Incidence and causes of new onset thrombocytopenia in the medical intensive care unit of a tertiary referral centre in South India

Dissertation submitted in part fulfillment of the requirements for the M.D. Degree Branch XXI (Transfusion Medicine and Immunohaematology) examination of The Tamil Nadu Dr.M.G.R.Medical University Chennai to be held in May 2020.

Registration number: 201731052

Incidence and causes of new onset thrombocytopenia in the medical intensive care unit of a tertiary referral centre in South India

Dissertation submitted in part fulfillment of the requirements for the M.D. Degree Branch XXI (Transfusion Medicine and Immunohaematology) examination of The Tamil Nadu Dr.M.G.R.Medical University Chennai to be held in May 2020.

DECLARATION

This is to certify that this dissertation titled "**Incidence and causes of new onset thrombocytopenia in the medical intensive care unit of a tertiary referral centre in South India**" is submitted by me in partial fulfillment towards M.D. in Transfusion Medicine and Immunohaematology (Branch XXI) examination of the Tamil Nadu Dr. M.G.R Medical University, to be held in May 2020.

I have independently reviewed the literature, standardized the data collection methodology and carried out the evaluation toward completion of the thesis.

Dr Raja Vasanth S.,

PG Registrar,

Department of Transfusion Medicine and Immunohaematology,

Christian Medical College,

Vellore.

CERTIFICATE

This is to certify that this dissertation titled "**Incidence and causes of new onset thrombocytopenia in the medical intensive care unit of a tertiary referral centre in South India"** is a bonafide work done by **Dr. Raja Vasanth S.** in partial fulfillment of rules and regulation from the **M.D. BRANCH XXI (Transfusion Medicine and Immunohaematology)** Degree examination of the Tamil Nadu Dr. M.G.R Medical University, to be held in May 2020.

Dr. Joy John Mammen, MBBS, MD

Professor and Head,

Department of Transfusion Medicine and Immunohaematology,

Christian Medical College,

Vellore.

Dr. Anna B Pulimood, MBBS, MD, PhD

Principal,

Christian Medical College,

Vellore.

CERTIFICATE

This is to certify that this dissertation titled **"Incidence and causes of new onset thrombocytopenia in the medical intensive care unit of a tertiary referral centre in South India**" is a bonafide work done by **Dr. Raja Vasanth S.**, in partial fulfillment of rules and regulation from the **M.D. BRANCH XXI (Transfusion Medicine and Immunohaematology)** Degree examination of the Tamil Nadu Dr. M.G.R Medical University, to be held in May 2020.

The candidate has independently reviewed the literature, the data collection methodology and carried out the evaluation toward completion of the thesis.

Dr. Dolly Daniel, MBBS, MD

Professor, Thesis Guide & Supervisor

Department of Transfusion Medicine and Immunohaematology,

Christian Medical College, Vellore

PLAGIARISM CERTIFICATE

URKUND

Urkund Analysis Result

Analysed Document:	201731052 TNMGR University.docx (D57226381)
Submitted:	10/18/2019 11:30:00 AM
Submitted By:	rajavasanth19@gmail.com
Significance:	4 %

CERTIFICATE – II

This is to certify that this dissertation work titled **"Incidence and causes of new onset thrombocytopenia in the medical intensive care unit of a tertiary referral centre in South India"** is of the candidate **Dr Raja Vasanth S.** with registration number – **201731052** for the award of **M.D. degree in the branch of Transfusion Medicine and Immunohaematology**. I personally verified the Urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains pages from introduction to conclusion and result shows four percentages (4**%**) of plagiarism in the dissertation.

Dr. Dolly Daniel, MBBS, MD,

Professor, Thesis Guide & Supervisor

Department of Transfusion Medicine and Immunohaematology,

Christian Medical College, Vellore

ACKNOWLEDGEMENT

First of all, I would like to thank God the Almighty for giving me the strength and grace and for providing me with this opportunity. This journey would have been impossible without His Grace and blessings.

I would like to express my deepest gratitude to my professor, **Dr. Dolly Daniel,** Department of Transfusion Medicine and Immunohaematology, for giving me the opportunity to complete this dissertation under her able guidance. Her depth of knowledge and attention to details are inspirational without which the concept and execution of this project would have been impossible.

I am indebted to my professors **Dr. Joy Mammen** and **Dr. Sukesh C Nair**, Department of Transfusion Medicine and Immunohaematology for their constant support and encouragement throughout my post-graduate years.

I extend my sincere thanks to **Dr. Abhishek** and **Dr. Binila Chacko,** Department of Medical critical care unit, for their invaluable help and inputs in the clinical aspects of my study.

I extend my sincere thanks to Mrs. Thenmozhi and Mrs. Poornima, Department of the Biostatistics, for their patience and input in statistical analysis.

I am very grateful to all the technologists and auxiliary staff of blood bank and coagulation lab, CMC, for their support.

Finally, I hearty thank all my family members, friends and colleagues, for being a great inspiration and also for their relentless love, care, help and guidance.

- Raja Vasanth

ABBREVIATIONS:

NOT	New Onset Thrombocytopenia
ICU	Intensive care unit
TTP	Thrombotic thrombocytopenic purpura
HIT	Heparin induced thrombocytopenia
MICU	Medical Intensive Care Unit
MHDU	Medical high dependency unit
DIC	Disseminated intravascular coagulation
DIT	Drug-induced thrombocytopenia
HUS	Haemolytic uraemic syndrome
ARDS	Acute respiratory distress syndrome
MAHA	Microangiopathic hemolytic anemia
UFH	Unfractionated heparin
LMWH	Low molecular weight heparin
PF4	Platelet Factor 4
IPF	Immature platelet fraction
PT	Prothrombin Time
APTT	Activated partial thromboplastin time
P2Yx	Purinergic receptor
GPCR	G protein-coupled receptors
TLR	Toll-like receptors

APACHE II	Acute Physiology and Chronic Health Evaluation II
SAPS	Simplified Acute Physiology Score
SOFA	Sequential Organ Failure Assessment
SIRS	Systemic inflammatory response syndrome
FDP	Fibrin degradation products
ISTH	International Society on Thrombosis and Haemostasis
ULvWF	Ultra large von Willebrand factor multimers
DITP	Drug induced immune thrombocytopenia (DITP)
PaGIA	Particle gel immunoassay
PIFA	Particle immunofiltration assay
TMA	Thrombotic microangiopathy
ADAMTS13	A Disintegrin-like And Metalloprotease with ThromboSpondin type I repeats

ABSTRACT

Objectives

1. To study the incidence, causes and the transfusion requirements of new onset thrombocytopenia in the medical intensive care unit.
2. To study the impact of new onset thrombocytopenia on outcomes of critically ill patients in medical intensive care unit (Hospital mortality, Ventilator free days, Requirement of vasopressor support, Acute kidney injury, Need for renal replacement therapy)

Materials and Methods

This prospective observational cohort study was carried out in the Medical Intensive Care Unit. All consecutive adult patients (age >18 years) who got admitted to MICU/MHDU with a normal platelet count (>150,000/μL) and who gave informed consent were included in the study, except for pregnant women. The platelet count of each enrolled patient was followed up for a period of 14 days or until their discharge from ICU (which ever came earlier).Patients who developed thrombocytopenia, after 48 hours of admission to ICU were further investigated for underlying causes. Subsequently the data for transfusion requirements, ventilator supports, inotrope requirements and hospital mortality were obtained and analyzed.

Results

In the eight month study from Oct 2018 to May 2019, 303 patients were enrolled in the study and the incidence of NOT in our study population is 22.8%. Sepsis-associated thrombocytopenia (72.50%) was the major cause for NOT. The difference in hospital

mortality between patients with and without NOT (56.5% versus 22.6%) showed statistical significance (p value <0.013) with an associated significant increase in ICU length of stay, transfusion requirements and development of acute kidney injury in patients with NOT (p value <0.001).

Conclusion

The incidence of NOT (22.8%) in our study population is comparable with that of the other international studies. Patients with NOT had 2.43 times the risk for mortality and significantly higher requirement of transfusion support and acute renal injury. Thus, it is evident that NOT in a patient during ICU stay has significant prognostic value in defining the outcomes (in terms of mortality) and planning transfusion requirements.

LIST OF FIGURES

LIST OF TABLES

CONTENTS

INTRODUCTION

Thrombocytopenia is one of the most common clinical conditions found in patients admitted in intensive care unit (ICU). It is defined as a drop in platelet count to less than 150,000/µL(1). While some patients are admitted into the ICU with preexisting thrombocytopenia, a sub group of patients develop thrombocytopenia during their course in the intensive care setting – referred to as new onset thrombocytopenia (NOT).
NOT has emerged as a significant finding that has shown association with patient outcomes, increased transfusion requirements, length of hospital stay, and acute kidney injury necessitating renal replacement therapy (13). However, literature is predominantly from the developed world and there is very limited data from India.

The causes for NOT in a patient admitted into ICU may vary and are usually secondary to underlying disease. The wide spread reason for NOT is predominantly found secondary to acquired causes such as sepsis, coagulopathy, drugs, etc(2) and reasons could be multifactorial. These include decreased platelet production, increased peripheral destruction – due to either immune or non immune causes, or a redistribution of platelets in the circulation.

In a critical care setting, from a clinical perspective, unless a platelet count drops below 100,000/µL, thrombocytopenia usually is not considered to be clinically significant, in terms of bleeding. Very often this risk of bleeding is seen in patients with severe

thrombocytopenia with a platelet count <50,000/µL, where the associated incidence of mortality is higher. A rapid assessment is necessary in such patients with increased bleeding risk to exclude treatable serious underlying conditions. Thus the cause for thrombocytopenia in an intensive care setting should necessarily be diagnosed, to treat patients efficiently (2).

Management of patients with NOT varies based on the causes for thrombocytopenia. NOT in a critically ill patient is often associated with prolonged hospital stay with an increased transfusion requirements due to their tendency to bleed (1).However, all patients with thrombocytopenia do not require platelet transfusions and most often treatment of the underlying disease is sufficient enough for the platelet recovery (2).In crucial circumstances, this treatment modality is complicated by the concomitant presence of thrombosis and thrombocytopenia, as in case of thrombotic thrombocytopenic purpura (TTP), heparin induced thrombocytopenia (HIT), etc, where the substitution of platelet concentrates can lead to life-threatening side effects(3).

On analyzing the significance of NOT in ICU, the incidence and prevalence varies depending on the development level of countries, geographical distribution and also based on the application centers (medical, surgical, mixed)(2).

Therefore in this context NOT can predispose a patient to increased risk of bleeding with an impact in patient's morbidity. Most of the studies describing this significance of NOT

and its causes are from western literature. Limited data is available from India, particularly relating to the causes of NOT. Considering the extreme variability and differences in disease profiles seen in our country, it remained essential to study the causes of NOT in our setting which might be helpful in guiding appropriate testing and interventions.

AIM

To study the incidence, causes and transfusion requirements of new onset thrombocytopenia in the medical intensive care unit of a tertiary referral centre in South India.

OBJECTIVES

- Primary objective:

  To study the incidence of new onset thrombocytopenia, it's various causes and transfusion requirements in a medical intensive care unit.

- Secondary objective:

  To study the impact of new onset thrombocytopenia on outcomes of critically ill patients in medical intensive care unit with regards to

  a. Hospital mortality
  b. Ventilator free days
  c. Requirement of vasopressor support
  d. New onset acute kidney injury
  e. Need for renal replacement therapy

MATERIALS AND METHODS

Setting:

This study was conducted in Christian Medical College, Vellore, Tamil Nadu. It is a teaching hospital providing tertiary medical care service to the residents of Vellore and surrounding districts of Tamil Nadu and some parts of Andhra Pradesh and Kerala. It also serves as a referral centre for patients from rest of India and South East Asia.

This was a prospective observational cohort study carried out by the department of transfusion medicine and division of critical care in the medical intensive care unit, of Christian Medical College and Hospital, Vellore, India. The study was approved by the Research and Ethics committee of the Institutional Review Board, Christian Medical College, Vellore. (IRB Min No: 11290 [OBSERVE] dated on 04.04.2018).

Study period:

The study was done between October 2018 and May 2019.

Study design:

Prospective observational cohort study

Study population:

All consecutive patients, who were admitted into the medical intensive care unit (MICU), / MHDU, and who met inclusion criteria.

Sample size:

Sample size was calculated based on the studies by Lim et al. and Mehta et al.

Table 1: Sample calculation

Single Proportion - Absolute Precision				
Expected Proportion	0.325	0.3	0.25	0.26
Precision (%)	5	5	5	5
Desired confidence level (1- alpha) %	95	95	95	95
Required sample size	337	323	288	296

Formula:

$$n = \frac{Z^2_{1-\alpha/2} p(1-p)}{d^2}$$

Where,

P : Expected proportion

d : Absolute precision

1- $\alpha/2$: Desired Confidence level

Inclusion criteria:

1) All medical patients who were admitted into MICU/MHDU during the study period
2) Hospitalized patients who got readmitted to MICU/MHDU during the study period.
3) Patients with a platelet count > 150,000/µL at time of admission into MICU / MHDU

Exclusion criteria:

1) Patients admitted for < 48 hours into MICU/MHDU.
2) Age < 18 years
3) Pregnant women
4) Patients with platelet count <150,000/µL at time of admission into MICU / MHDU

Definitions and diagnostic criteria followed:

a) <u>Thrombocytopenia:</u>

Thrombocytopenia was defined as a platelet count of <150,000/µL.

b) <u>New onset thrombocytopenia:</u>

New onset thrombocytopenia was defined as two or more consecutive platelet counts <150,000/µL, obtained at least 12 hours after admission to ICU.

c) Disseminated intravascular coagulation:

Disseminated intravascular coagulation (DIC) was considered to be present when the D-dimer level was elevated in addition to two of the following criteria: prolonged prothrombin time (PT), decreased fibrinogen, or platelet count<150,000/µL.

d) Drug-induced thrombocytopenia:

The diagnosis of drug-induced thrombocytopenia was considered only upon resolution of thrombocytopenia after discontinuation of the suspected drug.

e) Shock:

Shock was defined as the need for vasoactive drugs (> 5 µg/kg/min of dopamine or dobutamine or norepinephrine at any dose) for at least an hour.

f) Septic shock:

Septic shock was diagnosed when shock, associated with documented or assumed infection without any other identifiable cause of shock.

g) Sepsis:

Sepsis was defined as the presence of infection with an associated organ failure. In the context of infection, patients should have two or more of the following: temperature >38.3°C (101°F) or <36.0°C (96.8°F); tachycardia >90 bpm; tachypnoea >20 breaths/minute or $PaCO_2$<4.3 kPa (32 mmHg); hyperglycaemia (blood glucose >7.7 mmol/L [>140 mg/dL]) in the absence of diabetes mellitus; acutely altered mental status; leukocytosis (WBC count >12×10^9/L [12,000/microlitre]); leukopenia (WBC count

$<4\times10^9$/L [4000/microlitre]); or a normal WBC count with >10% immature forms. (Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) (2016))

h) Thrombotic thrombocytopenic purpura – Haemolytic uraemic syndrome (TTP-HUS):

The diagnosis of TTP-HUS was considered in any patient with thrombocytopenia evidenced by microangiopathy. In these patients ADAMTS 13 assay was done. The disease consists of the following pentad:

- Microangiopathic hemolytic anemia
- Thrombocytopenic purpura
- Neurologic abnormalities
- Fever
- Renal disease

i) Heparin Induced Thrombocytopenia (HIT):

The diagnosis of HIT was considered when a patient met the definition of thrombocytopenia which is not explained by other causes, after the use of unfractionated heparin (UFH) or low molecular weight heparin (LMWH), and tested positive for PF4/heparin antibodies (2).

j) Scoring system for HIT: (Refer Table 2, in annexure)

Study implementation:

All patients who fulfilled inclusion criteria were included in the study after obtaining informed consent. From Oct 2018 to May 2019, 303 patients who met the inclusion criteria were included in this study (As per the IRB approval, a minimum of 296 patients were required for the study).

