7
absence of Coagulopathy	0

Table 7: showing all patients with deranged LFT had coagulopathy

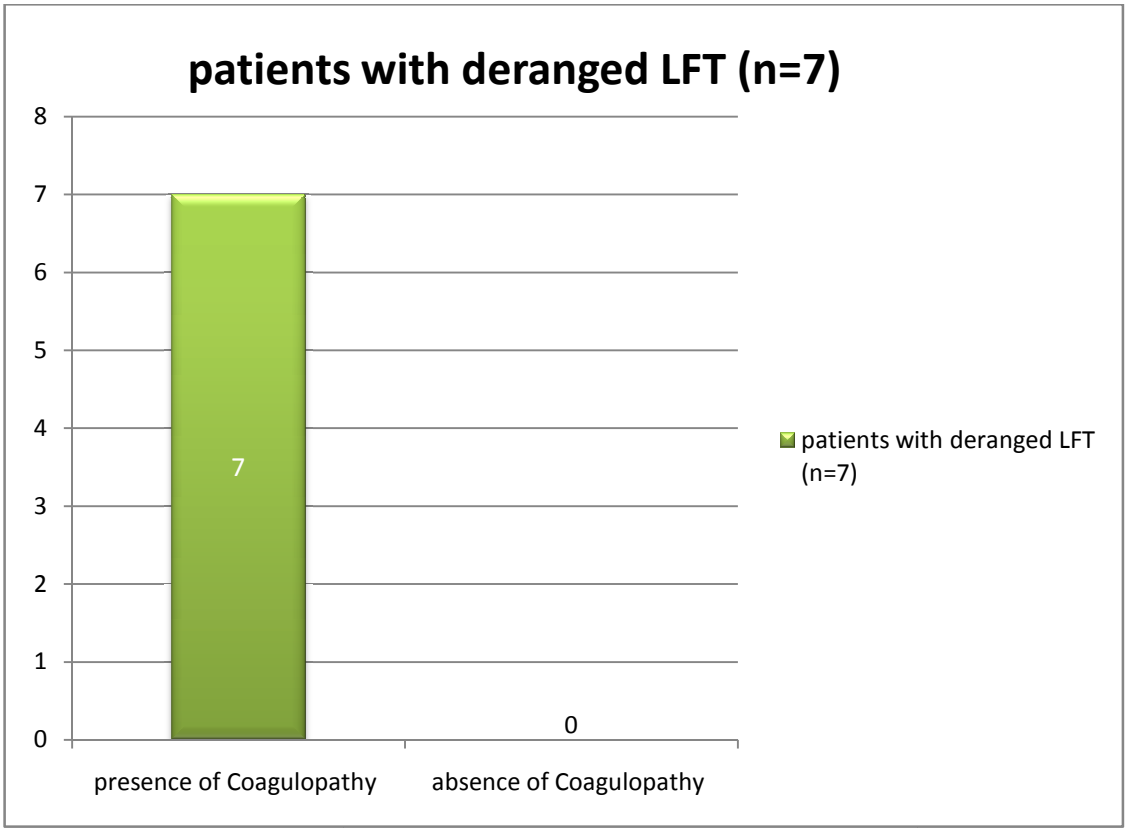


Figure 7: showing all patients with deranged LFT had coagulopathy

The coagulation abnormality was seen in almost all patients with deranged LFT. Commonest bleeding was in the form of melena followed by hemetemesis and oral cavity bleed in our study.

Anemia	No of patients
presence of anemia	36
absence of anemia	14

Table 8 : shows the prevalence of anemia in our study population

Anemia was based on peripheral smear which showed microcytic hypochromic anemia in 36 out of 50 patient. Remaining 14 patients showed normal study.

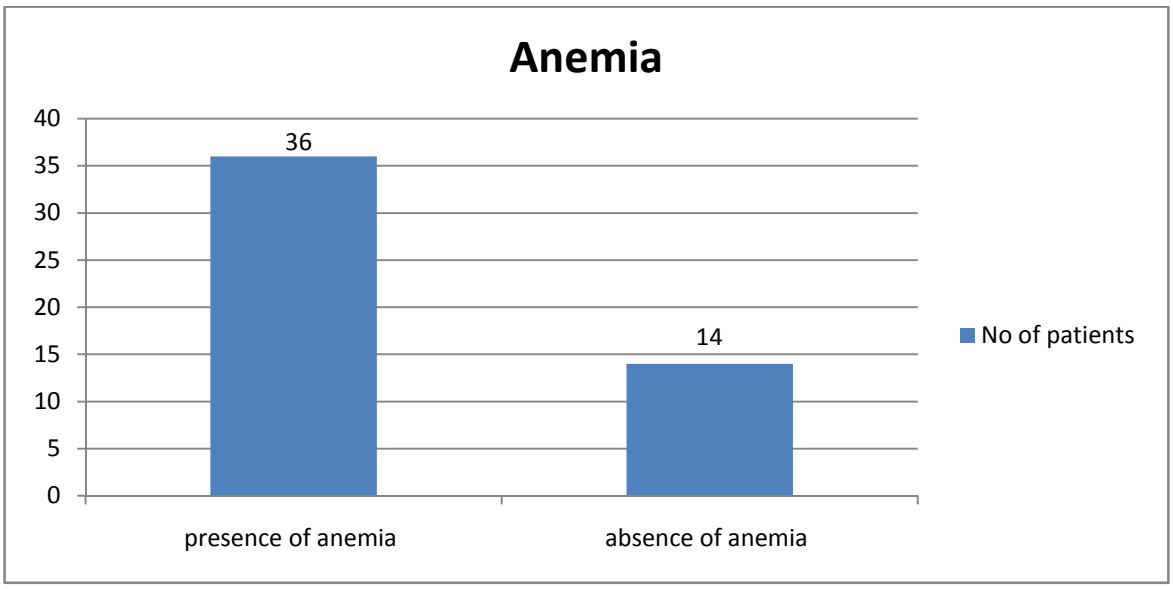


Figure 8 : shows the prevalence of anemia in our study population

Anemia also plays its role in bleeding diathesis particularly in renal failure. When Hematocrit falls less than 30 there is loss of axial red blood cell flow and platelets are not pushed to endothelial side which can prolong bleeding time.

Thrombocytopenia	No of patients
presence	23
absence	27

Table 9 : shows the prevalence of thrombocytopenia in our study population

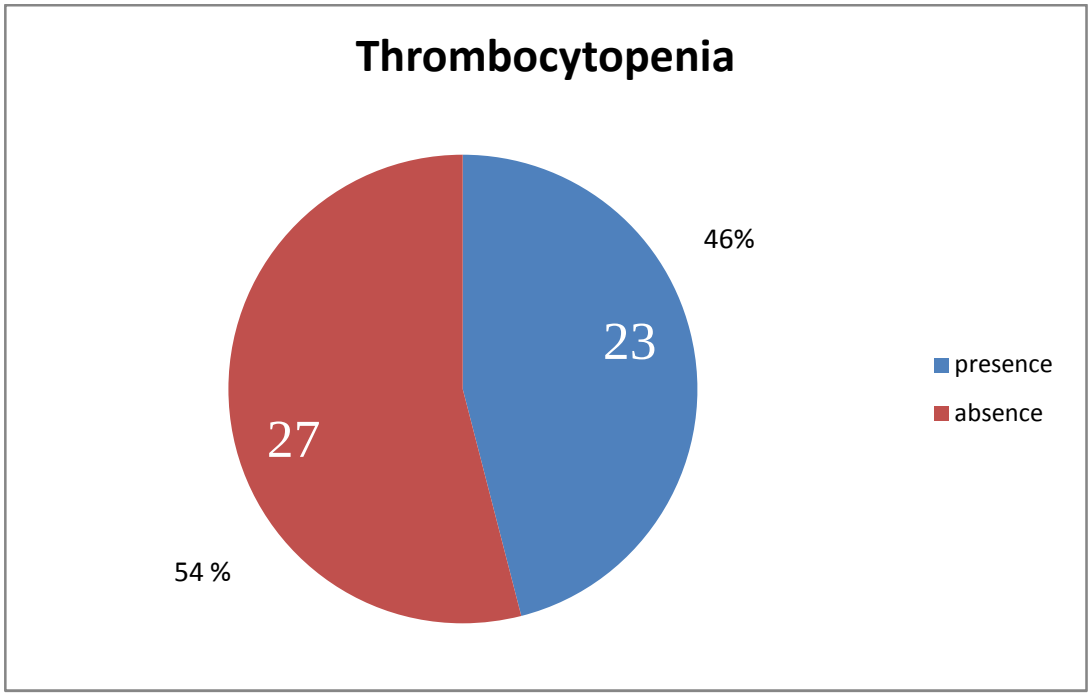


Figure 9 : shows the prevalence of thrombocytopenia in our study population

Thrombocytopenia is the most common coagulation abnormality in ICU patients. In our study 46 % of study population was found to have thrombocytopenia. In critically ill patients cut off value of 1,00,000 cells / cu.mm can be used instead of the usual 1,50,000 as there is no significant bleeding tendency to occur between these cutoff values.

platelet count (cells/cu.mm)	No. of patients
1 lakh to 80,000	13
79,000 to 50,000	6
49,000 to 20,000	3
<20,000	1

Table 10 : shows the severity of thrombocytopenia in our study population

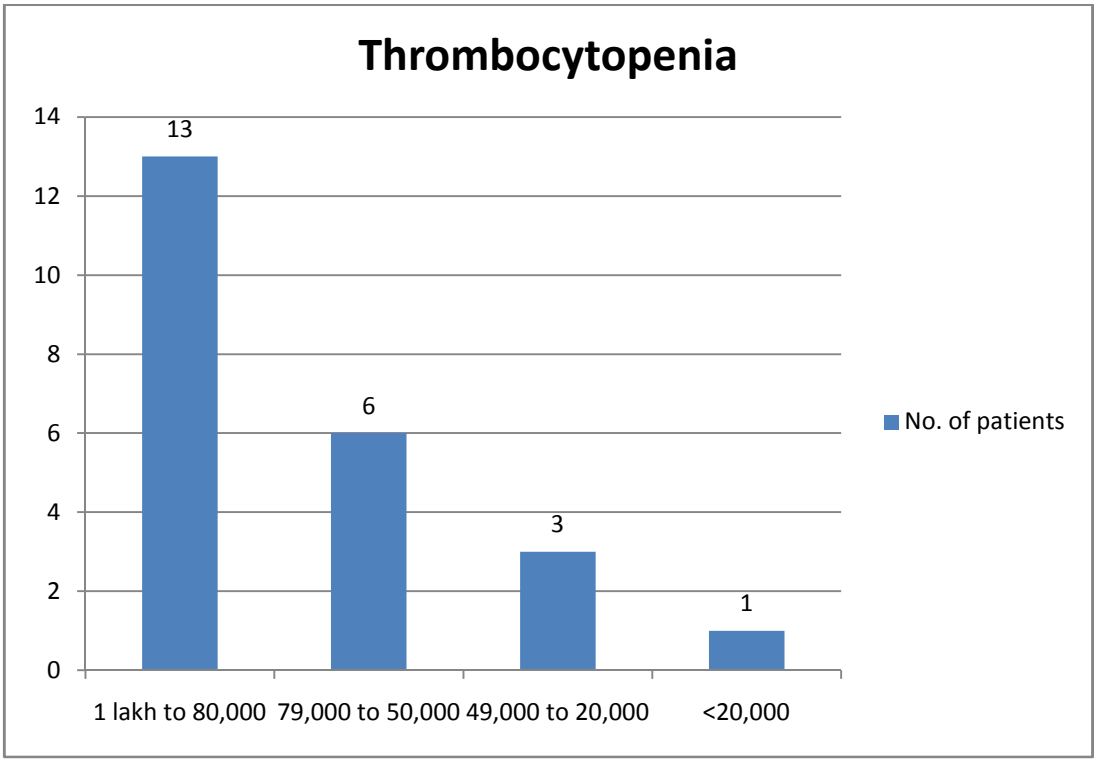


Figure 10 : shows the severity of thrombocytopenia in our study population

Majority of patients (13) had platelet counts between 80,000 and 1 lakh which may not cause major bleeding per se. 3 patients had platelet count between 20,000 and 49,000 cells/cu.mm. Only one patient had platelet count less than 20,000 cells/cu.mm.

Clinical bleeding	No. of patients with coagulopathy
presence	14
absence	12

Table 10 : shows the occurrence of clinical bleeding in our study population who had abnormal coagulation

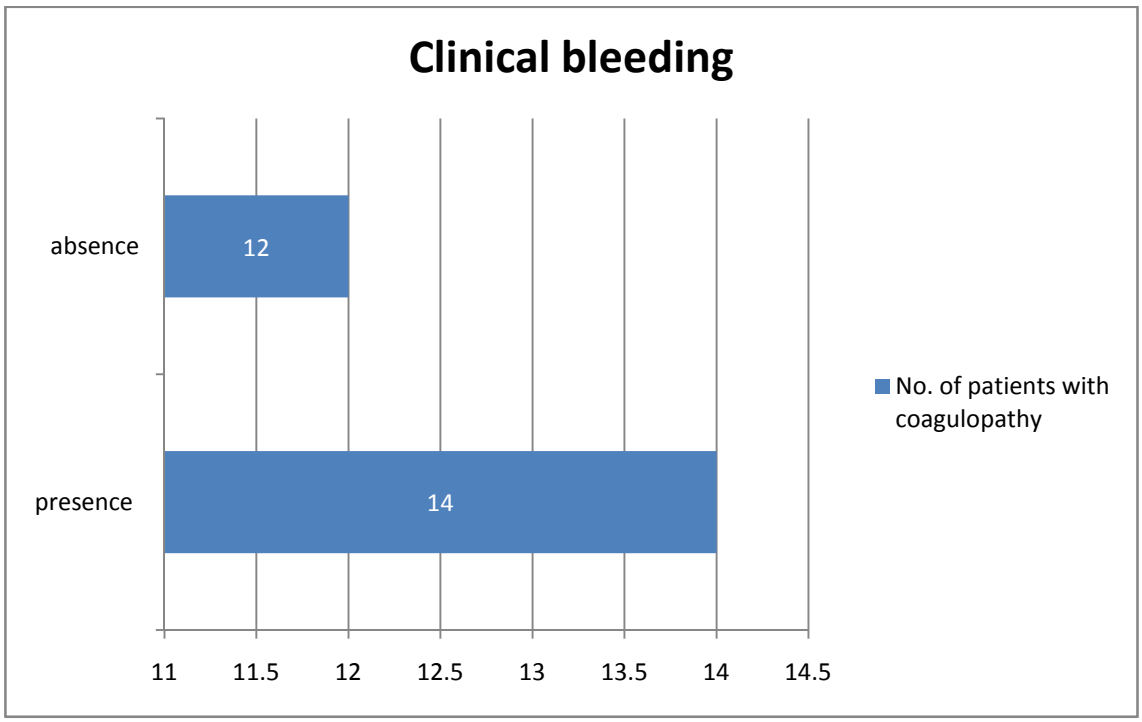


Figure 10 : Shows the occurrence of clinical bleeding in our study population who had abnormal coagulation

More than half of the patients who had abnormal coagulation parameters had clinical bleeding.

Clinical bleeding type	No. of patients
Melena	7
Epistaxis	1
Oral cavity bleed	1
Skin bleed	3
Hematuria	2

Table 11 : shows the occurrence of site of clinical bleeding in our study population who had abnormal coagulation

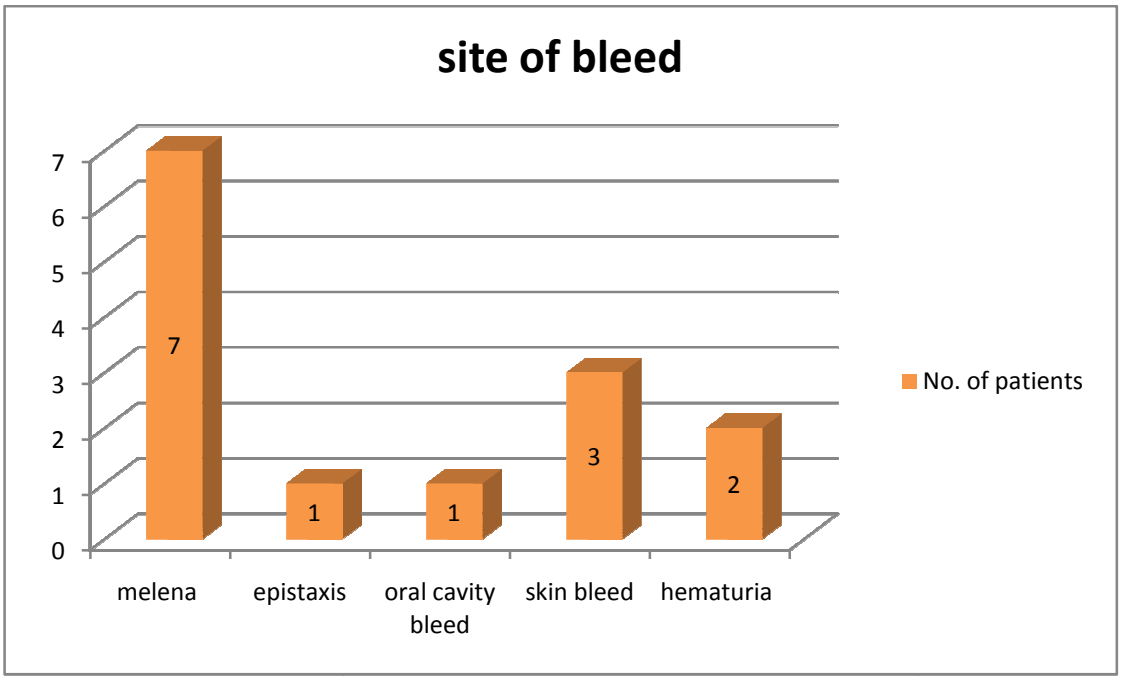


Figure 11 : shows the occurrence of site of clinical bleeding in our study population who had abnormal coagulation

Melena was the most common bleeding manifestation followed by skin bleed. Not even a single patient in our study had life threatening bleeding episode.