Admission platelet count was done for all the patients from ICU, as per routine protocol. Subsequently platelet counts were performed to identify patients with NOT.

Patients were followed up for a period of 14 days or till their stay in ICU (If the ICU admission was <14 days). The platelet counts were monitored on days 3, 5, 10 and 14 respectively. Patients who developed thrombocytopenia are considered as the cases and were further investigated for their definite causes. The patients who did not develop thrombocytopenia during follow up were considered as controls. Outcomes, as described above were documented in both the groups.

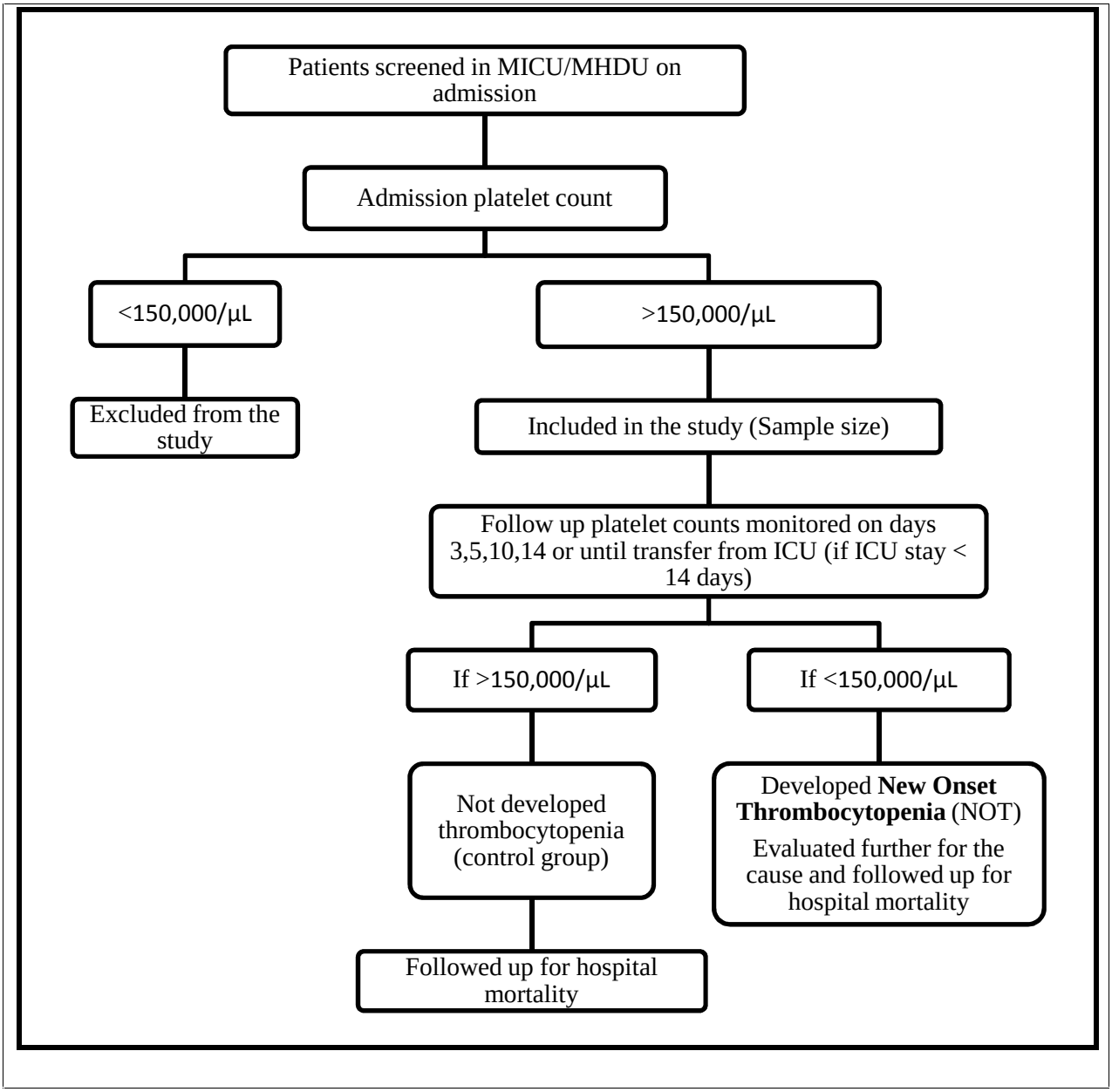

Figure 1 Study algorithm

For evaluating the cause of thrombocytopenia in the patient group (with NOT) the following tests were done –complete blood count, immature platelet fraction, peripheral smear examination, prothrombin time and aPTT. Significant drug history of the patients with NOT were also analyzed.

If heparin induced thrombocytopenia was suspected a 4T's scoring (Explained in Table 2) was done and if the pre-test probability of HIT is more (>4), anti PF4/heparin antibody assay was performed.

To establish the cause for NOT, the most common causes for NOT were assumed as sepsis-associated thrombocytopenia, drug induced thrombocytopenia, heparin-induced thrombocytopenia (HIT) and TTP/HUS like syndromes.

Thus a diagnostic algorithm was used to differentiate and define each specific cause for thrombocytopenia.

1. NOT with proven sepsis, and no abnormal coagulation parameters – will be considered as sepsis-associated thrombocytopenia.
2. NOT, with prolonged PT and aPTT with or without peripheral smear abnormalities – D Dimer and fibrinogen was performed. Combinations of test results are used to define DIC.
3. NOT with Normal PT and aPTT, and normal peripheral smear, but with a positive drug history – If heparin was implicated, and 4T'sscore suggestive – HIT screen test was performed. If other drugs implicated – were proved based on recovery of platelet count after the offending drug is discontinued.
4. NOT with normal PT and aPTT and fragmented red cells on peripheral smear. History of the Pentad to define TTP was collected. In those patients, ADAMTS13

assay was performed to distinguish TTP / HUS. Other tests such as LDH, renal function data were also followed.

5. Any other unusual unexplained cause – detailed history was documented to assign a cause for thrombocytopenia. If not possible – they are classified as etiology unknown (unclassified).

Statistics:

Data entry was done by using EPIDATA software and converted to Microsoft excel sheet for analysis. Data was analyzed using Microsoft excel and IBM SPSS Statistics 21 software. Frequencies and percentages were performed for presenting all categorical variables. Pie charts and bar charts were used for graphical representation. Pearson's Chi square test was used for finding statistical significance and p value <0.05 was considered as statistically significant. The risk factor analysis was performed using logistic regression analysis. Odd's ratios with 95% CI were presented.

LITERATURE REVIEW

CONTENTS

LITERATURE REVIEW

PLATELET MORPHOLOGY AND FORMATION:

Platelets were first discovered by Zimmerman in 1860, and subsequently their function in clotting of blood was described by Zimmerman and Hayran in 1878 (4). Platelets , derived from megakaryocytes are anucleated cells with a life span limited to around 5 – 7 days (5). Normal platelet counts range between about 150,000 –450,000/µL and platelets are found circulating in the peripheral blood with an average life span of 10 days. Of the entire platelet pool in a normal individual nearly 2/3rdis found in the circulation and the remaining 1/3rd in the spleen (4). Following the activation of platelets in haemostasis or at the end of their life platelets are removed from the circulation by the neutrophils and the macrophages and are transported to the spleen and thus it gets removed from the body (5).

FUNCTIONS OF PLATELETS:

Platelet function can be classified into two main categories -

1) Platelet function / role in haemostasis and thrombosis
    a) Platelet clot formation
    b) Platelet granule secretion
    c) Eicosanoid and prostaglandin formation in the platelet
2) Non-traditional function of platelets

- Platelet role in thrombosis and haemostasis

A) Platelet clot formation

In circulation, primary role of platelet is to maintain primary haemostasis and blood flow within the vessel. To accomplish this, platelets flows in close proximity to the vessel wall. Several stages are required for their activation to happen, which starts with the adhesion of platelets to the sub endothelial extracellular matrix by its interaction with specific receptors namely, GP1b/V/IX complex, GPVI and αIIβ1 receptors (5). Additional to this the circulating platelets are activated through the formation of secondary signals via the oxygenases COX-1 and 12-LOX pathways and also through granule secretions(5,7).

a) Platelet granule secretion

There are three types of granules are thought to be present in platelets.

- First type is the *dense granule*. Each platelet has about 4-6 dense granules with more than 200 small molecules found in each dense granules which include ATP, calcium, ADP, 5-HT, and epinephrine. When platelets get activated, dense granules fuses with plasma membrane of the platelets leading to the release of its content in to extracellular vascular spaces. Such a highly studied platelet receptor associated with dense granule release is the purinergic receptor (P2Yx).
- Second type of granule is the *alpha granule*. Each platelet has reported to have about 60-80 alpha granules. A number of larger proteins from the alpha granules are released in to the circulation or on the surface of platelet following the

activation of platelets. P-selectin, an important marker of platelet activation is released from the alpha granules.

- The third type of granule present in the platelet is the *lysosomal granule* which helps in degradation of proteins.

By positive feedback mechanism, the granules which are released during platelet activation, helps in recruiting new platelets into the growing thrombus. Some of these granules act by signaling the surrounding endothelium and blood cells. Thus following a vascular injury, platelet activation and clot formation play an important role in wound healing (5).

b) Eicosanoid and prostaglandin formation in the platelet

Following the initial activation, the bioactive lipids which are formed in the platelet plays important role in reinforcing the primary signal initiated through thrombin and collagen (8). Oxidation of free fatty acids produces majority of the lipid products. Eicosanoids and prostaglandins formed in the platelet or in other blood cells or endothelium plays certain role in regulating normal platelet function in haemostasis and thrombosis(5).

- <u>Non –traditional function of platelets</u>

The traditional role of platelet is limited to maintain an adequate haemostasis in the vessel under normal conditions and also causes an occlusive thrombus under pathological

conditions. There are few other role of platelets have been proposed which are independent of either haemostasis or thrombosis. It includes-

1. Platelets role in immunity.

   Platelet expresses all nine Toll-like receptors (TLRs) and these expression patterns differ by gender(9,10). Few studies have shown the ability these TLRs in autophagy. However the mechanism remains unclear(11).
2. Another function of platelet is to sample the blood environment, by presenting the foreign bacteria or virus to the other immune cells in circulation.
3. Regulated release of micro-particles.

THROMBOCYTOPENIA IN ICU

Thrombocytopenia is a laboratory finding which is frequently observed in patients admitted in ICU. The many co morbidities that are observed in a critically ill patient are the reason for this frequent existence of thrombocytopenia in ICU settings. A platelet count of <150,000/µL is considered as thrombocytopenia. Severe thrombocytopenia is defined when the platelet count is <50,000/µL (12).

Thus based on the laboratory values thrombocytopenia can be divided into:

1. Mild: 100,000 – 150,000/µL,
2. Moderate: 50,000 – 100,000/µL and
3. Severe: <50,000/µL. (66)

The six major mechanisms which can induce thrombocytopenia in an ICU patients are as follows(12):

1) Hemodilution,
2) Increased platelet consumption (Very common in patients in ICU after bleeding, tissue trauma and disseminated intravascular coagulopathy[DIC]),
3) Increased platelet destruction (i.e., immune mechanisms),
4) Decreased platelet production,
5) Increased platelet sequestration, or
6) Laboratory artifact – pseudothrombocytopenia.

These multiple pathophysiological mechanisms are due to dilution, thrombin – mediated platelet activation, extracellular histones, hemophagocytosis, ADAMTS13 deficiency and complement activation. From the perspective of patient management, the development of thrombocytopenia in ICU mostly indicates physiological decompensation and serious organ failure, rather than a primary hematologic disorder. Thus combining the past information of the patient along with the present observation of platelet trajectory in the patient's clinical course gives basic guidance in evaluating the diagnosis for thrombocytopenia.

FREQUENCY OF THROMBOCYTOPENIA IN ICU PATIENTS:

Many studies have demonstrated thrombocytopenia in about 35% - 45% of ICU patients. Moreover severe thrombocytopenia has been seen in about 5% - 20%. The incidence of thrombocytopenia, as described in literature ranges between 13.0% - 44.1% (13). However it is acknowledged that the incidence and prevalence of thrombocytopenia is variable and can be dependent on the timing and frequency of platelet monitoring, the definition of thrombocytopenia and the study population (13). When compared to medical ICU patients, surgical ICU patients have a higher incidence of severe thrombocytopenia. Thus the prevalence of thrombocytopenia at the time of admission to ICU is around 20% -30% and also a similar percentage of patients develop thrombocytopenia during their course of treatment (having a normal platelet count on admission) (12).

THROMBOCYTOPENIA – MARKER OF ORGAN IMPAIRMENT

Platelets are the key cellular components which play an important role in haemostatic mechanisms. It also has a vital role in several other physiological functions. Thus, thrombocytopenia occurring in critically ill patients are often against a background of multifactorial pathology (12) often with associated organ impairment such as renal failure, acute lung injury (ALI)/acute respiratory distress syndrome and other vascular leakage syndromes.

For diagnosing impending renal failure (acute), a declining platelet count in association with an underlying cause for renal impairment is often considered to be an easily-available laboratory marker. Many studies have demonstrated this significance of thrombocytopenia in patients with acute kidney injury (Ono et al (2006). A study by Claus et al (2009) emphasized the role of platelet aggregation in the development of renal impairment on the background of increased severity of systemic inflammation like sepsis. It has been demonstrated that a decreased ADAMTS13 activity with an increased plasma VWF levels leads to platelet aggregation in such patients(14).

Similarly, platelets play an important role in the development of acute lung injury (ALI). ALI is a life threatening pulmonary syndrome which is often seen in ICU patients and remains the main cause for serious morbidity and mortality with prolonged hospital stay. Platelets are integral to the barrier function of alveolar capillary endothelium. In critically ill patients with thrombocytopenia, this barrier integrity gets disrupted, leading to pulmonary edema.

In addition, the stability of the vasculature is maintained by platelets by the release of cytokines and growth factors which enable the closing of the small intercellular gaps at the vascular endothelial level. Thus it is important to note that the bleeding in most patients with thrombocytopenia is due to the disruption of the vascular integrity of the endothelium(14).

THROMBOCYTOPENIA – PROGNOSTIC MARKER

Thrombocytopenia is considered as a marker to assess the severity of illness in critically ill patients(15). It is also considered as a key prognostic factor in critically ill patients even in the absence of bleeding. A platelet count of <100,000/µL is associated with increased hospital stay and higher mortality. It has also been demonstrated that patients with thrombocytopenia are more likely to receive blood products with a longer requirement of mechanical ventilation (16).

There are multiple scoring systems available to assess the severity and prognosis of critically ill patients admitted to ICU. Some of the scores like Acute Physiology and Chronic Health Evaluation II (APACHE II), Simplified Acute Physiology Score (SAPS), Mortality Probability Model (MPM), Multiple Organ Dysfunction Score (MODS) and Sequential Organ Failure Assessment (SOFA) were used to assess the disease severity on admission. They have also been used to predict the outcome in ICU patients (17). Along with thrombocytopenia, critically ill patients have a higher MODS, SAPS and APACHE scores when compared to patients with a normal platelet count at the time of admission in ICU (18).

Between the survivors and non survivors in ICU, the admission platelet count does not seem to impact (18). However the platelet factors which strongly correlated with increased mortality are prolonged thrombocytopenia and severe refractory

thrombocytopenia where there is a lack of platelet increment despite appropriate intervention (Strauss et al (2002)) (19).Thus the severity of thrombocytopenia is a good prognostic indicator as evidenced by various studies (18). While there might be various underlying illnesses causing the severe thrombocytopenia, platelet count individually has been shown to correlate inversely with mortality(18).

Another critical factor for prognostication is the duration of thrombocytopenia. In studies showing the differences between the survivors and non survivors in ICU, the non survivors had significantly longer duration of thrombocytopenia (19). The study by Akca et al, 2002, showed a biphasic pattern of platelet counts in ICU patients with an initial sudden decrease followed by an increase in the platelet count. This is attributed to a physiological response to stress. However, the study also demonstrated that, out of the 204 thrombocytopenic patients, 67 had no relative increase in platelet count on day 14 and their mortality rate was significantly greater (30% vs. 11%) (73). Thus similar to the duration of thrombocytopenia, changes in platelet count over time is also considered as a relevant prognostic factor which is as good as APACHE II score in critically ill patients(14).

MECHANISMS CAUSING THROMBOCYTOPENIA IN ICU PATIENTS

There are multifactorial mechanisms responsible for the development of thrombocytopenia in an ICU setting. The common mechanisms are:

1) Massive consumption
2) Platelet destruction
3) Decreased production
4) Platelet sequestration

- Massive Consumption:

The clot formation secondary to a massive hemorrhage is often associated with thrombocytopenia due to massive consumption of the circulating platelets. In addition to this setting, patients also receive massive transfusions which can further dilute platelet counts(20).

DIC is a condition which is commonly associated with platelet consumption and the most common mechanism put forth is the thrombin-mediated platelet activation. However in few patients there will be a parallel consumption of coagulation factors ("overt" disseminated intravascular coagulation (DIC)) and in others a non-overt DIC is implicated(21). Hence, serial monitoring of routine coagulation measures are suggested to distinguish a non-overt DIC when there is a decrease in platelet count(22).

Thrombocytopenia seen in TTP is also associated with platelet consumption. However in TTP activation of the coagulation cascade is not seen.

Another condition which is associated with platelet consumption is the HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) occurring in pregnancy. The mechanism of thrombocytopenia in HELLP syndrome is due to the endothelial damage

occurring at the areas of placental ischemia leading to platelet activation and aggregation and thus forming local haemostatic plugs (23).

- Platelet Destruction

Immune mediated phenomena usually results in increased platelet destruction. Platelet autoantibodies could be demonstrated in patients with ITP, however the absence of the same cannot rule out ITP completely (25). At most of the times, ITP secondary to a viral infection, the virus specificity antibodies show cross-reactivity with normal platelet antigens (26). In some patients with ITP, the immune mediated mechanism can lead to decreased platelet production. Hence the diagnosis of ITP often remains as a diagnosis of exclusion (27).

Heparin induced thrombocytopenia (HIT) is also a condition which follows immune mediated mechanism. Thrombocytopenia which occurs due to heparin is entirely different from other forms drug-induced thrombocytopenia (DIT). It occurs in about 2% of patient receiving heparin treatment and is complicated by the development of thrombosis. Circulating antibodies to the complexes containing platelet factor 4 (PF4) and heparin are usually seen in most of the patients with HIT. Subsequently many platelet micro particles involves in the clot formation leading to thrombocytopenia (28).

- Decreased Production

Certain diseases and some toxic therapies directly suppress or damages bone marrow to develop thrombocytopenia. The common drugs which cause bone marrow suppression are the drugs used for chemotherapy. However as certain drugs suppresses bone marrow

entirely it is often associated with development of pancytopenia. Some acute viral infections associated with parvovirus and cytomegalovirus can cause thrombocytopenia. But these infections will usually not cause pancytopenia.

Alcohol abuse is one another cause for the development of thrombocytopenia. The several mechanisms which were postulated are,

1) Direct toxic effect of alcohol on megakaryocytes leading to decreased platelet production.
2) Concomitant dietary deficiency of B12 and/or folate associated with alcohol abuse will exacerbate thrombocytopenia with decreased platelet production.
3) Patients with chronic alcoholic cirrhosis with splenomegaly, can cause splenic sequestration of platelets leading to thrombocytopenia (28).

- Platelet Sequestration

Splenomegaly in a patient can cause increased sequestration of platelets. In the presence of splenomegaly, the splenic sequestration of platelets will increase from 33% to 90% of the total platelet mass. The common conditions associated with splenomegaly are portal hypertension, cirrhosis and polycythemia vera. In critically ill patients admitted in ICU, splenomegaly is seen in association with certain conditions like infection and congestive cardiac failure and can develop thrombocytopenia. Clinical bleeding is not seen in such patients despite significant thrombocytopenia as the total platelet mass and survival remains normal. In such conditions whenever there is a coagulation pathway signaling, the sequestered platelets will enter in to the general circulation, thereby achieving haemostasis.

Extracellular histone is one of the newly identified reasons for thrombocytopenia in critically ill patients. The mechanism is due to platelet aggregation. In a recent study it has been demonstrated that the development of moderate to severe thrombocytopenia is predicted with high levels of histone during the course of ICU stay (24).

CAUSES FOR THROMBOCYTOPENIA IN ICU

Based on the above mentioned mechanisms the causes for thrombocytopenia in ICU patients are broadly classified (Refer to Table 3, in annexure).

Although many causes have been described for thrombocytopenia in ICU, it remains a challenge for its confirmatory diagnosis. Thus in many occasions the cause is not identified. However, identifying the underlying cause is critical as it helps to guide appropriate management and also aids in predicting the prognosis. In a medical ICU setting the most common causes described for thrombocytopenia are (13,14,22):

- ***Thrombocytopenia associated with sepsis***
- ***Disseminated intravascular coagulation (DIC)***
- ***Drug induced thrombocytopenia (DIT)***
- ***Heparin induced thrombocytopenia(HIT)***
- ***Thrombotic thrombocytopenic purpura – Hemolytic uremic syndrome (TTP-HUS)***

THROMBOCYTOPENIA AND SEPSIS:

Sepsis is a syndrome involving immune system dysregulation, in response to infection with few non-immunologic mechanisms involving cardiovascular, neuroendocrine and metabolic pathways. It is a major public health problem due to its high prevalence and high mortality rate. Blood platelets play important roles in sepsis and thus it has gained attention in the recent decades. The reasons are-

1. Alterations in the platelet count are frequently encountered in an ICU setting. It accounts for about 20-50% of the patients getting admitted in ICU (18,19,74). Hence thrombocytopenia or the non-resolving thrombocytopenia is often associated with poor outcome.
2. Platelets play important role in coagulation and the maintenance of haemostasis. Hence it contributes in DIC.
3. Apart from the normal function of platelets in thrombosis and haemostasis, it serves as an essential factor in immune response, by responding to infections and maintaining the tissue integrity and also contributes to pathogen killing and tissue repair.

Thus platelets have an effective role in resolution of inflammation, enabling vascular protection and repairing of damaged tissues. With these functions, platelets can be described in the pathophysiology of multi-organ dysfunction (MOD)(29).

Pathophysiology in sepsis

- *Sepsis and dysregulated host response to infection:*

In sepsis the activation of innate immune system causes a systemic inflammatory condition which is characterized by the increased production of pro-inflammatory mediators and immune cell activation. The prognosis of patient's in sepsis is directly linked to the duration and magnitude of inflammatory response. The primary mechanism in triggering this innate immune response is mainly by pathogens and pathogen associated molecular patterns (PAMPs). Sepsis is usually associated with systemic-associated inflammatory response syndrome (SIRS) and in the progression of sepsis, an immunosuppressive state evolves making the outcome poor (29).

- *Platelets in inflammatory reaction and coagulation:*

Platelets are activated in pathological conditions, thereby multiple agonists are generated which further activates more platelets (30). In normal healthy vasculature, the activation of platelets is prevented by the inhibitory signals (nitric oxide and prostacyclin) circulating in close proximity to the vessel wall. When disruption of the endothelium happens, platelets get activated leading to its aggregation and subsequent activation of the coagulation cascade. The activated platelets releases numerous pro-inflammatory mediators like cytokines, chemokines, eicosanoids, vasoactive amines and few components of proteolytic cascades. These mediators will act directly or indirectly by activating of the bystander target cells. Endothelial cells (EC) and leukocytes are the primary targets for platelets.

As a result of platelet activation, the coagulation system and the inflammatory cascade get activated. Certain pro-inflammatory cytokines which were released during platelet activation also activates coagulation cascade and releases a number of inflammatory effectors, like thrombin, which in turn can again activate coagulation cascade. These mediators will further impair anticoagulant and fibrinolysis mechanisms leading to the dysregulation of coagulation system in sepsis. One of the dreadful complications of sepsis is DIC.

- *Platelets in vascular and tissue integrity:*

Platelets provide the necessary materials for endothelial repair which includes EC growth-promoting material, anti-apoptotic mediators and attractants for the progenitor cells. Thus they assists in vascular healing (31).

- *Platelets in multi-organ dysfunction syndrome (MODS):*

Sepsis is commonly associated with MOD and its complications. The markers of endothelial injury are usually elevated in sepsis according to its severity. The key features associated with the microvascular alterations in MOD are

  - Inflammation,
  - Thrombosis, and
  - Capillary perfusion.

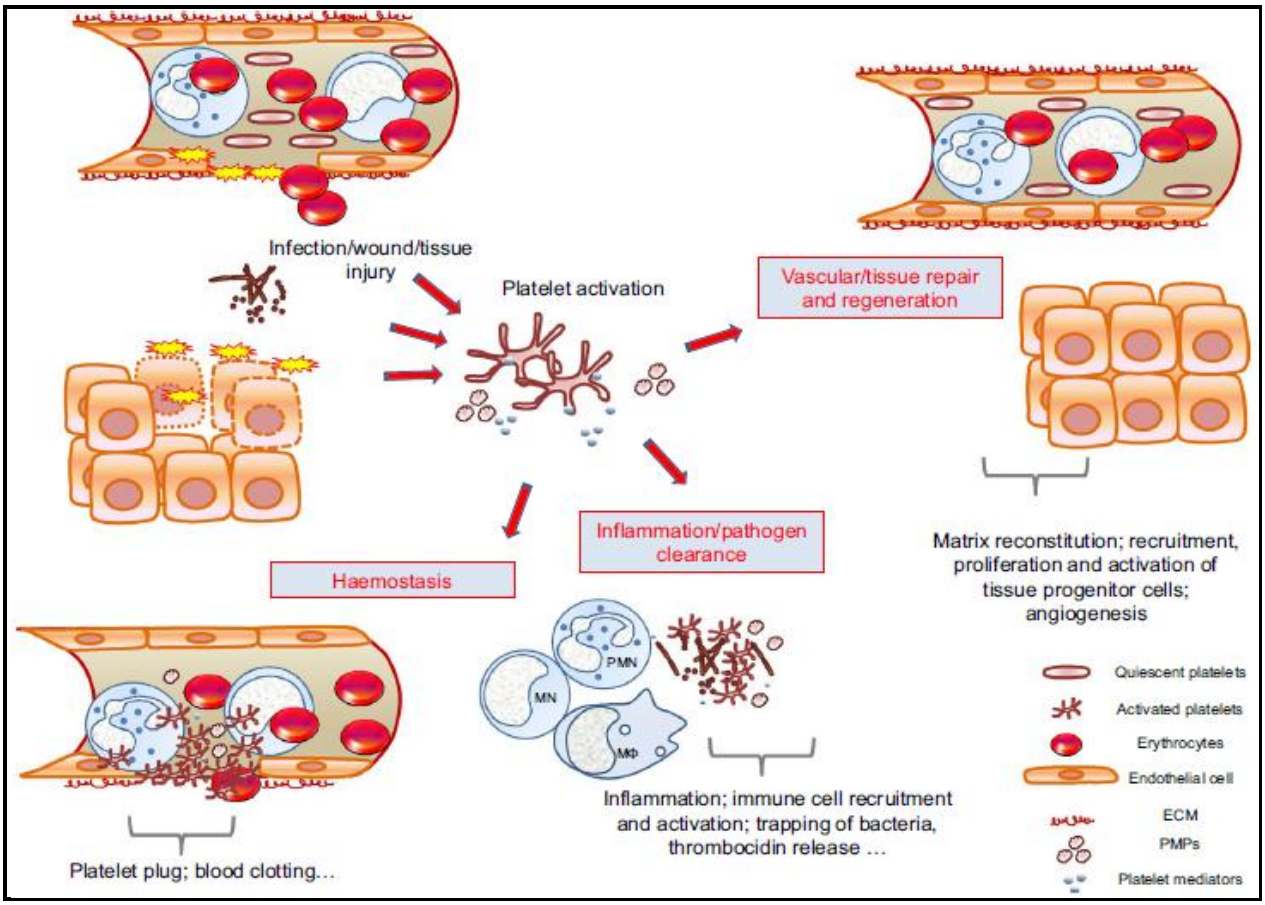

Figure 2 (29) Integral role of platelets in immune response, linking haemostasis, inflammation, pathogen clearance and tissue repair

As described before, platelets and ECs are activated in sepsis through many signals which can again activate platelets, thus contributing to MOD(29).

a) Platelets and acute lung injury (ALI) in sepsis:

The lung vascular endothelium injury happens due to dysregulated inflammation and coagulation dysfunction. This alteration in the alveolar-capillary barrier leads to the formation of pulmonary edema (32). The hallmark of ALI begins with the neutrophil

influx. Platelet plays important role in the activation and recruitment of neutrophils in the lung. Thus platelet mediated neutrophil activation results in the release ofcytokines, reactive oxygen species, chemokines and NET generation leading to tissue damage (33,34).