Antithrombotic drug usage	No. of patients
Yes	6
No	44

Table 12 : shows the usage of antithrombotics in our study population

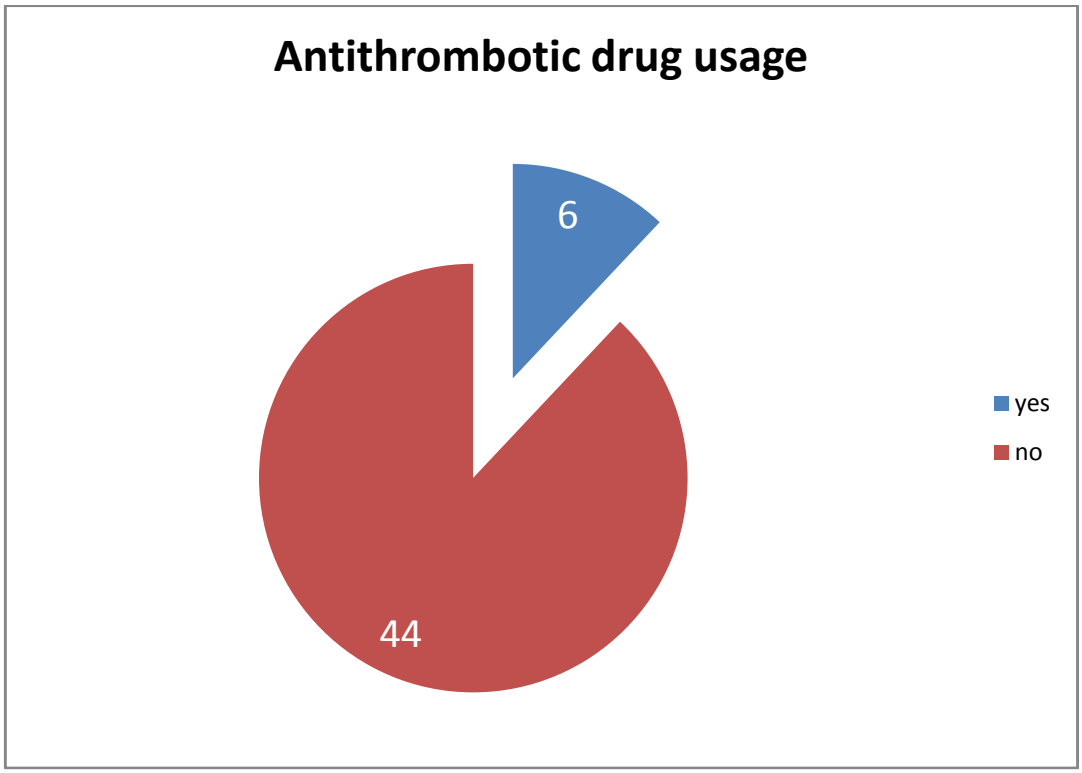


Figure 12 : shows the usage of antithrombotics in our study population

Antithrombotic drug usage	No. of patients
Aspirin	1
Acitrom	1
Heparin	4

Table 13 : shows the type of antithrombotics used in our study population

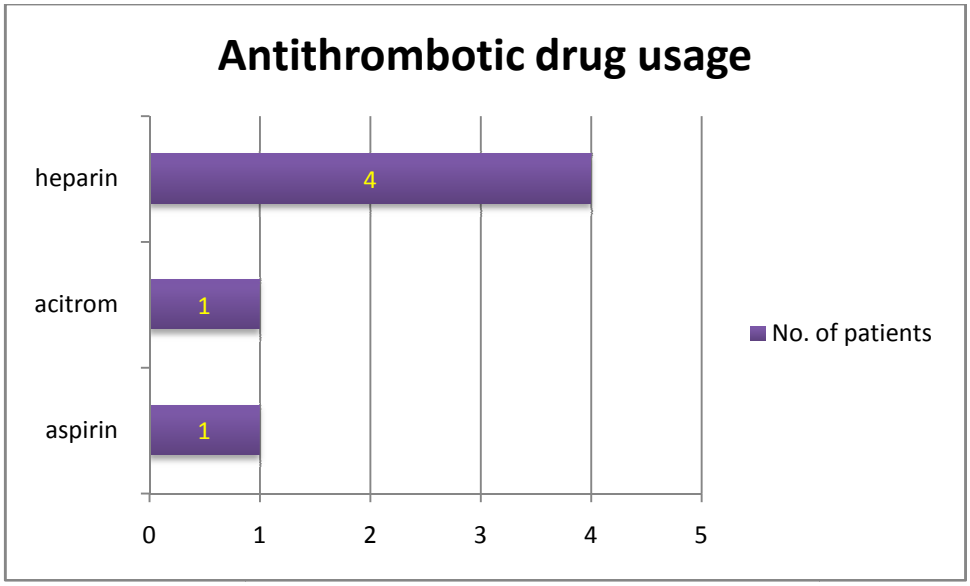


Figure 13 : shows the type of antithrombotics used in our study population

Antithrombotic drug usage	No. of patients
Presence of clinical bleeding	4
Absence of clinical bleeding	2

Table 14 : shows clinical bleeding in our study population who was on antithrombotics for some indications

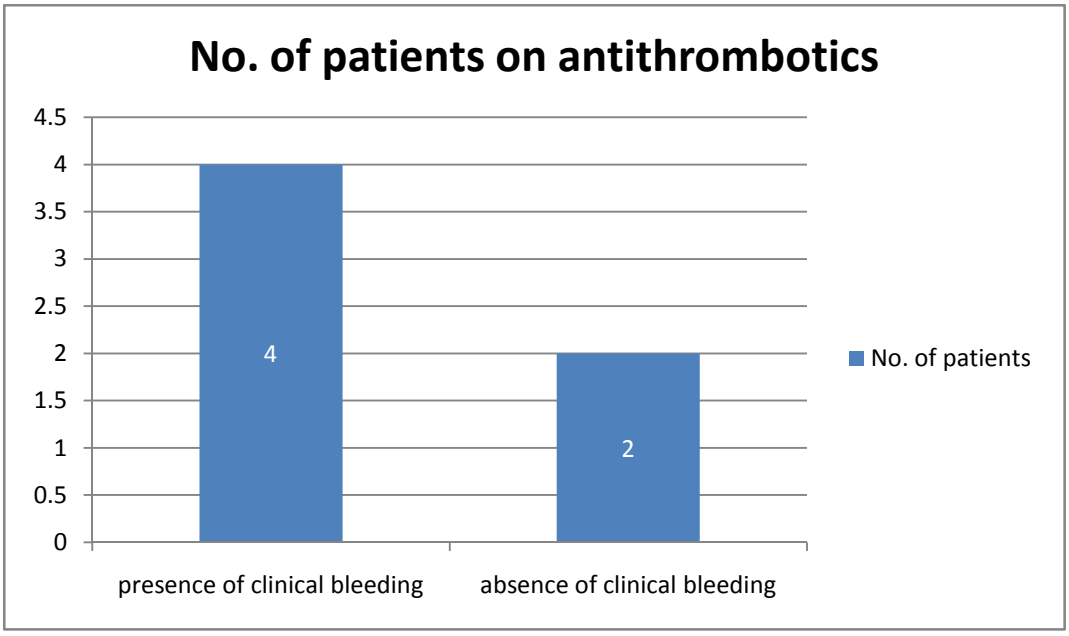


Figure 14 : shows clinical bleeding in our study population who was on antithrombotics for some indications

Antithrombotic are commonly used in ICU patients. The problem with these drugs arises when patient develops clinical bleeding or when a invasive procedure is planned. In our study six patients was on antithrombotics. Out of six, four patients developed clinical bleeding. Heparin was the frequent drug that was used.

PT INR	No. of patients
prolonged	3
normal	47

Table 15 : study population and PT INR prolongation

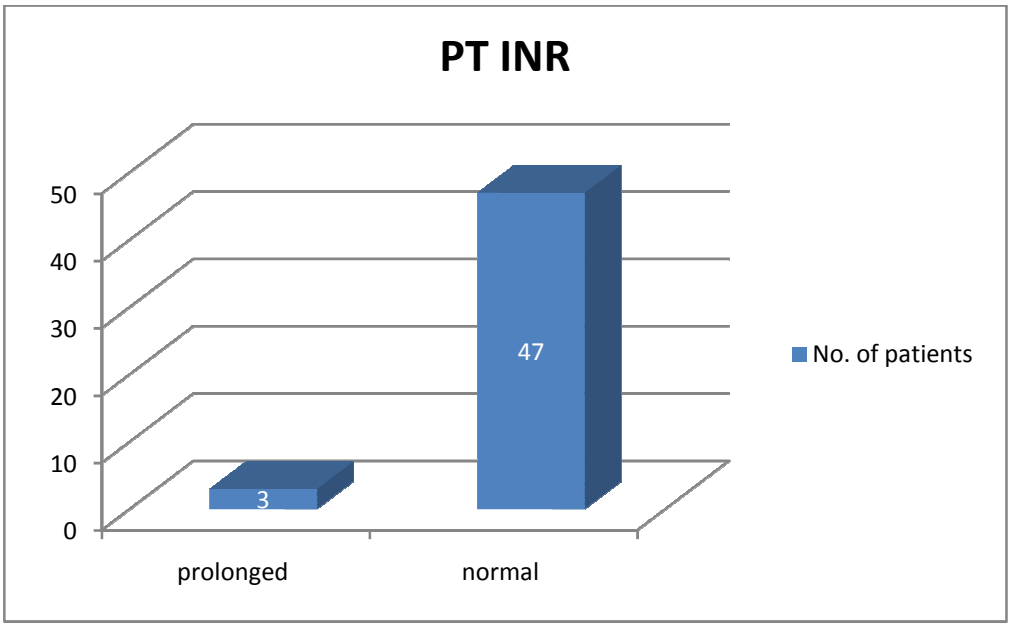


Figure 15 : study population and PT INR prolongation

Out of fifty patients studied 3 patients had PT prolongation.

aPTT	No. of patients
prolonged	10
normal	40

Table 16 : study population and aPTT prolongation

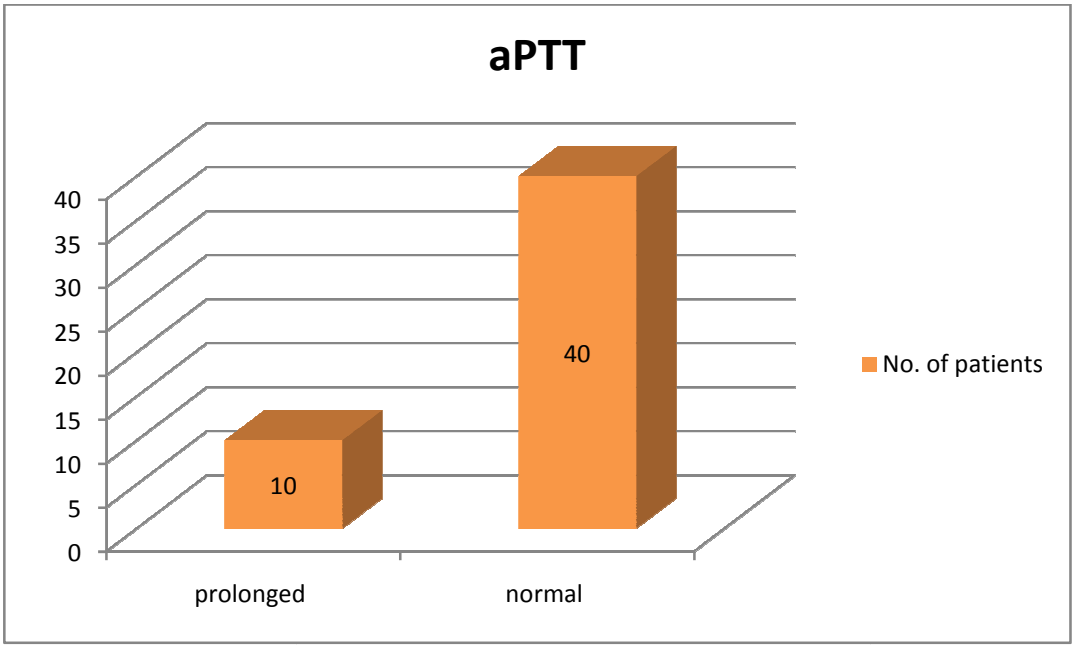


Figure 16 : study population and aPTT prolongation

Out of fifty patients studied 10 patients had aPTT prolongation.