Certain genetic background also plays important role in ALI in terms of associated morbidity and mortality. Platelet count to a certain extent is determined by genetic factors. Few genetic studies showed the association of acute respiratory distress syndrome (ARDS) and low platelet counts. Genetic variants in the LRRC16A locus (6p22) are often associated with low platelet count and interestingly, a single nucleotide polymorphism within this locus link the risk of ARDS with low platelet counts(29).

b) Platelets and acute kidney injury (AKI) in sepsis

Another major sepsis related complication is acute kidney injury (AKI) which is often complicated by hemodynamic disturbances. AKI is associated with decreased glomerular filtration rate and other microcirculation alterations. In sepsis related AKI, a varying characteristic of apoptosis and tubular necrosis is observed (35). Apart from renal hypoperfusion, the immune response pathways which were associated with inflammation are of much importance in AKI progression. In patients with sepsis and sepsis related AKI there will be an elevated level of microparticles and PMPs seen. However their role in AKI remains unclear (36,37).

c) Platelets and organ-organ crosstalk in sepsis

An important organ-to-organ deleterious communication happens in sepsis. Platelets acts as a vector in these communications by exchanging pro-inflammatory and pro-coagulant signals to the distant organs, resulting in their injury (38).

Evaluation and management of thrombocytopenia in sepsis

Identifying the causes for thrombocytopenia is very much essential for patient management. Most of the time treating the underlying condition remains the primary focus of management. Platelet transfusion is the next option which has to be decided in patients with thrombocytopenia because in certain patients platelet transfusions might be deleterious and ineffectual. In patients with sepsis, even with adequate platelet transfusions, inadequate platelet count increment is observed (39).

As multiple mechanisms play a role in the development thrombocytopenia in ICU with regards to sepsis, diagnosis remains a challenge. In sepsis, the decreased production of platelets in the bone marrow can result from the underlying disease conditions and also by the inhibitory effects of the pathogen toxins, drugs and other inflammatory mediators. But the essential cause for thrombocytopenia in patients with sepsis is by peripheral mechanisms. The reduction in platelet half-life by their destruction/consumption is linked to the events occurring in sepsis, such as coagulopathy and immune mechanisms (29).Thus multiple factors has to be evaluated in diagnosing the cause for thrombocytopenia in sepsis (40).

In critically ill patients, the common cause for thrombocytopenia is seen secondary to sepsis. In ICU patients the kinetics of platelet count is often biphasic, characterized by a moderate decrease in the initial few days followed by a rise (Akca et al, 2002). NOT and early onset thrombocytopenia are associated with a poor prognostic significance in ICU patients. Similarly a poor out come in hospitalized patients are often linked to the magnitude and duration of thrombocytopenia with absence of platelet increments (29).

To delineate the mechanism of thrombocytopenia in sepsis, systematic investigations with routinely available tests would help. An early rise of reticulated platelets along with the percentage of immature platelet fraction will help in predicting the progression of sepsis (41).

In sepsis, platelets are perceived as bystanders where their destruction is related to the infection severity and hosts immune response to the infection (29). Hence treating the underlying sepsis remains the main stay of management.

Disseminated Intravascular Coagulation (DIC) and thrombocytopenia

DIC is a clinical condition characterized by the systemic activation of coagulation without any specific localization. This activated coagulation system can form fibrin inside the vessels and ultimately resulting in the thrombotic occlusion of midsize and

small vessels (42). This uncontrolled thrombin generation in turn may result in exhaustion of coagulation proteases and platelets leading to increased risk of haemorrhagic complications. Thus, a patient in DIC can present with both bleeding and thrombotic complications.

Clinical conditions associated with DIC

DIC in ICU patient's, commonly occurs secondary to an underlying disease and has been associated with most of the life-threatening conditions. The common conditions associated with DIC are (42)-

1) Sepsis
2) Trauma
    - Severe tissue injury
    - Head injury
    - Fat embolism
3) Cancer
    - Myeloproliferative disorders
    - Solid organ tumors (eg, pancreatic carcinoma, prostatic carcinoma)
4) Obstetrical complications
    - Amniotic-fluid embolism, Abruption placentae
5) Vascular disorders
    - Aortic aneurysm, giant hemangioma
6) Immunologic disorders

- Severe allergic reactions
- Transplant rejections
- Hemolytic transfusion reaction

7) Reactions to toxins
   - Snake venom
   - Drugs, amphetamines

- *Infectious diseases:*

Infection associated with septicemia is the commonest causes of DIC. Particularly in patients with bacterial infections, DIC is more frequently reported. In patients with gram-negative sepsis, an overt DIC can occur in about 30-50% of patients (43,44).

- *Severe trauma:*

Trauma's associated with brain injury are frequently associated with DIC. The mechanisms such as, release of fat and phospholipids from tissue into circulation, endothelial damage and hemolysis may contribute to the systemic activation of coagulation. About 50-70 percent of patients with systemic inflammatory response syndrome secondary to trauma, develop DIC (44,45).

- *Cancer:*

DIC can occur as a complication to both solid tumors and hematological malignancies. Around 10-15% of patients with metastasized tumors and acute leukemia develop DIC (75). The expressed tissue factors on the surface of tumor cells are often responsible for DIC.

- *Obstetrical disorders:*

Few obstetrical conditions such as abruption placentae, pre-eclampsia and amniotic fluid embolism are often complicated with DIC. It occurs in about 50% of patients with these complicated conditions (46). A thromboplastin-like material is leaked in to the circulation causes activation of coagulation. Most often these obstetrical conditions results in fulminant DIC and hence the disorder is usually short-lived and self-limiting.

- *Giant hemangiomas:*

These conditions can cause local activation of the coagulation system. There will be a local consumption of coagulation factors and platelets leading to systemic depletion. However these activated coagulation factors in turn reaches the systemic circulation and causes DIC. Around 25% of patients with giant hemangiomas may develop features of DIC (42).

- *Microangiopathic hemolytic anemia:*

It comprises of TTP, HUS, malignant hypertension, chemotherapy-induced microangiopathic hemolytic anemia and the HELLP syndrome (hemolysis, elevated liver enzymes and low platelet count occurring in association in patients with preeclampsia). The features include development of endothelial damage leading to the activation, adhesion and aggregation of platelets, formation of thrombin and an associated impairment of fibrinolysis.

Pathophysiology in DIC

The pathogenesis of DIC involves an uncontrolled generation of thrombin by the activated coagulation system and an impaired fibrinolytic system. These mechanisms are mediated by several proinflammatory cytokines. The primary mediator for activation of coagulation system is interleukin-6. The tumor necrosis factor α will activate coagulation system indirectly by activating interleukin-6. Thus it is an important mediator for the dysregulation of physiological anticoagulation and fibrinolytic pathways.

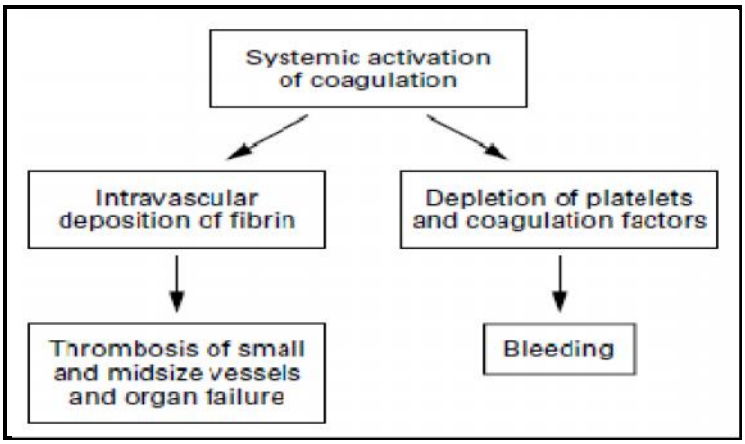

Figure 3 (42) Mechanisms - disseminated intravascular coagulation

The three pathologic features that occurs in DIC are-

1) Generation of thrombin
2) Defects in inhibitors of coagulation
3) Fibrinolytic defect

- *Generation of thrombin*

Systemic generation of thrombin in DIC is mainly mediated via the extrinsic pathway involving tissue factor and activated factor VIIa. The exact source of tissue factor is not clear. However in response to proinflammatory cytokines, tissue factors may be expressed on the mononuclear cells and also on the vascular endothelial cells.

- *Defects in inhibitors of coagulation*

In patients with DIC, all the physiologic anticoagulants are affected, including antithrombin III, protein C and tissue factor- pathway inhibitor. There will be a markedly reduced level of antithrombin III and impairment of protein-C system which will further compromise the regulation of the activated coagulation system. The reduction in the activity of protein-C is due to multiple factors including, impaired protein synthesis, decrease in levels of free fraction protein S (essential cofactor of protein C) and cytokine mediated decrease in the activity of endothelial thrombomodulin.

Tissue factor plays an important role in triggering the coagulation in DIC. Tissue factor-pathway inhibitor will inhibit this tissue factor. Though there is no functional defect or acquired deficiency of tissue factor-pathway inhibitor identified in patients with DIC, there is a significant dysregulation happens in its activity.

- *Fibrinolytic defect*

At the time of maximal activation of coagulation, fibrinolytic system is largely suppressed by the sustained increase in plasma level of plasminogen activator inhibitor-1(42).

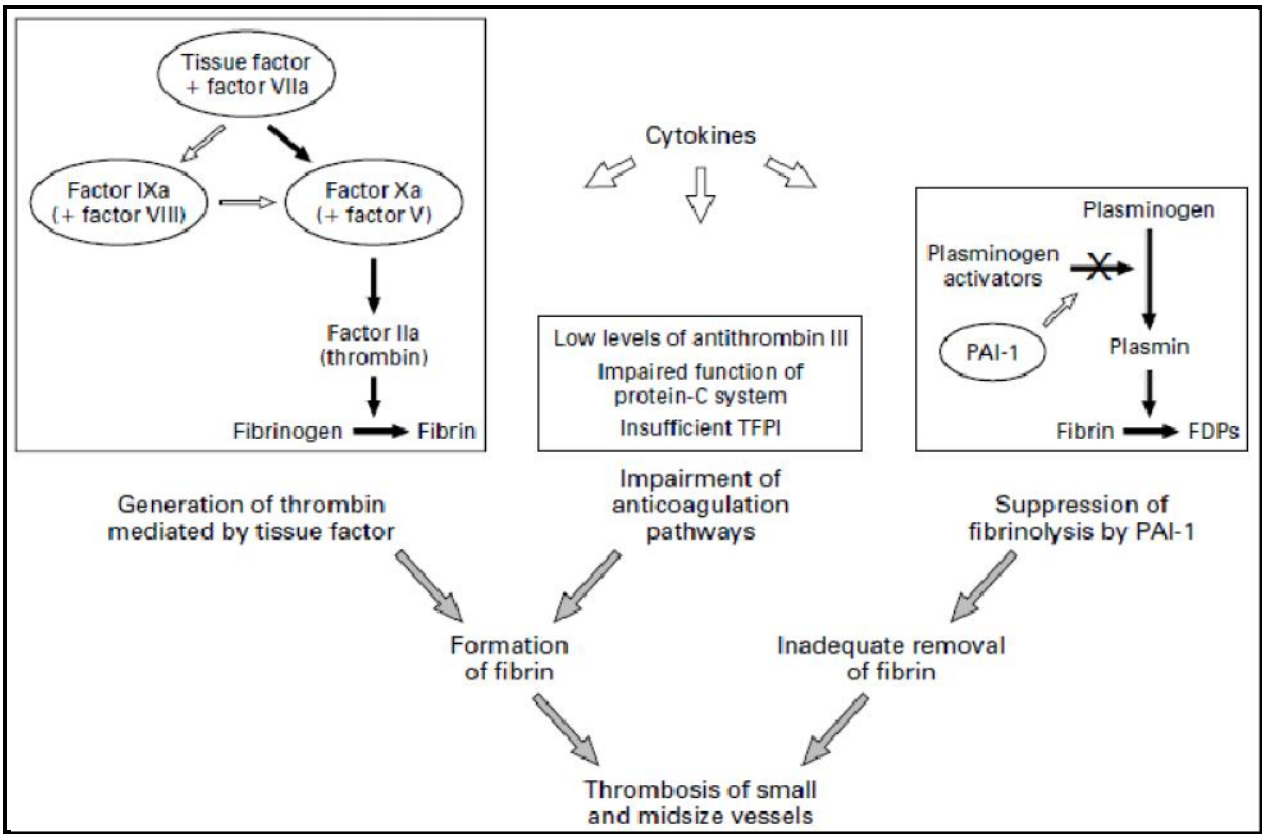

Figure 4 (42) Pathogenic pathways - In disseminated intravascular coagulation

Evaluation and management in DIC

The diagnosis of DIC is made only in the presence of clinical condition which is supported by relevant laboratory results. Multiple laboratory tests are done to evaluate the cause for DIC. This includes

- PT, APTT and platelet counts – to access the degree of coagulation factor activation and consumption.
- D-dimer and fibrinogen – Indirectly measures the fibrin formation.