Fibrinogen abnormality	No of patients
Yes	17
No	43

Table 17 : study population and fibrinogen abnormality

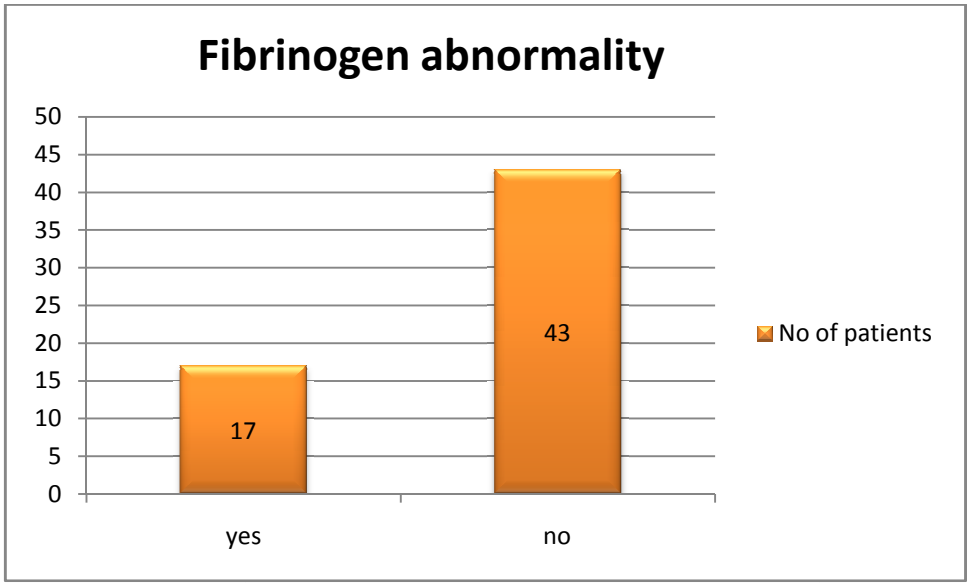


Figure 17 : study population and fibrinogen abnormality

None of the study patient had hypofibrinogenemia. 17 patients had hyperfibrinogenemia i.e fibrinogen levels >450 mg/dl.

Hyperfibrinogenemia can be elevated in sepsis, atherosclerosis, coronary artery diseases and other chronic inflammatory states. Hence it is always interpreted along with other coagulation tests.

PT and aPTT	No. of patients
prolonged	2
not prolonged	48

Table 18: study population and combined PT and aPTT abnormality

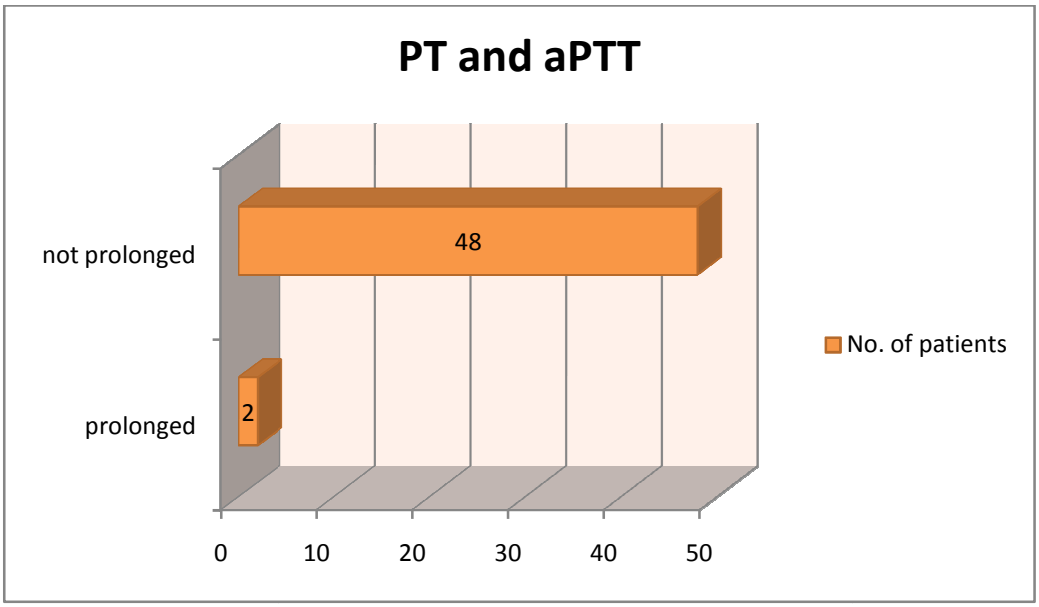


Figure 18: study population and combined PT and aPTT abnormality

Out of fifty patients only 2 patients had combined PT and aPTT prolongation

D dimer positivity	No of patients
Yes	43
No	7

Table 19 : study population and D dimer positivity

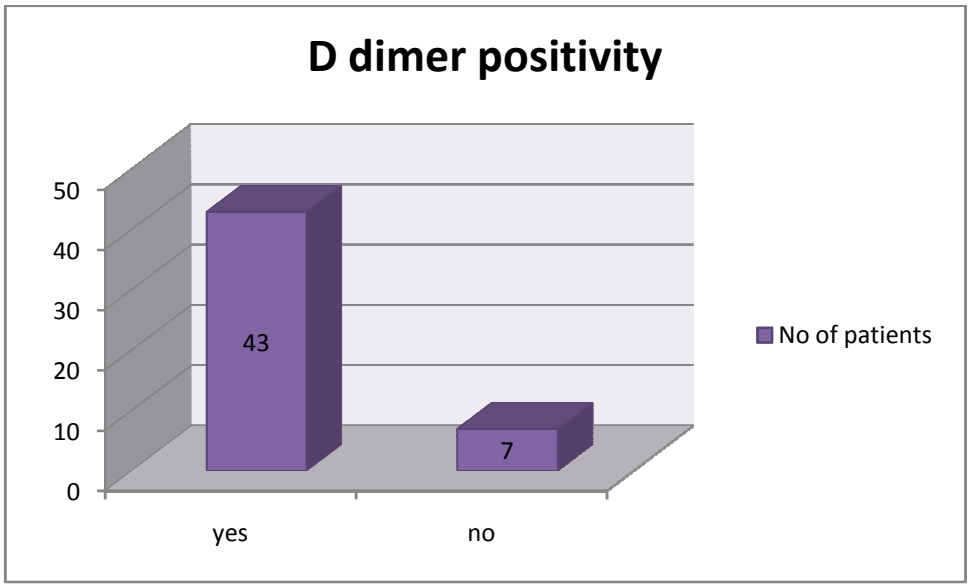


Figure 19 : study population and D dimer positivity

Almost majority of patients (43) had D dimer positivity. Like fibrinogen D dimer results should always be interpreted along with other coagulation tests. D dimer is sensitive but not a specific marker for pulmonary embolism. It can be elevated in inflammatory conditions, liver disease and even in pregnancy.

Thrombocytopenia + PT and aPTT prolongation + D dimer positivity	No. of patients
Present	1
Absent	49

Table 20 showing patients with thrombocytopenia + PT and aPTT prolongation + d dimer positivity

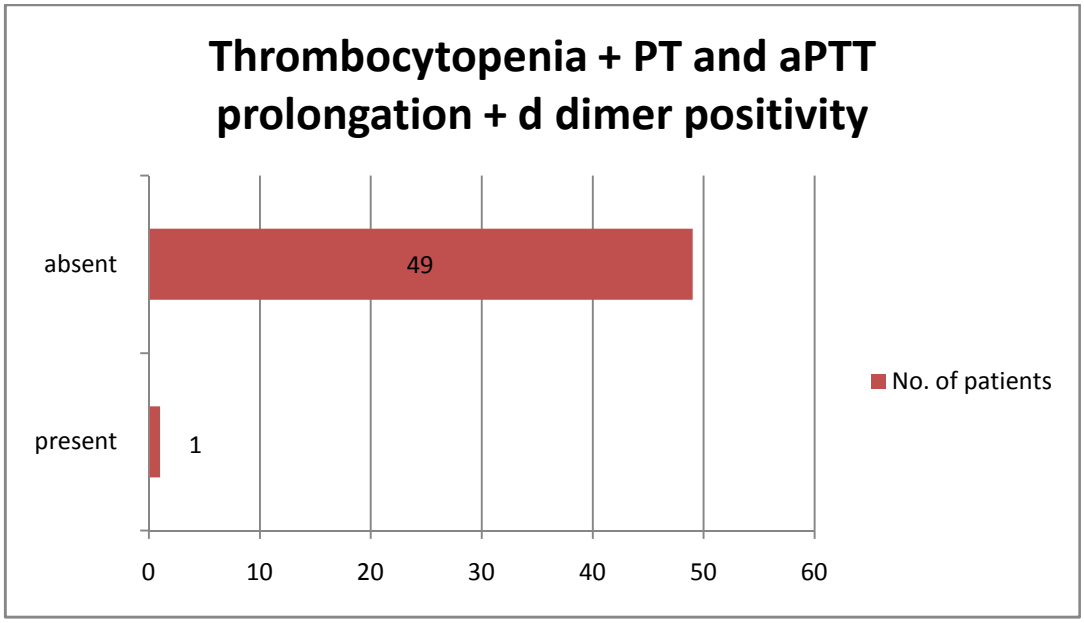


Table 20 showing patients with thrombocytopenia + PT and aPTT prolongation + d dimer positivity

Only one patient had thrombocytopenia + PT and aPTT prolongation + d dimer positivity. That patient had developed DIC secondary to Sepsis

Etiology of coagulpathy	No. of patients
DIC	**1**
Sepsis	**8**
Liver disease	**4**
Renal disease	**3**
Antithrombotic drug induced	**4**
Immunological thrombocytopenia	**0**
Others	**6**

Table 21 showing the common causes of coagulopathy in our study population.

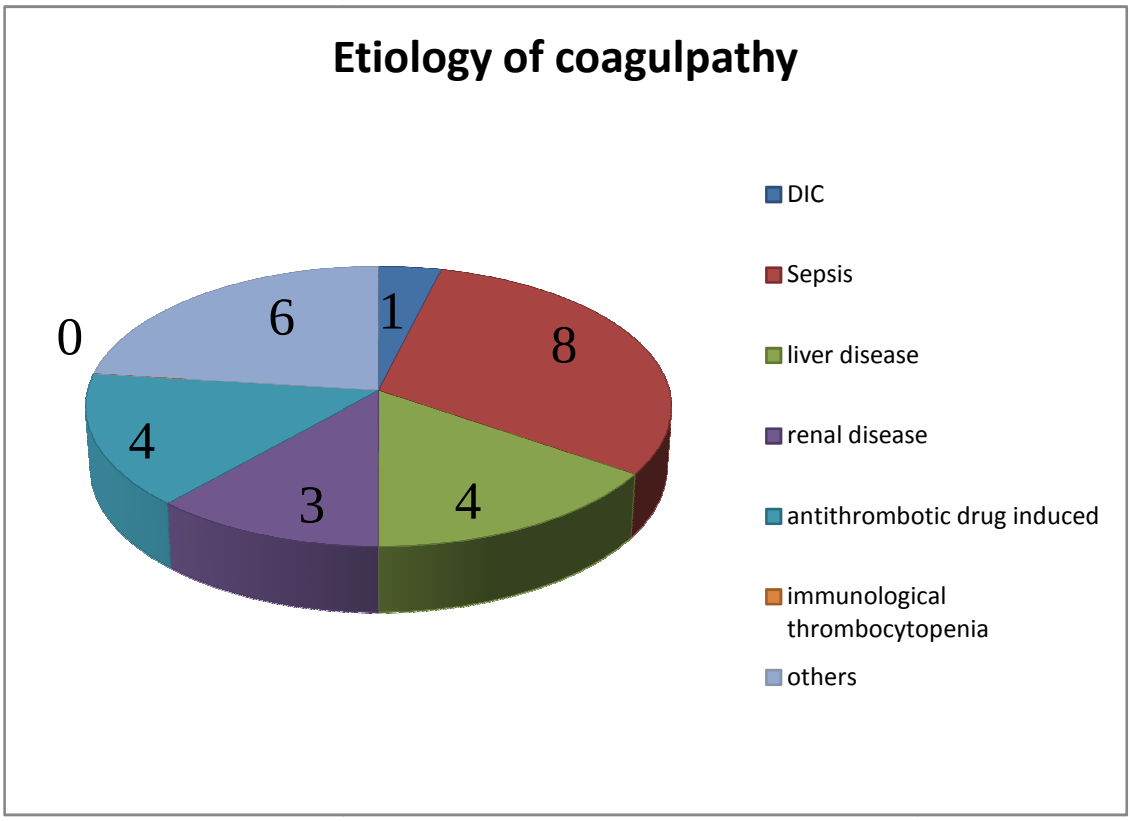


Figure 21 showing the common causes of coagulopathy in our study population.

As in any other ICU patients sepsis ranks first in causing coagulopathy followed by liver failure and antithrombotic drugs and renal failure. We did not have any case of immune mediated thrombocytopenia

DISCUSSION

DISCUSSION

Coagulopathy is common in critically ill patients. The spectrum varies from mild abnormality in coagulation parameters to life threatening bleeding. The coagulopathy in critical care patients is usually multifactorial.

With the latest update on management of coagulopathies, recently guidelines have arrived when to correct a coagulation abnormality which was lacking previous years.

The main aim of the study was to study the incidence and type of coagulation abnormality that occurs in critically ill patients in the ICU set up in RGGGH. We also had a secondary objective to study the common etiologies behind these coagulopathies in ICU patients.

Almost half the patients had coagulopathy in our study . The incidence was higher in the younger age group as they form the majority. Nearly 50 % of renal failure patients in our study had coagulopathy. Almost all patients with liver failure in our study had bleeding diathesis.

More than 50 % of patients with coagulopathy had clinical bleeding while others had only a laboratory abnormality in coagulation parameters. 70% of patients had anemia which can contribute to bleeding tendency by loss of laminar blood flow. Melena was the most common clinical bleed that we noted.

Nearly half the study population exhibited thrombocytopenia and majority of them had their platelet counts between 80,000 and 1,00,000 cells /cu.mm which is less likely to cause major bleeding episode. This study confirms with previous studies that thrombocytopenia is the most common coagulation abnormality.

Antithrombotic drugs were given only to 6 patients in our study out of which 4 had clinical bleeding thus emphasizing that antithrombotic drugs can create trouble when a critical care patient is planned for an invasive procedure.

Only 3 out of 50 and 10 out of 50 patients had PT and aPTT prolongation respectively. Only 2 patients had prolongation of both PT and aPTT. This shows that abnormal PT, aPTT are not so common in ICU patients.

Only one patient had thrombocytopenia along with prolonged PT and aPTT who had DIC secondary to Sepsis. Such patients show dismal outcome.

Nearly 86 % had D dimer positivity. But only the patient with thrombocytopenia and prolongd PT and aPTT was considered to have DIC. In other patients D dimer would have elevated non specifically in fibrinolytic conditions like liver disease, inflammation, pregnancy, trauma.

Fibrinogen was not low in any of the patient. Instead we had elevated fibrinogen in 30 % of study population which shows that fibrinogen can be elevated in conditions like chronic inflammatory states like atherosclerosis, sepsis and pregnancy.

D dimer and Fibrinogen should be interpret only with other coagulation parameters. In our study only one patient has significant D dimer positivity who developed DIC secondary to sepsis.

Regarding the etiology behind the coagulopathy sepsis was found to be the leading cause for coagulopahties which goes along with previous studies done in critical care patients.

Renal failure and liver failure are next in line to cause coagulopathy. Use of antithrombotics is also a significant cause of bleeding tendency in our study. We didn’t encounter any case of immune mediated thrombocytopenia like TTP which requires prompt recognition .

CONCLUSION

The inferences that this study brought :

1. **Coagulopathy is very common in critical care patients**
2. **Thrombocytopenia is the commonest abnormality in hemostatic workup.**
3. **Sepsis is the major cause for abnormal coagulation which can lead to DIC in critical care patients**
4. **Use of antithrombotic drugs in critical care patients can be troublesome when an invasive procedure is planned.**

A rationale approach must be developed in treating critical care patients with abnormal coagulation parameters. Too much aggressive transfusions can do more harm than good. A good clinical judgement is required along with the current knowledge for treating such patients.

BIBLIOGRAPHY

1 .Vanderschueren S, De Weerdt A, Malbrain M, et al. Thrombocytopenia and prognosis in intensive care. Crit Care Med 2000; 28:1871–1876

2 .Strauss R, Wehler M, Mehler K, et al. Thrombocytopenia in patients in the medical intensive care unit: bleeding prevalence, transfusion requirements, and outcome. Crit Care Med 2002; 30:1765–1771

3. Baughman RP, Lower EE, Flessa HC, et al. Thrombocytopenia in the intensive care unit. Chest 1993; 104:1243–1247

4. Bonfiglio MF, Traeger SM, Kier KL, et al. Thrombocytopenia in intensive care patients: a comprehensive analysis of risk factors in 314 patients. Ann Pharmacother 1995; 29:835–842

5 .Chakraverty R, Davidson S, Peggs K, et al. The incidence and cause of coagulopathies in an intensive care population. Br J Haematol 1996; 93:460–463

6**.** Innerhofer P, Westermann I, Tauber H, et al. The exclusive use of coagulation factor concentrates enables reversal of coagulopathy and decreases transfusion rates in patients with major blunt trauma. Injury 2013;44:209-16.

7. Ziegler B, Schimke C, Marchet P, Stögermüller B, Schöchl H, Solomon C. Severe pediatric blunt trauma — successful ROTEM-guided hemostatic therapy with fibrinogen concentrate and no administration of fresh frozen plasma or platelets. Clin Appl Thromb Hemost 2013; 19:453-9.

8**.** Hiippala S. Replacement of massive blood loss. Vox Sang 1998;74: Suppl 2:399-407.

9. Spahn DR, Cerny V, Coats TJ, et al. Management of bleeding following major trauma: a European guideline. Crit Care 2007;11:R17. [Erratum, Crit Care 2007;11:414.]

10**.** Rourke C, Curry N, Khan S, et al. Fibrinogen levels during trauma hemorrhage,response to replacement therapy,and association with patient outcomes. J Thromb Haemost 2012;10:1342-51.

11. Owings JT, Gosselin RC, Anderson JT, Battistella FD, Bagley M, Larkin EC: Practical utility of the D-dimer assay for excluding Thromboembolism in severely injured trauma patient**s.** *J Trauma* 2001, 51**:**425- 429.Critical Care Vol 10 No 4 Levi and Opal

12. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJJ: Efficacy and safety of recombinant human activated protein C for severe sepsis**.** *N Engl J Med* 2001, 344: 699-709.