The laboratory abnormalities observed in DIC are

- Thrombocytopenia
- Elevated fibrin degradation products (FDPs)
- Prolonged PT and APTT
- Low fibrinogen level

In early stages of DIC, platelet count and fibrinogen levels usually remains normal. A progressive drop in platelet count is a sensitive sign to evaluate DIC (76). This indicates the ongoing usage of platelets by thrombin-induced activation. The depletion of coagulation factors is usually reflected by prolonged clotting times, substantiated by the measurement of one or two selected coagulation factors.

Measurement of plasma fibrinogen level is often advocated in the evaluation of DIC. However as fibrinogen is an acute phase reactant the plasma level remains in the normal range in most of the times. However in cases with severe DIC hypofibrinogenemia is observed. Measurement of certain selected coagulation inhibitors like antithrombin III or protein C may provide important prognostic information.

Certain tests like D-dimers or fibrin-degradation products will be helpful in differentiating DIC from other clinical conditions which are associated with thrombocytopenia and abnormal coagulation tests. Severe liver disease is a clinical condition in which the differentiation of DIC is difficult, as both these conditions has similar laboratory abnormalities. In such conditions, identifying the underlying cause for the liver disease will be helpful (77).

Certain more specialized laboratory tests which are not commonly available are

- Measurement of soluble fibrin and
- Sensitive assays that can measure the generation of thrombin – to detect prothrombin activation fragment F_{1+2} or thrombin-antithrombin complexes.

These tests are much more helpful in diagnosing DIC but are not routinely available. These tests have sensitivity and specificity of about 80-90% in diagnosing DIC. They are helpful in complicated clinical situations but are not used in general clinical practice (77).

ISTH scoring system:

A scoring system has been recommended by the ISTH (International Society on Thrombosis and Haemostasis) subcommittee in diagnosing an overt DIC (Refer Table 4, in annexure). It has a five step diagnostic algorithm to calculate a score based on few simple laboratory results.

A score of 5 or more from four parameters are required for the diagnosis of an overt DIC. It is a sensitive tool to diagnose DIC in both infectious and non-infectious clinical conditions with sensitivity of 91% and specificity of 97%. There is also a strong correlation exists between increasing DIC score and mortality. The odds ratio for mortality of 1.25-1.29 has been demonstrated for each point increase in DIC score (48). Thus this score serves as an independent predictor of mortality as confirmed by many studies (49). It has also been demonstrated that patients with sepsis and DIC has a higher mortality rate when compared to patients without DIC (50).

Management

Treatment of the underlying disease remains the cornerstone in the management of patients in DIC. Often the treatment fails when the underlying disease is not adequately treated. The supportive measures are often necessary to get optimal treatment result,which varies between patients with bleeding complications and thrombotic complications.

Some of the supportive management includes the following modalities of therapy.

1) Anticoagulants

Patients in DIC will be benefited with the interruption of coagulation system by anticoagulants. In few experimental studies heparin has shown to partially inhibit the activation of coagulation in patients with DIC related to sepsis. To eliminate the risk of venous thromboembolism adequate prophylaxis is necessary. However the safety of heparin is often debated in patients with bleeding complications (42).

2) Platelets and plasma

In patients requiring invasive procedures, the bleeding risk increases with low levels of platelets and coagulation factors. In such patients, transfusion of platelets and plasma has shown a better outcome (51). The prophylactic administration of platelets or FFP is usually not recommended in patients who are not bleeding and who are not at a high risk of bleeding. To ameliorate or to correct the coagulation defects, large volumes of plasma might be necessary. The usage of coagulation- factor concentrates is generally not advocated as it might contain activated coagulation factors which will invariably exacerbate the pre-existing coagulation disorder (76).

3) Concentrates of coagulation inhibitors

Acquired deficiency of antithrombin III is almost invariably seen in patients with DIC, which is also one of the most potent natural inhibitor of coagulation. Administration of this inhibitor in patients with sepsis or with septic shock has shown beneficial effects in the improvement of DIC. Antithrombin III treatment in patients with severe DIC is considered as a supportive line of management. However the substantial costs of this treatment remains a major limiting factor (76).

4) Antifibrinolytic agents

It may be effective in patients with bleeding manifestations. Their usage in DIC is generally not recommended, as the deposition of fibrin in this disorder is due to insufficiently controlled fibrinolysis. However there has been a clear exception in case of DIC associated with cancer, especially coagulopathy associated with acute promyelocytic leukemia where antifibrinolytic therapy has controlled coagulopathy (42).

5) Other therapeutic options would be targeting the tissue factor activity and supplementing protein C system. However these are in the various phases of clinical trials (77).

Clinical relevance and prognosis

The morbidity and mortality risk in DIC depends on the intensity of the coagulation disorder and underlying clinical condition of the patient. However the risk of bleeding varies between patients. From various studies it is well known that DIC increases the risk of organ failure leading to death. The occurrence of DIC is often associated with an unfavorable outcome and it serves as an independent predictor for mortality (42). With the evidence from few prospective clinical studies, the risk of death doubles when DIC occurs in association with sepsis or severe trauma (78).

DRUG INDUCED THROMBOCYTOPENIA (DIT)

DIT was initially described with quinine about 140 years ago. Due to the lack of clinical evidence the incidence of DIT is not well known. The challenges in identifying DIT include the following factors (52):

1. Multiple other potential causes for thrombocytopenia coexists in ICU patients
2. Lack of standard definition for DIT
3. Lack of proper timing of platelet count monitoring to diagnose DIT
4. Inappropriate over and under suspicion of DIT in clinical practices.

Though the above mentioned limitation exists, about 10 million persons per year are suspected with DIT and 25% of critically ill patients are expected to have DIT. Patients with DIT often develop moderate to severe thrombocytopenia with platelet count of < 50,000/µL(52).

Drugs associated with DIT

Table 5: Drugs associated with decrease in Platelet Count(53)

Abciximab	Irinotecan	Haloperidol	Rifampin
Acetaminophen	Linezolid	Ibuprofen	Simvastatin
Ampicillin	Naproxen	Quinidine	Sulfisoxazole
Carbamazepine	Oxaliplatin	Quinine	Tirofiban
Eptifibatide	Phenytoin	Valproic Acid	Trimethoprim-sulfamethoxazole
Ethambutol	Piperacillin	Vancomycin	

Mechanisms in DIT

The thrombocytopenia occurring in association with drugs could be of the following reasons-

1. Decreased platelet production secondary to bone marrow suppression
2. Increased platelet destruction
3. Platelet sequestration

Drug induced thrombocytopenia occurs either due to immune or non-immune mechanisms. The DIT caused as a result of non-immune mechanisms is mainly

secondary to bone marrow suppression. Hence it might take several weeks for the thrombocytopenia to develop. However in patients with immune mediated DIT (Refer Table 6, in annexure), the median time for thrombocytopenia to develop is 14 days (54).

Diagnosis of DIT

In patients presenting with acute thrombocytopenia, where the cause is uncertain, drug induced immune thrombocytopenia (DITP) should be suspected. A careful and brief history of drug exposure is necessary to evaluate DIT. In the initial presentation, DITP can be misdiagnosed as acute autoimmune thrombocytopenic purpura (AITP) as both has same characteristic features. A criterion by George et al serves as a tool to establish the cause for DITP (Refer Table 7, in annexure).

The laboratory evaluation of DIT in critically ill patients includes the following investigations-

- Complete blood cell count
- Peripheral blood smear examination and measuring the mean platelet volume
- Platelet survival studies -
    - Platelet clearance study through radio-labeled platelet studies with $_{51}Cr$ (chromate)
    - Non-isotopic platelet labeling method
- Bone marrow studies – aspiration and biopsy
- Testing for immune mediated drug induced thrombocytopenia

- Platelet associated antibody detection
- Serotonin release assay
- Heparin Platelet Factor 4 Enzyme-Linked Immunosorbent Assay
- Drug-specific antibodies testing

Detection of platelet bound immunoglobulins will help in diagnosing DITP. This could be accessed by different techniques like, flowcytometry, complement fixation, platelet lysis methods and induction of platelet procoagulant activity or passive hemaglutination. However the sensitivity of these techniques in detecting drug dependent antibodies is uncertain (54).

Management of DIT

Whenever DIT is suspected the timing and severity of thrombocytopenia should be assessed. This is to determine the probability of particular suspected drug. In the setting of ICU with critically ill patients, DIT can coexist with other causes, as thrombocytopenia is often multifactorial. On deciding of to discontinue the offending drug, the risk vs. benefit must be evaluated (57).

- If the expected complication of thrombocytopenia is greater than the risk of discontinuing the offending drug, then the particular drug should be discontinued immediately.
- An alternative medication can be started with a different chemical structure.

- If the thrombocytopenia is not severe and if the patient's clinical condition allows, eliminating the suspected drug one by one may provide useful information.

As described above, though there are tests available to detect the presence of drug dependent antibodies their usefulness is often limited (52). The reason is due to the delay in obtaining results. Another reason is that the presence of antibodies in a patient does not always predict a reaction. There is also lack of adequate sensitivity and specificity for these tests. Thus the role of these test are limited to the effective prevention of the episodes of DIT in future (57).

Bleeding associated with severe thrombocytopenia typically ceases in 1-2 days after discontinuation of the drug. In immune mediated DIT, the median time for platelet recovery is 4-10 days (52). The recovery time may be prolonged in patients with associated organ failure. As a rule in general, if the platelet count does not recovers in 2 weeks after discontinuation of the drug, then the cause of the thrombocytopenia should be re-evaluated. Most often it is due to multiple foci. Re-challenging with the offending drug to establish diagnosis for thrombocytopenia should be avoided (54).

In patients with symptomatic thrombocytopenia, platelet transfusions can be administered, which is also applicable to patients with high risk of bleeding and severe thrombocytopenia. Platelet transfusions are contraindicated in patients with heparin induced thrombocytopenia. There is an excellent prognosis is observed when the

offending drug is discontinued. The role of other medications such as IVIG, corticosteroids, platelet growth factors and plasmapheresis in DIT is uncertain (54,57).

HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

In critically ill patients heparin is widely used for both therapeutic as well as prophylactic therapy in thromboembolic diseases. HIT is the most serious complication of heparin therapy (58). IT is an immune-mediated prothrombotic complication which occurs with UFH and to a lesser extent with low molecular weight heparin (59).

Pathophysiology of HIT

In patients with activated platelets, heparin can cause mild platelet aggregation in vivo. This ultimately results in thrombocytopenia due to increased sequestration of platelets in spleen. In HIT, thrombocytopenia may develop as a result of immune or non-immune mechanisms (58).

Clinically HIT can be differentiated in to two types-

1. HIT type I – A benign non-immune condition
2. HIT type II – Immune mediated syndrome caused by antibody to the PF4/heparin complex.

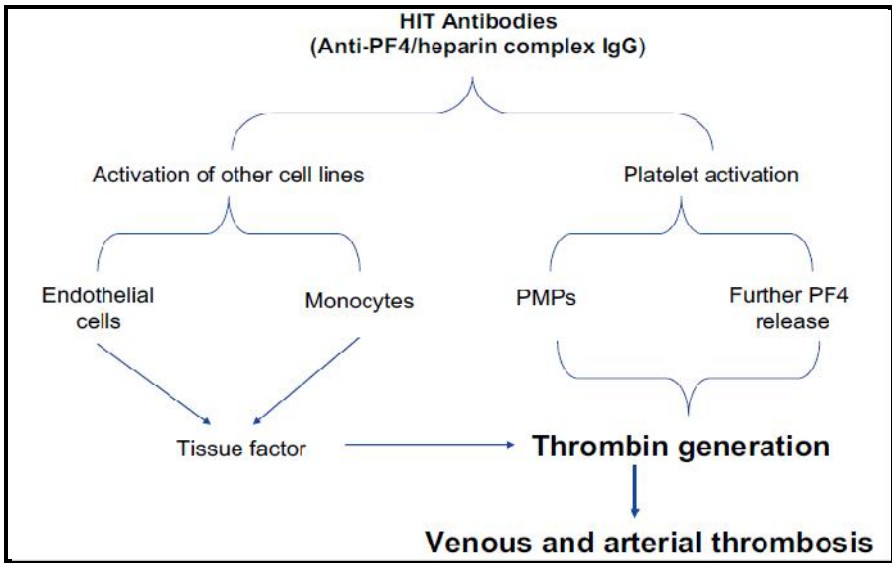

Figure 5 Pathogenesis of HIT

- *Non-immune HIT:*

It is a self limiting condition which is not associated with any major complications and occurs in about 10-30% of patients within 4 days after getting exposed to heparin. In type I, heparin binds to PF4 and inhibits adenyl cyclase and causes mild thrombocytopenia. The platelet counts rarely falls below 100,000/µL (58).

- *Immune-mediated HIT:*

It is characterized by an immunological response when a patient is exposed to heparin. It is complicated by absolute or relative thrombocytopenia with increased risk of thrombosis. Heparin causes structural change to the PF4 granule released from platelets and in turn form PF4/heparin complex. An immune response is triggered against this complex leading to the formation of IgG antibodies. Further the antibodies via Fc-receptors cause platelet activation and increase the risk of forming arterial thrombosis.

Clinical manifestations:

1. *Thrombocytopenia*

In about 85-90% of patients with HIT, thrombocytopenia is the first sign with a drop in platelet count below 150,000/µL or more than 50% reduction from the baseline platelet count. Thrombocytopenia usually occurs 5-10 days after the initiation of heparin therapy (typical onset HIT) as the immune system might take several days to produce sufficient amount of anti-PF4/heparin antibodies (58).

In patients with preformed anti-PF4/heparin antibodies, a rapid onset of thrombocytopenia could develop. These antibodies are mostly formed as a result of the previous exposure of patient to heparin. In such patients certain local reactions like fever, skin lesions, rigors / chills etc, can occur during the administration of heparin. Thrombocytopenia may also develop in some patients after the termination of heparin therapy and represents the delayed onset of HIT. This mechanism is due to the presence of large numbers of anti-PF4/heparin antibodies leading to additional activation of platelets in the absence of heparin (58).

2. *Thrombotic complications*

Around 30-70% of patients with HIT develop thrombotic complications. Thrombotic event occurs in about 40% of HIT patients prior to the development of thrombocytopenia. However, the magnitude of thrombocytopenia usually correlates with the risk of thrombosis (60). The common complications associated with HIT are (DVT) deep vein

thrombosis and pulmonary thromboembolism (PTE) with the chance of developing venous thrombosis is greater than arterial thrombosis (61).

3. *Other complications*

The bleeding risk is relatively low in patients with HIT even if platelet count falls below 20,000/µL. In some patients bleeding can occur as a result of platelet dysfunction secondary to an underlying condition such as uremia.

Scoring system for HIT

The 4T's scoring system helps to predict the pretest probability of HIT (Refer Table 2, in annexure).

Laboratory diagnosis of HIT

Laboratory tests can be performed to detect the presence of HIT antibodies in patients with suspected HIT. There are two types of assays available which are-

a) *Functional assays*

The functional assays are based on the in vitro activation of platelets which are identified based on the presence of IgG-HIT antibodies. These assays have a high specificity when the controls are performed appropriately. Functional assays include

1. Heparin-induced platelet activation (HIPA)
2. Serotonin release assay (SRA)

The drawbacks of these tests are the high turn-around time and are performed only in few experienced laboratories.

b) Antigen assays

Enzyme-linked immunoassays (ELISA) are the most commonly used tests to detect HIT antibodies. These assays will non-specifically detect antibodies against PF4/heparin complex. ELISA assays are highly sensitive assays with lower specificity when compared to functional assays.

The other assays available are

1. Particle gel immunoassay (PaGIA)
2. Particle immunofiltration assay (PIFA)

<u>Management of patients with HIT</u>

The treatment principles of patients diagnosed with HIT can be summarized as (79)-

A) Three do's
    1. Do stop heparin
    2. Do start alternative anticoagulation
    3. Do documentation of the diagnosed HIT in the medical records
B) Three don'ts
    1. Don't give warfarin
    2. Don't give prophylactic platelet transfusions
    3. Don't proceed with inferior vena cava filter
C) Three diagnostics
    1. HIT antibodies are tested
    2. Test for DIC
    3. Evaluate for DVT and other thrombotic complications

All heparin usage should be stopped when the clinical suspicion of HIT is established. Prophylactic transfusion of platelet is not indicated, as it might subsequently leads to platelet activation. In a critically ill patient these treatment principles should never be applied indiscriminately because of many reasons (80).

- HIT is diagnosed only in a few number of patients admitted to ICU.
- Critically ill patients often develop renal and hepatic dysfunctions leading to an accumulation of anticoagulants. Thus the risk of bleeding is increased in these patients.
- Coagulopathy which is commonly found in ICU patients can confound the PTT-adjusted direct thrombin inhibitor therapy.

Alternative anticoagulation:

Alternate anticoagulant can be started when there is high clinical suspicion of HIT despite thrombocytopenia. The choice for alternative anticoagulant is decided based on the availability, preferences and associated medical conditions. After stopping heparin, a non-heparin, non vitamin K antagonist anticoagulant might be started (80).

1. Indirect factor Xa inhibitors – danaproid and fondaparinux
2. Direct thrombin inhibitors – lepirudin, argatroban, bivalirudin

Immunotherapies:

Plasmapheresis has been advocated in patients with HIT, having risk of thrombosis and undergoing cardiac surgery. This has been done in few studies, when patients are having a previous history of HIT with current tests showing anti PF4/heparin antibodies. In few

studies the use of IV immunoglobulin (IVIG) has been documented in patients with refractory HIT.

Outcomes:

The clinical outcome in patients with HIT may vary based on the severity and underlying clinical condition. About 20-68% of patients with HIT develops thrombotic event. However, mortality rate in patients with HIT differs.

Thrombotic microangiopathy syndrome

Thrombotic microangiopathy (TMA) is a group of disorder characterized by microangiopathic hemolytic anemia, thrombocytopenia and organ dysfunction due to platelet agglutination in the micro vasculatures (61). TMA remains as a serious life threatening disease requiring an early diagnosis and an urgent therapeutic management for better outcomes.

<u>Types of TMA</u>

The two main types are (81),

1. Thrombotic thrombocytopenic purpura (TTP) – frequently characterized by multiple organ involvement
2. Hemolytic uremic syndrome (HUS) –predominantly associated with renal involvement

Both TTP and HUS shares similar clinical features. There are multiple other forms of TMA's exists which are frequently associated with underlying diseases. Some common disorders which are associated with thrombocytopenia and microangiopathic hemolytic anemia are(62)-

- Systemic infection
- Systemic cancer
- Severe preeclampsia, eclampsia, HELLP syndrome
- Severe hypertension
- Autoimmune disorders (e.g., systemic lupus erythematosus, systemic sclerosis, antiphospholipid syndrome)
- Hematopoietic stem-cell or organ transplantation

Pathophysiology:

The initial process common to all forms of TMA is the activation of the vascular endothelium leading to the formation of local platelet aggregation and subsequent formation of microthrombi in the circulation. There are various factors required for this activation of the endothelium to happen which includes infection, drugs, stem cell transplantation, etc.

- *In thrombotic thrombotic thrombocytopenic purpura:*

The von willebrand factor (vWF) and ADAMTS13 plays important role in TTP. Physiologically vWF is a large multimeric glycoprotein which triggers the formation of platelet clot. It also helps in the transport of clotting factor VIII. The vWF multimers

have more intense hemostatic properties than monomers. The ADAMTS13 is a metalloprotease which helps in cleaving vWF multimers to monomers. In TTP due to low level of ADAMTS13 activity, there will be a significant accumulation of ultralarge vWF (ULvWF) in the plasma. These ULvWF has significant procoagulant activity leading to excessive platelet aggregation and microthrombi in the circulation (81).

- *In hemolytic uremic syndrome:*

In HUS, the intravascular coagulation specifically involves the renal microcirculation. The two distinguished forms of HUS are,

  - Post-diarrheal HUS – Mainly affects younger children (1-5 years).
  - Atypical HUS – Occurs in the absence of diarrheal diseases. It is usually found in older children and adults.

Post-diarrheal HUS is the most frequent form of HUS (90% of cases). The main reason is due to the toxins produced by bacteria. The bacteria those are responsible for this type of HUS were (81)-

Escherichia coli	Salmonella typhi
Shigella dysenteriae	Camphylobacter jejuni
Yersinia pseudotuberculosis	

In post-diarrheal HUS, massive amount of toxins are produced by the bacteria during their colonization phase. In turn these toxins enter the systemic circulation by internalization through specialized receptors. With the help of neutrophils they are

subsequently transferred to the target tissues, i.e., the kidney. The damaged renal endothelium will cause activation of platelets leading to thrombocytopenia.

Atypical HUS is a rare form and occurs in about 7-10% of cases. It is characterized by the absence of any gastrointestinal infections. The cause for atypical HUS is poorly distinguished. One of the mechanisms hypothesized is due to the deficiency of factor H which can induce excessive consumption of C3 fraction of the complement ultimately leading to increased activation of neutrophils. This activated nutrophils will cause excessive platelet aggregation.

Clinical features and diagnosis

The prevalence of TMA disorders in the critical care patients is about 0.35% of the entire admissions (82). The classic pentad features of TTP includes,

1. Fever
2. Altered mental status
3. Microangiopathic hemolytic anemia
4. Thrombocytopenia
5. Renal insufficiency

However the entire pentad features are seen in less than 40% of cases (63). The diagnosis of TTP should always be considered in a patient with anemia, thrombocytopenia and a

coexisting organ failure. In HUS, renal failure is predominantly seen and is classically associated with severe hypertension.

The laboratory findings which could be observed are (81)-

- Microangiopathic hemolytic anemia
    - Fragmented red blood cells (schistocytes) on peripheral blood smear
    - Reticulocytosis
    - Increased indirect bilirubin level
    - Decreased haptoglobins
    - Negative direct Coombs test
- Thrombocytopenia
    - Platelet count often lower than 20,000/µL
- Coagulation studies
    - Normal APTT and PT
    - Negative DIC screen
- Markedly increased lactate dehydrogenase (LDH) level (tissue ischemia and hemolysis)
- Variably increased creatinine level (HUS >TTP)

<u>Management and prognosis</u>

TMA requires emergency treatment hence early diagnosis is necessary. TMA disorders always have an unpredictable outcome.

- *Symptomatic treatment*

All the aggressive intensive care management protocols should be followed. Whenever necessary the supportive measures like ventilatory supports, vasopressor requirements, dialysis, anticonvulsants, antihypertensive medications, antibiotics and packed cell transfusions should be started appropriately. Platelet transfusions are contraindicated unless and until there is an uncontrollable massive bleeding.

- *Specific treatment – plasma therapy*

Plasma therapy should be started at the earliest in patients with TTP as it has been proved beneficial. The plasma therapy could either be a fresh frozen plasma transfusions or a plasma exchange. However, plasma exchange is often beneficial and hence it is preferred over FFP transfusions. It serves as the first line of management in patients with TTP.

- *Second-line adjuvant therapy*

High dose of corticosteroids remains the second line of treatment. In the absence of any contraindications, steroids can be given following plasma exchange.

- *Others*

Other forms of TMA disorders are often associated with underlying clinical conditions like pregnancy, hematopoietic stem cell transplantation, cancer, drugs or toxins, HIV infection, etc and should be managed by treating the underlying causes.

The prognosis of TMA disorders is considerably poor prior to the introduction of plasma therapy. Since then the prognosis in terms of mortality has improved. However TMA syndromes associated with severe organ dysfunction and requiring an ICU admission have higher mortality (81).

APPROACH TO NEW ONSET THROMBOCYTOPENIA IN ICU

New onset thrombocytopenia was defined as two or more consecutive platelet counts <150,000/μL, obtained at least 12 hours after admission to ICU.

NOT is always associated with an unfavorable prognosis as evidenced by many studies, reported an association between thrombocytopenia and poor outcomes (16, 18). Sprung et al. reported the relative risk of mortality of 1.7 in patients with thrombocytopenia and sepsis in ICU patients. Similarly, Vanderschueren et al. (18) noted that patients with thrombocytopenia had significantly greater ICU mortality (33.8% vs 9.3%) and significantly longer ICU LOS (8 vs 5 days) compared to those without thrombocytopenia. The increased risk of mortality is due to the following reasons (68)-

- **a.** Thrombocytopenia is a marker of severe organ dysfunction and is frequently seen in patients with greater disease severity.
- **b.** Thrombocytopenia is often associated with an underlying disease processes and due to its severity, patients with thrombocytopenia requires intensive care management.
- **c.** Thrombocytopenia is often associated with haemostatic derangement and complicated by bleeding, transfusion, and thrombosis which may adversely affect the patient's prognosis.

As the cause for thrombocytopenia in ICU is often multifactorial, correcting one of its causes may not normalize the low platelet count. Hence a multipronged approach is

necessary. The severity of thrombocytopenia reflects on symptomatic bleeding and has an adverse prognosis. Even in patients with moderate thrombocytopenia, organ failure is often observed. The classical view for thrombocytopenia in ICU is usually associated with thrombin-mediated platelet activation. As described earlier platelets has multi-function in different organ systems, thus it is observed as a common finding secondary to various co-morbidities in patient admitted to ICU (22).

Practice pointers to identify the cause for thrombocytopenia

- ***Rapidity of onset of thrombocytopenia***

Immune mediated cause for thrombocytopenia is often indicated by an acute drop in platelet count. Drug-induced thrombocytopenia is one of the classical example for an acute drop of platelet count due to the formation of drug-dependent platelet reactive antibodies (64). One of the common difficulties in establishing the diagnosis of DIT, in a patient admitted in ICU is that the patients are often being treated with multiple drugs. In patients with septic or any inflammatory disorders a gradual development of thrombocytopenia is observed (Warkentin, 2015a,b).

- ***Timing of onset of thrombocytopenia***

Thrombocytopenia developing in the first 2-3 days of ICU admission is often due to patient's clinical status itself (postoperative state or trauma). HIT is classically seen 5 days after the exposure to heparin (14). However in case of a recent previous exposure to heparin (within the previous 100 days) the onset may be rapid.

- ***Thrombocytopenia in combination with thrombosis***

HIT is often characterized with the development of thrombocytopenia in association with large-vessel venous thrombosis or arterial thrombosis. Thrombocytopenia and macrovascular thrombosis can be seen in combination in patients with antiphospholipid syndrome. In patients with overt DIC microthrombi can develop leading to multiorgan failure.

- ***Absolute platelet count value***

The severity of thrombocytopenia is useful in establishing a differential diagnosis.

- ***Thrombocytopenia in patients with confirmed sepsis***

Systemic inflammatory response syndrome (SIRS) or sepsis is the most common cause for thrombocytopenia in patients getting admitted to ICU. As multiple factor contributes to sepsis-associated thrombocytopenia, treating patients with a single approach may not help in the recovery of platelet count. The key for the treatment in sepsis is the supportive treatment with a focus on treating the sepsis episode (14).

- ***Thrombocytopenia with an abnormal coagulation profile***

In the presence of thrombocytopenia, an abnormal coagulation profile usually denotes an extensive thrombin generation and it is commonly seen in septic DIC. Low fibrinogen level may also be found in association in patients with DIC. However as fibrinogen is an acute phase reactant, supranormal fibrinogen levels may be seen in DIC. Other clinical marker like D-dimer levels, which is markedly raised in DIC will help to differentiate it from an underlying liver disorder (22).

- ***Thrombocytopenia in patients with artificial devices***

Three-fourths of patient receiving continuous renal-replacement therapy is reported to develop thrombocytopenia (65). The reason is due to the adherence of platelets to the dialysis-filtration membrane. Other artificial machines associated with thrombocytopenia are the cardiac-assist devices and the extracorporeal membrane-oxygenators.