13. Gando S, Nanzaki S, Sasaki S, Kemmotsu O: Significant correlations between tissue factor and thrombin markers in trauma and septic patients with disseminated intravascular coagulation. *Thromb Haemost* 1998, 79**:**1111-1115.

14. Mavrommatis AC, Theodoridis T, Orfanidou A, Roussos C, Christopoulou-Kokkinou V, Zakynthinos S: Coagulation system and platelets are fully activated in uncomplicated sepsis. *Crit Care Med* 2000, 28**:**451-457.

15 . Acharya SS , Coughlin A , Dimichele DM ; North American Rare Bleeding Disorder Study Group . Rare Bleeding Disorder Registry: defi ciencies of factors II, V, VII, X, XIII, fibrinogen and dysfibrinogenemias . *J Thromb Haemost* . 2004 ; 2 (2):248 - 256 .

16 . Whitlatch NL , Ortel TL . Thrombophilias: when should we test and how does it help? *Semin Respir Crit Care Med* . 2008 ; 29 (1): 25 - 39 .

17 . Khan S , Dickerman JD . Hereditary thrombophilia . *Thromb J* .2006 ; 4 : 15.

18 . McVey JH , Boswell E , Mumford AD , Kemball-Cook G , Tuddenham EG . Factor VII defi ciency and the FVII mutation database. *Hum Mutat* . 2001 ; 17 (1): 3 - 17 .

19. Bernard GR , Ely EW , Wright TJ , et al . Safety and dose relationship of recombinant human activated protein C for coagulopathy in severe sepsis . *Crit Care Med* . 2001; 29(11): 2051- 2059.

20 . Drews RE . Critical issues in hematology: anemia, thrombocytopenia, coagulopathy, and blood product transfusions in critically ill patients . *Clin Chest Med* . 2003; 24 (4): 607 – 622

21. Toh CH, Hoots WK. The scoring system of the Scientific and Standardisation Committee on Disseminated Intravascular Coagulation of the International Society on Thrombosis and Haemostasis: a 5-year overview. J Thromb Haemost 2007;5:604-6.

22. Haug KB, et al. LPS from Neisseria meningitidis is crucial for inducing monocyte- and microparticleassociated tissue factor activity but not for tissue factor expression. Innate Immun 2012;18:580-91.

23. Osterud B, Flaegstad T. Increased tissue thromboplastin activity in monocytes of patients with meningococcal infection: related to an unfavourable prognosis. Thromb Haemost 1983;49:5-7.

24. Nieuwland R, Berckmans RJ, McGregor S, et al. Cellular origin and Procoagulant properties of microparticles in meningococcal sepsis.

Blood 2000;95:930-5.

25. Ranieri VM, Thompson BT, Barie PS, et al. Drotrecogin alfa (activated) in Adults with septic shock. N Engl J Med 2012;366: 2055-64.

26. Afshari A, Wetterslev J, Brok J, Moller AM. Antithrombin III for critically ill patients. Cochrane Database Syst Rev 2008; 3:CD005370.

27. Abraham E, Reinhart K, Opal S, et al. Efficacy and safety of tifacogin (recombinant tissue factor pathway inhibitor) in severe sepsis: a randomized controlled trial. JAMA 2003;290:238-47.

28. Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. Br J Haematol 2009;145:24-33.

29. Slichter SJ. Evidence-based platelet transfusion guidelines. Hematology Am Soc Hematol Educ Program 2007:172-8

30. Bleeding and Coagulopathies in Critical Care Beverley J. Hunt, M.D. N Engl J Med 2014;370:847-59. DOI: 10.1056/NEJM

31. Laboratory Studies in Coagulation Disorders; Renu Saxena, Meganathan Kannan and Ved P Choudhry Department of Hematology, All India Institute of Medical Sciences, New Delhi, India; Indian Journal of Pediatrics, Volume 74 July, 2007

32. Coagulopathy in Critically ill Patients; Arthur P. Wheeler and Todd W. Rice: CHEST 2010; 137(1):185–194

33. Coagulation abnormalities in critically ill patients; Marcel Levi and Steven M Opal*:* Critical Care 2006, 10:222

ANNEXURES

ABBREVIATIONS USED IN THE TEXT

AIDP	**-**	**Acute Inflammatory Demyelinating Polyradiculopathy**
AKI	**-**	**Acute Kidney Injury**
APC	**-**	**Activated Protein C**
APLA	**-**	**Anti Phospholipid Antibody syndrome**
aPTT	**-**	**activated Partial Thromboplastin Time**
BUN	**-**	**Blood Urea Nitrogen**
COPD	**-**	**Chronic Obstructive Pulmonary Disease**
CKD	**-**	**Chronic Kidney Disease**
DCLD	**-**	**Decompensated Chronic Liver Disease**
DIC	**-**	**Disseminated Intravascular Coagulation**
DITP	**-**	**Drug Induced Thrombocytopenic Purpura**
DVT	**-**	**Deep Venous Thrombosis**
EDTA	**-**	**Ethylene Diamine Tetraacetic Acid**
FDP	**-**	**Fibrin Degradation Product**
FEU	**-**	**Fibrinogen Equivalent Unit**
FFP	**-**	**Fresh Frozen Plasma**
HELLP	**-**	**Hemolysis Elevated Liver enzymes Low Platelet count**
HIT	**-**	**Heparin Induced Thrombocytopenia**
HUS	**-**	**Hemolytic Uremic Syndrome**
ICU	**-**	**Intensive Care Unit**

INR	**-**	**International Normalized Ratio**
ITP	**-**	**Idiopathic Thrombocytopenic Purpura**
LDH	**-**	**Lactate DeHydrogenase**
MELD	**-**	**Model for End stage Liver Disease**
PF4	**-**	**Platelet Factor 4**
SLE	**-**	**Systemic Lupus Erythematosus**
TMA	**-**	**Thrombotic Micro Angiopathies**
TRALI	**-**	**Transfusion Related Acute Lung Injury**
TTP	**-**	**Thrombotic Thrombocytopenic Purpura**
VWF	**-**	**Von Willebrand Factor.**

PROFORMA

LABORATORY EVALUATION OF BLEEDING DIATHESIS IN MEDICAL ICU PATIENTS

Name: **Age:** **Sex:**

Patient ID: **Contact number:**

Occupation:

Presenting complaints :

Duration of illness : **duration of stay in IMCU:**

Primary diagnosis:

Examination findings :

General examination : **vital signs:**

CVS: **RS:** **P/A:** **CNS:**

If there is clinical bleeding mention the site.

INVESTIGATIONS

1. Complete Blood Count:

Hb: **TC:** **DC: P L E M**

ESR: **PCV:** **Platelet:**

2. Renal Function Tests:

Blood Urea: **Sr.Creatinine:**

Sr. Na: **Sr. K:**

3.Liver function tests

Total bilirubin : **AST:** **Total protein:**

Direct bilirubin : **ALT:** **S.Albumin:**

Indirect bilirubin **ALK:**

4.Hemostasis profile:

PT: test **aPTT: test** **INR:**

control **control**

D-dimer: **fibrinogen :** **platelet:**

Peripheral smear:

Specific investigations if any :

Antithrombotic drug usage:

If yes mention the drug, dosage and duration and indication :

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. M. Sathish Kumar,
Post Graduate,
Institute of Internal Medicine,
Madras Medical College,
Chennai – 600003.

Dear Dr. M. Sathish Kumar,

The Institutional Ethics Committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled **"Laboratory evaluation of bleeding diatheses in medical ICU"** No.25062014

The following members of Ethics Committee were present in the meeting held on 03.06.2014 conducted at Madras Medical College, Chennai-3.

1.	Dr. C. Rajendran, M.D.	-- Chairperson
2.	Dr. R. Vimala, M.D., Dean, MMC, Ch-3.	-- Deputy Chair Person
3.	Prof. Kalaiselvi, MD., Vice-Principal, MMC, Ch-3	-- Member
4.	Prof. Nandhini, M.D. Inst. of Pharmacology, MMC, Ch-3.	-- Member
5.	Dr. G. Muralidharan, Director Incharge , Inst. of Surgery	-- Member
6.	Prof. Md Ali, MD., DM., Prof & HOD of MGE, MMC, Ch-3.	-- Member
7.	Prof. Ramadevi, Director i/c, Biochemistry, MMC,Ch-3.	-- Member
8.	Prof. Saraswathy, MD., Director, Pathology, MMC, Ch-3.	-- Member
9.	Prof. Tito, Director, i/c. Inst. of Internal Medicine, MMC	-- Member
10.	Thiru. Rameshkumar, Administrative Officer	-- Lay Person
11.	Thiru. S. Govindasamy, BABL, High Court, Chennai-1.	-- Lawyer
12.	Tmt. Arnold Saulina, MA MSW	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/Chairman & Other Members

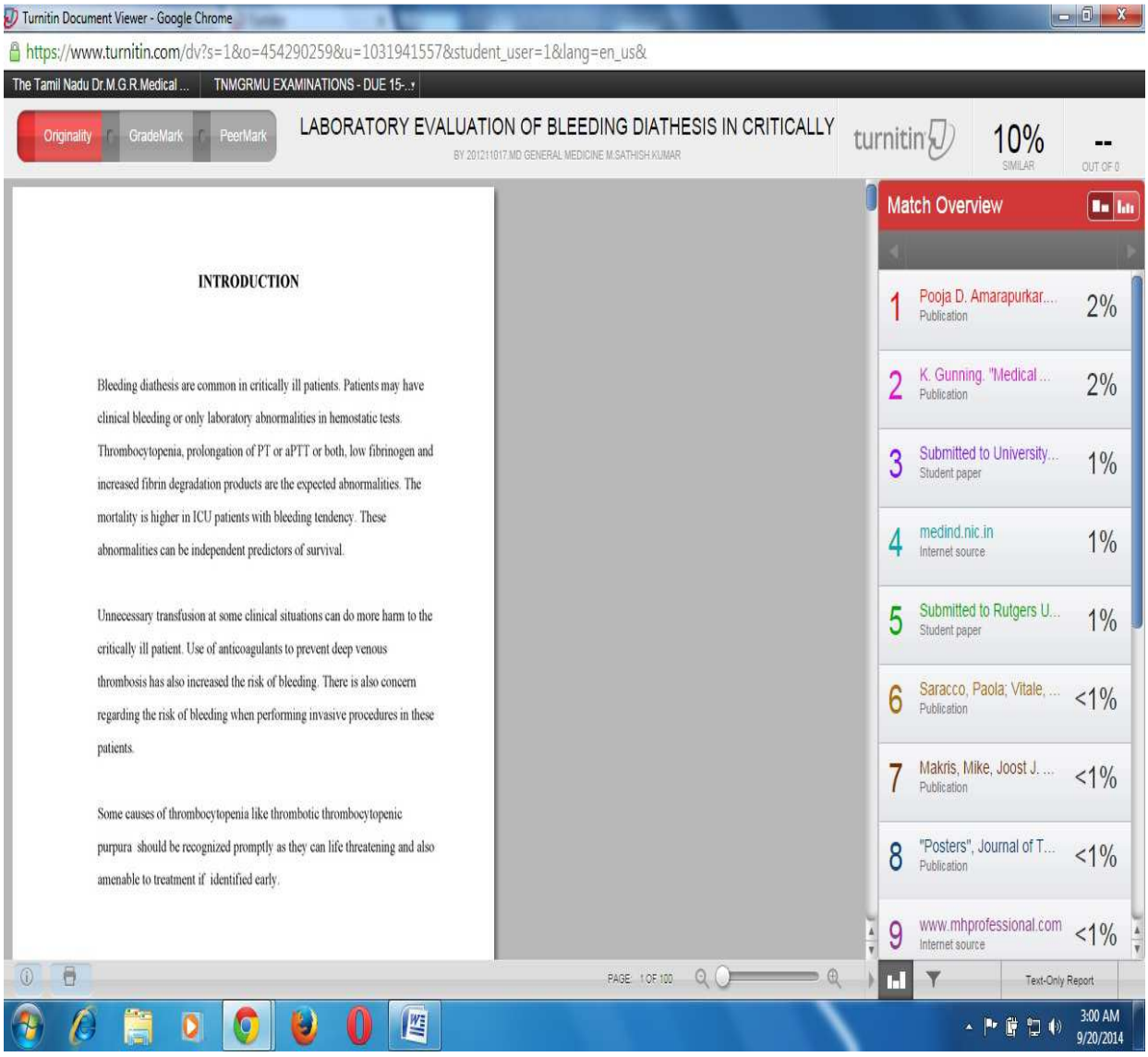
The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

13/6/14

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

Member Secretary, Ethics Committee

TURNITIN – PLAGIARISM SCREEN SHOT



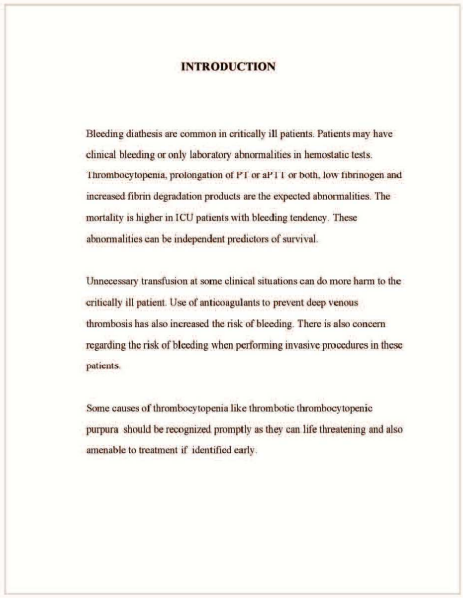
turnitin

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	201211017.md General Medicine M.S..
Assignment title:	TNMGRMU EXAMINATIONS
Submission title:	LABORATORY EVALUATION OF B...
File name:	dissertation.docx
File size:	3.24M
Page count:	100
Word count:	7,401
Character count:	45,453
Submission date:	20-Sep-2014 02:58AM
Submission ID:	454290259



INTRODUCTION

Bleeding diathesis are common in critically ill patients. Patients may have clinical bleeding or only laboratory abnormalities in hemostatic tests. Thrombocytopenia, prolongation of PT or aPTT or both, low fibrinogen and increased fibrin degradation products are the expected abnormalities. The mortality is higher in ICU patients with bleeding tendency. These abnormalities can be independent predictors of survival.

Unnecessary transfusion at some clinical situations can do more harm to the critically ill patient. Use of anticoagulants to prevent deep venous thrombosis has also increased the risk of bleeding. There is also concern regarding the risk of bleeding when performing invasive procedures in these patients.

Some causes of thrombocytopenia like thrombotic thrombocytopenic purpura should be recognized promptly as they can life threatening and also amenable to treatment if identified early.

INFORMATION SHEET

- We are conducting a study on "**LABORATORY EVALUATION OF BLEEDING DIATHESIS IN MEDICAL ICU PATIENTS"** among patients admitted in Medical ICU at the Government General Hospital, Chennai and for that your sample may be valuable to us.

- The purpose of this study is to diagnose the bleeding diathesis that commonly occur in critically ill medical ICU patients.

- We are selecting certain cases and if your specimen is found eligible, we may be using your 4ml of blood sample to be collected in sodium citrate tube to perform the following tests namely platelet count & peripheral smear, PT, aPTT, D-dimer and Fibrinogen. These tests in any way do not affect your final report or management.

- The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

- Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

- The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of investigator

Date Signature of participant

ஆராய்ச்சி தகவல் தாள்

சென்னை அரசு பொது மருத்துவமனையில் உள்ள தீவிர சிகிச்சை பிரிவில் அனுமதிக்கப்பட்டுள்ள நோயாளிகளுக்கு ஏற்படும் உதிரப்போக்கு நோய்களைப் பற்றிய ஒரு ஆராய்ச்சி இங்கு நடைபெற்று வருகின்றது.

தீவிர சிகிச்சை நோயாளிகளிடமிருந்து 4 மி.லி இரத்தம் பரிசோதனைக்கு அனுப்பப்படும். PT, aPTT, D-டைமர், பிளேட்லெட் அனுக்களின் அளவு (Fibrinogen) போன்ற பரிசோதனைகள் செய்யப்படும். இரத்தம் உறையும் தன்மையில் ஏற்படும் கோளாறுகள் கண்டுபிடித்து ஆராய்வதே இந்த ஆராய்ச்சியின் நோக்கமாகும்.

அதனால் தங்களது நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிப்பு ஏற்படாது என்பதையும் தெரிவித்துக்கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துக்களை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின்போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதை தெரிவித்துக்கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின்பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்த நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளையும் நோயின் தன்மை பற்றியும் ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சியின் முடிவின்போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

நாள் :
இடம் :

INFORMATION CONSENT FORM

Study Title	:	**LABORATORY EVALUATION OF BLEEDING DIATHESIS IN MEDICAL ICU PATIENTS**
Study Centre	:	Rajiv Gandhi Government General Hospital, Chennai.
Name	:	
Age/Sex	:	
Identification Number	:	

Patient may check (☑) these boxes

The details of the study have been provided to me in writing and explained to me in my own language ❑

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ❑

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ❑

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ❑

I hereby consent to participate in this study. ❑

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological and biochemical tests. ❑

Signature/thumb impression

Signature of Investigator

Patient's Name and Address:

Study Investigator's Name:

Dr. M.SATHISH KUMAR

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சி தலைப்பு

தீவிர சிகிச்சை பிரிவில் அனுமதிக்கப்பட்டுள்ள நோயாளிகளுக்கு ஏற்படும் உதிரப்போக்கு நோய்களைப் பற்றிய ஒரு ஆராய்ச்சி

பெயர்	:	தேதி	:
வயது	:	உள் நோயாளி எண்	:
பால்	:	ஆராய்ச்சி சேர்க்கை எண்	:

இந்த ஆராய்ச்சின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்துகொண்டு எனது சம்மதத்தை தெரிவிக்கிறேன்.

எனக்கு இரத்தப் பரிசோதனை செய்துகொள்ள சம்மதம்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின்பேரில் பங்கு பெறுகின்றேன். இந்த ஆராய்ச்சியில் இருந்து நான் எந்நேரமும் பின்வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்துகொண்டேன்.

நான் சொரியாஸிஸ் நோயில் ஏற்படும் கல்லீரல் பாதிப்பு மற்றும் மெடபாலிக் சிண்ட்ரோம் குறித்த இந்த ஆராய்ச்சியின் விபரங்களைக் கொண்ட தகவல் தாளைப் பெற்றுக்கொண்டேன்.

நான் என்னுடைய சுய நினைவுடனும் மற்றும் முழு சுதந்திரத்துடனும் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக்கொள்ள சம்மதம் தெரிவிக்கிறேன்.