- ***Heparin induced thrombocytopenia***

Majority of the patients in ICUs will be getting exposed to heparin. Hence in the event of thrombocytopenia, the 4Ts score should be calculated along with other laboratory assays to exclude or to confirm HIT.

- ***Bone marrow disorders***

Haematological malignancies can also be a cause for thrombocytopenia in ICU. It is found in association with anemia and severe infections. Thus a bone marrow examination is required in such cases when the blood film shows abnormalities.

MANAGEMENT OF THROMBOCYTOPENIA IN ICU

As thrombocytopenia occurs as a consequence of an underlying disease, the treatment of the underlying causative condition will improve the platelet count. Severe thrombocytopenia can lead to bleeding symptoms and hence platelet transfusion may be indicated. However the microvascular complications, like thrombosis should be evaluated thoroughly.

- ***Bleeding in thrombocytopenic patients***

Thrombocytopenic patients can bleed when the platelet count falls below 20,000/µL. The most common cause for thrombocytopenia in ICU is due to platelet consumption rather than hypoproliferative conditions (Tosetto et al, 2009). In such cases platelet transfusions may be harmful. Platelet dysfunction may also accompany in certain conditions like sepsis, uremia and trauma. Hence the bleeding threshold for these patients is even as higher as 50,000/µL (83). Despite severe thrombocytopenia, some patients may not bleed due to the endothelial activation and release of large amounts of vWF and hence the low platelet count is compensated (Hugenholtzet al, 2009).

- ***Platelet transfusions***

Despite of any evidence of benefit, platelet transfusions are often used to treat patients with thrombocytopenia. Around 30% of patients in ICU will receive transfusions and most of which are for prophylactic treatment (67). There are many guidelines available to recommend the platelet transfusion threshold.

The most commonly accepted platelet thresholds are as follows (14):

1. The platelet counts of $10 \times 9\ 10^9$/L for those without bleeding.
2. $20–30 \times 10^9$/L for bleeding patients with an associated coagulopathy (DIC) or severe hepatic or renal dysfunction.
3. In case of a suspected platelet dysfunction, a threshold of about 50×10^9/L is usually considered (84).

4. In patients with intracranial bleeding a higher threshold is recommended (>100 × 10^9/L).
5. If any patient is undergoing surgical or radiological interventions then prophylactic platelet transfusions are recommended. The threshold varies for different procedure.

The platelet transfusions are usually contraindicated in patients with TMA and HIT.

- ***Thrombosis in thrombocytopenic patients***

It is difficult to treat a patient with both thrombocytopenia and acute venous thrombosis. It is necessary to rule out certain thrombotic conditions like HIT, DIC and APS. After excluding these conditions, if the platelet count is > 50 × 10^9/L then initiating anticoagulant therapy is considered to be safer. If the platelet count is in between 30-50 × 10^9/L then anticoagulation with unfractionated heparin is chosen. Anticoagulation therapy when the platelet count is <30 × 10^9/L is often risky and requires efficient monitoring (14).

RESULTS

Study population:

During the eight-month (October 2018-May 2019) study period 556 patients admitted to medical ICU were screened for eligibility. 303 patients who met inclusion criteria and gave informed consent were enrolled in the study.

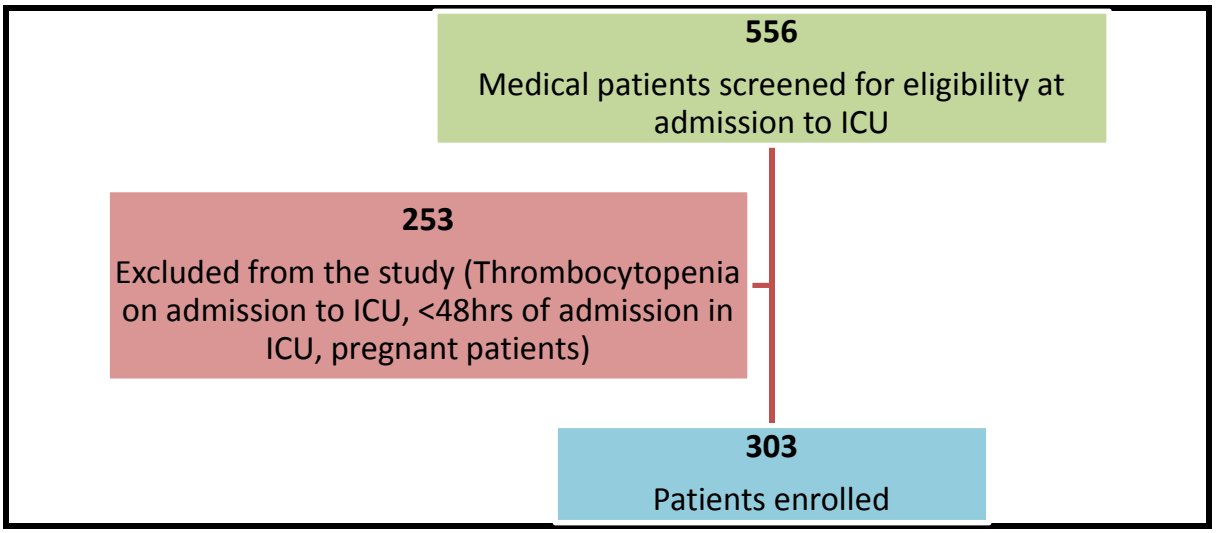

Figure 6 Study population

New Onset Thrombocytopenia (NOT) – Incidence:

69 patients out of 303 developed new onset thrombocytopenia. Thus the incidence of NOT in the study population is 22.8%.

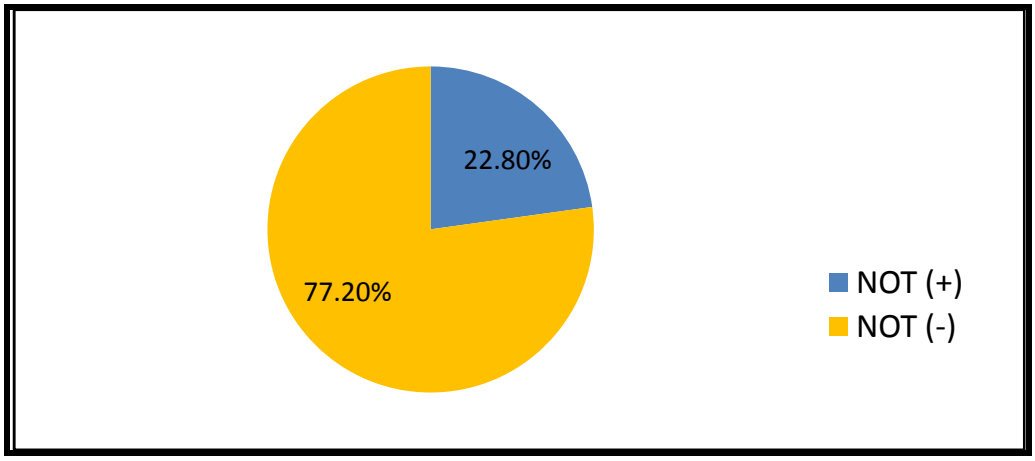

Figure 7 Incidence of NOT (n-303)

Gender characteristics:

Out of 303 patients enrolled in the study, 168 (55.4%) were males and 135 (44.6%) were females. This is comparable with that of the gender characteristics between the study groups (Patients with and without NOT)

A) Gender distribution of overall study population

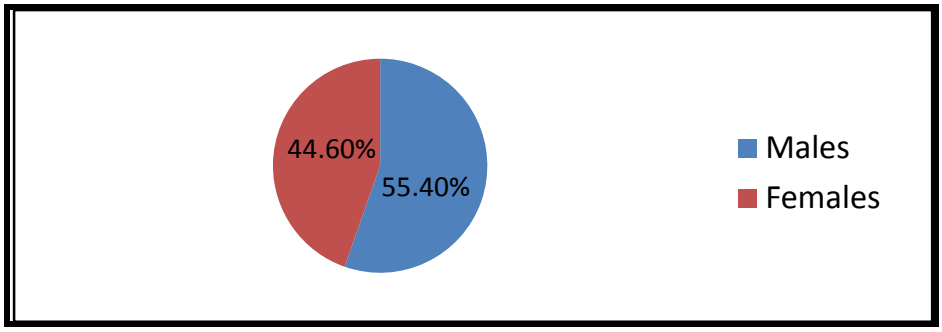

Figure 8 Gender distributions in overall study group (n-303)

B) Gender distribution of patients with NOT

Among 69 patient with NOT, 40 (58%) were males and 29 (42%) were females.

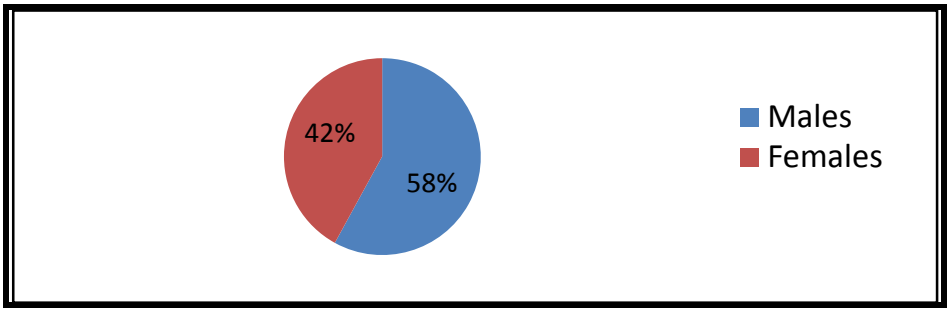

Figure 9 Gender distributions in patients with NOT (n-69)

C) Gender distribution in patients without NOT

In 234 patients without NOT, 128 were males and 106 were females.

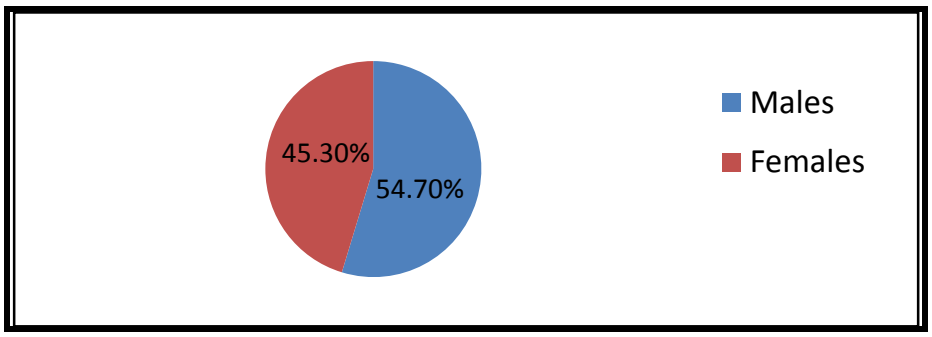

Figure 10 Gender distributions in patients with out NOT (n-234)

Age characteristics

The mean age of the study population was 52 years (Max. 91, Min. 18years).

Table 8: Age characteristics of the study groups

Group	Mean age (years)	SD	Range (years)
Overall	52.24	16.43	18-91
NOT	53.11	16.33	21-80
Without NOT	51.98	16.49	18-91

Reason for ICU admission

204 patients (67.30%) in the study population (303 patients) got admitted in the ICU for respiratory support.

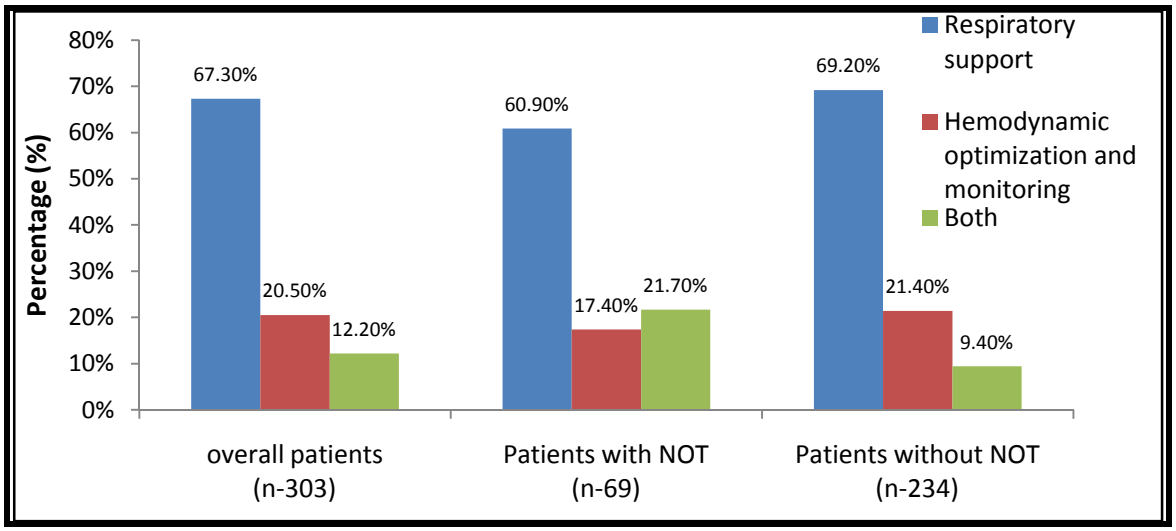

Figure 11 Reason for ICU admission

On admission ICU scorings

A) APACHE II Score

The median APACHE II score estimated on admission to ICU was 16.0 (SD, 7.48).

Table 9: APACHE II score of the study groups

Group	APACHE II	SD	Range (score)
Overall	16.02	7.48	1.0-42.0
NOT	16.78	7.58	4.0-42.0
Without NOT	15.79	7.45	1.0-40.0

The APACHE II score was comparable between patients with and without NOT.

B) Predicted mortality rate

The median predicted mortality rate was 22.25% (IQR, 11.30-38.90) for the entire study population which was comparable between the study groups.

Table 10: Predicted mortality rate for the study groups

Group	Predicted mortality rate (%)	IQR (Inter- quartile range)
Overall	22.25	11.30-38.90
NOT	23.50	12.90-42.40
Without NOT	21.00	11.30-35.50

Pre-existing co-morbidities in the study groups

The pre-existing co-morbidities were analyzed for the entire study population on admission to ICU.