கையொப்பம்

MASTER CHART

Name	Age	Sex	primary diagnosis	duration of stay in IMCU	Clinical bleeding
Prabavathy	52	F	Bronchiectasis	45 days	nil
Suresh babu	32	M	DCLD	5 days	yes
Vedhiammal	40	F	Sepsis	7 days	yes
Chitra	52	F	AIDP	14 days	no
Renuga	14	F	Viral encephalitis	10 days	yes
Kalaivani	23	F	Sepsis post partum	4 days	yes
Srinivasan	39	M	Pontine infarct	10 days	nil
Rayadu	49	M	COPD	12 days	nil
Punniyakodi	60	M	Meningoencephalitis	7 days	nil
Savithri	61	F	Carcinoma larynx	33 days	nil
Rukmani	65	F	Carcinoma breast	14 days	yes
Vinoth Kanna	45	M	DCLD	5 days	yes
Ganesan	50	M	Sepsis	7 days	yes
Ayapan	67	M	CKD,Stroke	10 days	nil
Narayanan	35	M	AIDP	5 days	nil
Saranya	21	F	Meningoencephalitis	5 days	nil
Chellamuthu	35	M	Heart failure	3 days	nil
Duraisamy	61	M	Stroke (ischemic)	8 days	yes
Mala	38	F	Ppneumonia,	3 days	nil
Sambasivam	50	M	Mucormycosis	14 days	nil
Vasudevan	68	M	Heart failure	13 days	nil
Jayaraman	78	M	Stroke	6 days	yes
Krishnan	55	M	Unknown primary	14 days	yes
Anjali	38	F	Myasthenia gravis	7 days	nil
Sundaram	44	M	DCLD	5 days	yes
Divya Bharathi	14	F	Meningoencephalitis	7 days	nil

Loganathan	58	M	AIDP	12 days	nil
Balan	66	M	COPD	20 days	nil
Jai Ganesh	18	M	CIDP	141 days	yes
Ramesh	30	M	Stroke	7 days	nil
Thirupathy	65	M	Status Epilepticus	5 days	nil
Nivedhitha	22	F	Meningoencephalitis	6 days	nil
Priya	18	F	Dengue hemorrhagic fever	4 days	yes
Kumar	47	M	Stroke	24 days	yes
Rajamanickam	48	M	Status Epilepticus	10 days	nil
Sadhana	13	F	AIDP	3 days	nil
Dhanalakshmi	56	F	Carcinoma cervix, CKD	7 days	nil
Krishnamoorthy	55	M	TB meningitis	38 days	nil
Purushothaman	13	M	status epilepticus	3 days	nil
Ram Kumar	20	M	AIDP	6 days	nil
Pooovarasan	13	M	RHD AR MR seizure	6 days	nil
Settu	50	M	Massive infarct CVA	17 days	nil
Meena	28	F	Eclampsia	6 days	yes
Chellaiah	65	M	DCLD	7 days	yes
Annammal	50	F	CKD, pulmonary edema	3 days	nil
Raju	34	M	AIDP	28 days	nil
Kannagi	41	F	MCTD	14 days	nil
Paranthaman	40	M	Diabetic foot, Sepsis	8 days	yes
Bakkiyalakshmi	37	F	POST PARTUM SEPSIS	45 days	yes
Santhanam	75	M	Cerebellar hemorrhage	5 days	nil

Name	site of bleed	Hb	peripheral smear	platelet count	PT	INR	aPTT
prabavathy	nil	6	MCHC	1,75,000	12.5	0.96	23.3
suresh babu	melena	8	MCHC	80,000	19.8	1.5	35.5
vedhiammal	melena, rash	8.8	MCHC	47,000	13.1	1	30.9
chitra	nil	9.8	MCHC	1,50,000	13.4	1.01	30.2
renuga	melena	9.4	MCHC	80,000	12.8	0.98	16.2
kalaivani	menorrhagia	7.5	MCHC	36,000	25	1.9	42
srinivasan	nil	11.3	MCHC	3,36,000	13.5	1.03	22.7
rayadu	nil	10.5	MCHC	80,000	13.8	1.05	25
punniyakodi	nil	12.5	normal study	1,26,000	13.2	1	26
savithri	nil	11.2	MCHC	1,64,000	13.5	1	24.4
rukmani	melena	8.5	MCHC	70,000	13.2	1.02	29.2
vinoth kanna	oral cavity bleed	8.2	MCHC	68,000	26	2.1	40
ganesan	skin bleed	11	MCHC	45,000	13.1	1.05	39.4
ayapan	nil	7.8	MCHC	82,000	13.2	1	29.4
narayanan	nil	13.5	normal study	2,25,000	14.2	1.08	24.6
saranya	nil	10.3	MCHC	1,67,000	13.8	1.05	21.6
chellamuthu	nil	10.5	MCHC	1,05,000	28	2.13	34
duraisamy	melena	8	MCHC	1,24,000	19.7	1.49	30.5
mala	nil	10.2	MCHC	72,000	14.4	1.09	31.5
sambasivam	nil	8.5	MCHC	88,000	14.1	1.07	46.5
vasudevan	nil	11.5	MCHC	1,08,000	14.2	1.08	30.2
jayaraman	melena	12.5	normal study	98,000	13.5	1.02	32.4
krishnan	melena	6.7	MCHC	1,52,000	33	2.45	67
anjali	nil	11.2	MCHC	1,89,000	14.1	1.07	29
sundaram	hemetemesis	7.4	MCHC	58,000	20.1	1.5	40
divya bharathi	nil	12.5	normal study	4,06,000	13.6	1.04	25.5
loganathan	nil	13.5	normal study	1,89,000	14.1	1.07	32.1
balan	nil	13	normal study	2,25,000	13.5	1.02	26.1

jai ganesh	melena	10.2	MCHC	98,000	14.2	1.08	27.4
ramesh	nil	13.5	normal study	1,24,000	15.4	1.17	79.8
thirupathy	nil	10.4	MCHC	2,60,000	15.2	1.16	21.9
nivedhitha	nil	12.5	normal study	87,000	14.5	1.1	22.5
priya	hematuria,epistaxis	10.5	MCHC	18,000	14	1.06	26.2
kumar	melena	12.8	normal study	1,06,000	13.1	1	23.2
rajamanickam	nil	12.4	normal study	1,45,000	15.1	1.15	31.2
sadhana	nil	11	MCHC	96000	14	1.07	28.9
dhanalakshmi	nil	7.5	MCHC	1,10,000	14	1.07	26
krishnamoorthy	nil	11.2	MCHC	1,09,000	15.2	1.16	30.5
purushothaman	nil	10	MCHC	2,13,000	14	1.07	36.5
ram kumar	nil	13	normal study	2,98,000	13.2	1	24.8
pooovarasan	nil	12.2	normal study	2,32,000	12.6	0.96	29.3
settu	nil	12.5	normal study	2,78,000	12.8	0.97	32
meena	melena	10.2	MCHC	84,000	15.2	1.16	32
chellaiah	melena	10.8	MCHC	80,000	15	1.14	40.7
annammal	nil	7.5	MCHC	89,000	14.2	1.08	30.4
raju	nil	13.5	normal study	2,45,000	13.1	1	22.4
kannagi	nil	6.9	MCHC	54,000	13	0.99	28.2
paranthaman	local site	9.8	MCHC	85,000	15.6	1.19	34
bakkiyalakshmi	hematuria	8.8	MCHC	68,000	11.7	0.9	18.5
santhanam	nil	10.2	MCHC	1,02,000	15.2	1.16	31.5

Name	D-dimer	fibrinogen	anticoagulant usage	blood urea	s.creatinine	AST/ALT	T.Bilirubin
Prabavathy	1.5	501	no	23	0.6	31/28	1
Suresh babu	4.3	202	no	36	1.2	60/32	3.2
Vedhiammal	6.56	640	no	53.5	1.77	76/35	1.5
Chitra	0.53	258	no	26	0.85	26/23	0.8
Renuga	6.66	366	no	26	0.9	42/28	0.7
Kalaivani	10.52	202	no	48	2.2	124/98	3.2
Srinivasan	2.46	440	no	41	1	46/38	0.9
Rayadu	1.8	220	no	30	1.4	44/32	1.2
Punniyakodi	1.98	226	no	32	1.5	48/28	1.1
Savithri	5.54	525	no	34	1.4	159/72	0.8
Rukmani	6.54	302	no	28	1.2	98/64	2.1
Vinoth kanna	5.68	248	no	68	2.5	78/36	4.2
Ganesan	5.01	468	no	114	5.7	70/31	2.4
Ayapan	1.4	235	no	98	4.8	56/24	0.8
Narayanan	0.48	408	no	28	1.1	48/22	0.9
Saranya	1.3	318	no	26	0.7	18/24	0.9
Chellamuthu	2.25	314	acitrom	30	1.2	48/26	0.8
Duraisamy	8.81	268	aspirin	158	4.6	122/92	0.8
Mala	3.54	246	no	102	1.8	126/84	1.8
Sambasivam	0.51	298	Heparin	113	3.1	18/15	0.8
Vasudevan	1.8	308	aspirin	45	1.5	68/44	1.2
Jayaraman	4.68	298	no	44	1.6	48/38	1.1
Krishnan	1.98	810	heparin	97.2	1.92	28/25	0.6
Anjali	0.64	424	no	38	1.2	26/19	0.8
Sundaram	2.84	324	no	42	1.8	68/42	2.5
Divya bharathi	0.92	250	no	38	1.3	54/42	0.9

Loganathan	0.86	354	no	45	1.2	35/22	0.8
Balan	1.54	412	no	35	1.1	45/32	0.8
Jai ganesh	1.76	314	no	24	0.7	27/161	0.9
Ramesh	2.47	374	heparin	28	1.2	58/29	1.2
Thirupathy	4.89	366	no	36	1.3	65/79	0.9
Nivedhitha	0.46	424	no	22	0.8	114/86	1.1
Priya	1.42	362	no	26	1.2	48/32	1.3
Kumar	6.22	399	no	29	0.8	50/74	1
Rajamanickam	3.36	392	no	39	1.4	89/65	1.2
Sadhana	0.58	237	no	26	0.9	236/289	1
Dhanalakshmi	1.56	308	no	98	5.5	154/122	1.5
Krishnamoorthy	1.65	252	no	35	1.4	178/122	1.6
Purushothaman	0.6	289	no	32	1	65/77	1.4
Ram kumar	0.76	384	no	22	0.8	22/18	0.8
Pooovarasan	0.56	354	no	22	0.8	38/34	0.8
Settu	6.88	324	no	40	1.5	56/34	0.9
Meena	4.68	282	no	28	1.2	88/68	1.4
Chellaiah	6.4	309	no	62	1.8	36/31	4.1
Annammal	3.89	238	no	108	6.7	78/64	1.2
Raju	0.7	298	no	32	1.1	38/24	0.8
Kannagi	4.31	490	no	84	0.8	34/27	1.2
Paranthaman	2.25	246	no	82	2.4	112/88	2.6
Bakkiyalakshmi	19.6	309	no	62	3.2	45/33	0.7
Santhanam	5.64	423	no	32	1.2	35/24	0.8