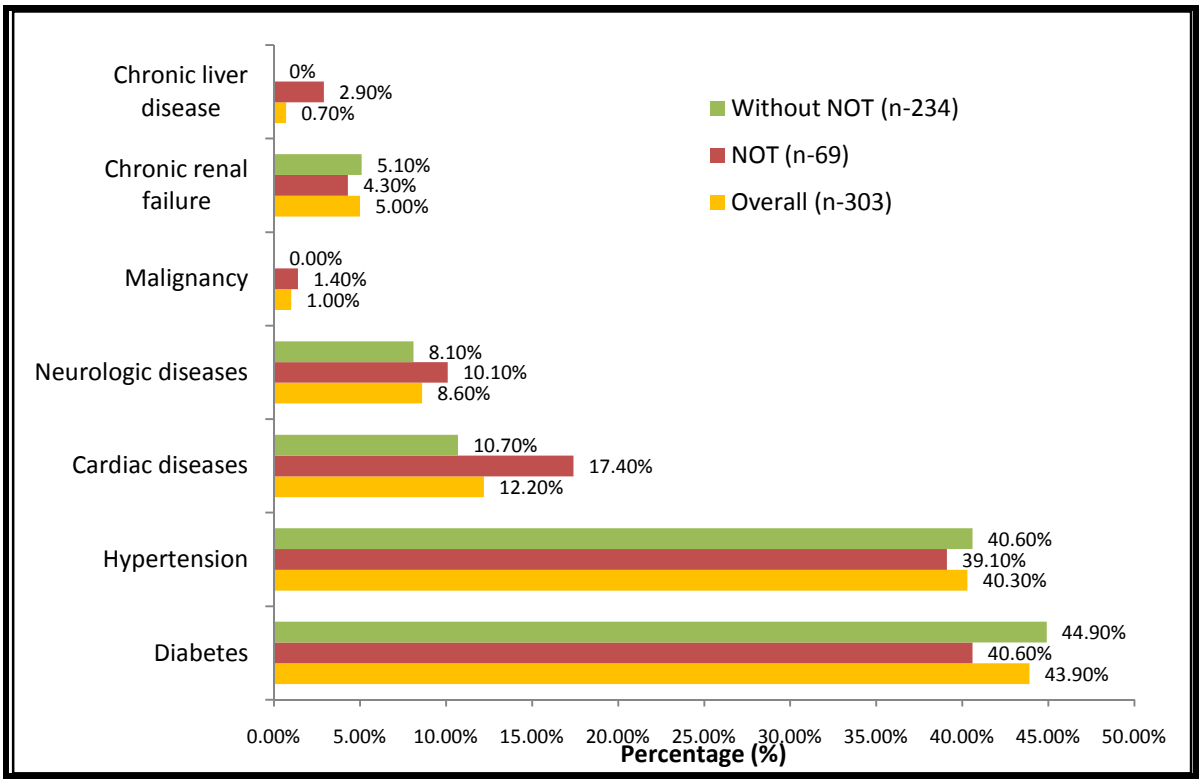

Figure 12 Pre-existing co-morbidities

At the time of admission to ICU, 133 (43.9%) patients had diabetes mellitus and 122 (40.3%) patients had systemic hypertension. Other co-morbid conditions like cardiac diseases (eg, ischemic heart disease, valvular heart disease), neurological diseases (eg, Cerebro-vascular accidents, seizure disorders), malignancy and chronic renal failure and liver diseases found to be less prevalent in the study population ((37)12.2%, (26)8.6%, (3)01%, (15)05% and (2)02% respectively). There are no significant differences observed between the existence of co-morbidities in patients with and without NOT.

Baseline investigations on admission

On admission to ICU, for patients who were enrolled in the study, the admission baseline characteristics were documented and analyzed.

Table 11: Baseline characteristics of the study population

Variable	Overall (n=303)	NOT (n=69)	Others (n=234)
Haemoglobin (g/dl) $	11.63 (2.7)	11.48 (2.8)	11.67 (2.6)
WBC (× 10^3/dL) @	14.2 (11; 20.2)	15.1 (10.6; 19.5)	14.1(11.1; 20.3)
Platelet count (Lakhs/mm^3)@	2.60 (2.0; 3.2)	2.10 (1.7; 2.6)	2.75 (2.2; 3.3)
Total Bilirubin (mg/dl) @	0.61 (0.3; 1.0)	0.95 (0.5; 1.3)	0.56 (0.3; 0.8)
Albumin (g/dl) $	3.34 (0.78)	3.09 (0.77)	3.42 (0.77)
Blood urea (mg/dl) @	38.0 (25.0; 67.2)	49.0 (26.0; 85.0)	37.0 (25.0; 64.0)
Sr. creatinine (mg/dl) @	1.15 (0.78; 1.81)	1.50 (0.93; 2.62)	1.04 (0.750; 1.62)
PH $	7.31 (0.16)	7.29 (0.18)	7.32 (0.15)

NOT: New onset thrombocytopenia; SD: Standard deviation; IQR: Inter-quartile range.

[N (%) - #, SD- $, IQR- @, Median- !]

The median haemoglobin on admission was 11.63mg/dl (SD, 2.73). The WBC and platelet counts are 14.2×10^3/dl (IQR, 11-20.2) and 2.60lakhs/mm^3 respectively. Similar to CBC parameters, others parameters like, total bilirubin, albumin, blood urea, creatinine and blood PH were also did not showed any significant difference between the study groups (Patients with and without NOT)

Causes of new onset thrombocytopenia (NOT)

Patients who developed NOT are further analyzed to identify the underlying causes. They were done based on the clinical correlation along with limited investigation findings, as described before.

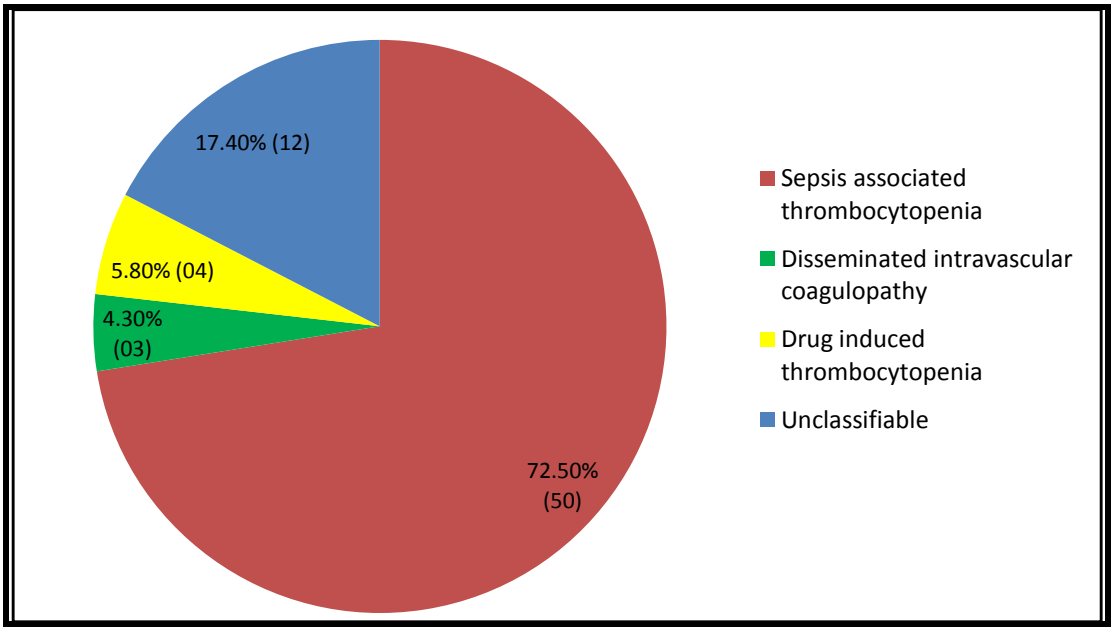

Figure 13 Causes of NOT

Out of the 69 patients with NOT, 50 (72.5%) patients had developed thrombocytopenia associated with sepsis. Three patients (4.3%) had thrombocytopenia associated with DIC. Four patients had DIT and the drugs associated were Carbamazepine, Phenytoin, Rifampicin and Cyclophosphamide.

Two patients on evaluation for heparin induced thrombocytopenia, had a high pre-test probability score, however on testing for anti-heparin/PF4 antibodies they demonstrated negative test results. For 12 patients the cause for NOT remained unclassifiable.

Specific treatments in the study groups

A) Vasoactive drugs requirement

The requirement of vasoactive drugs, namely, adrenaline, nor-adrenaline and vasopressin, during the course of admission in ICU were analyzed.

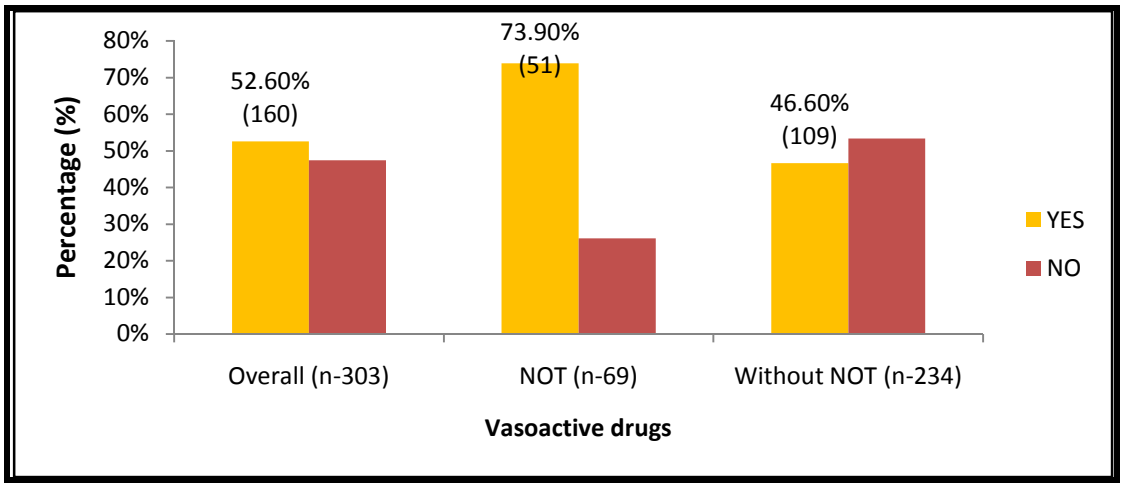

Figure 14 Vasoactive drugs requirement

- In patients with NOT 51 (out of 69) required vasopressor requirement and 109 (out of 234) required vasopressor support during the course of stay in ICU.
- On comparing the vasopressor (vasoactive drugs) requirements between patients with and without NOT, a statistically significant p value was observed (p value <0.001) (Refer to Table 12).

B) Hemodialysis requirement

The requirements of renal replacement therapy (RRT) were analyzed for the study population during their course of admission in ICU.

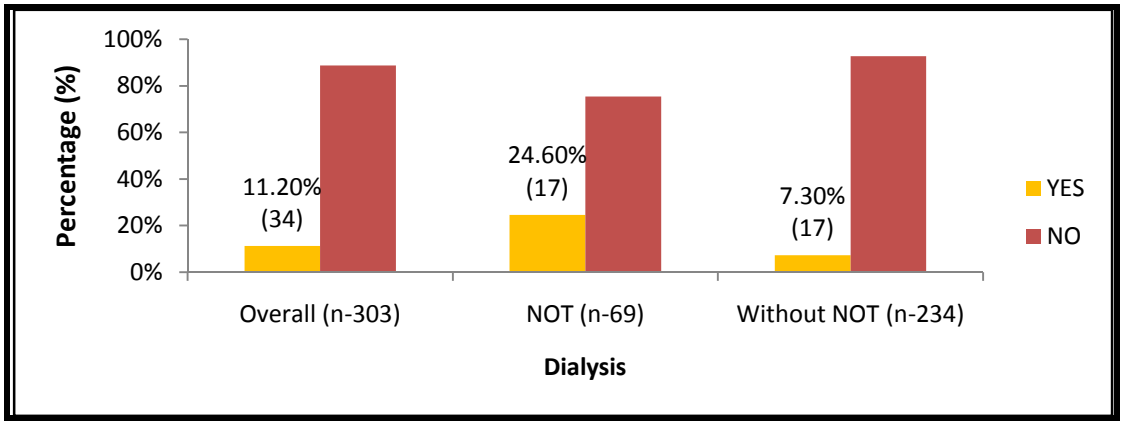

Figure 15 Hemodialysis requirement

- Comparison of dialysis/RRT requirements between patients with and without NOT showed a statistically significant p value (p value <0.001) as depicted in Table 12.

C) Transfusion requirements

Of the entire 303 patients, 77 (25.4%) patients required one or more blood/blood component transfusions.

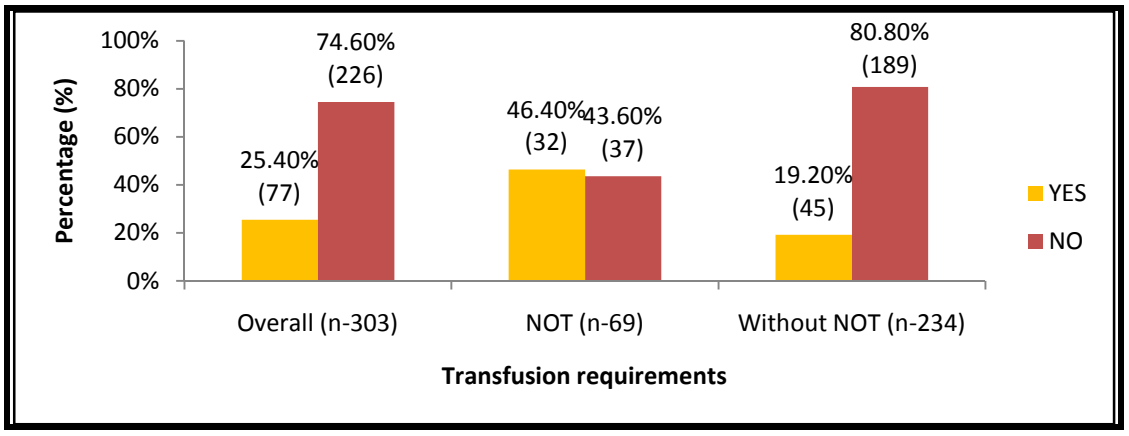

Figure 16 Transfusion requirements

- A statistically significant p value (p value < 0.001) is observed on comparison between the two groups (patients with NOT versus patients without NOT).

Table 12: Specific treatment details

Treatments	Overall (n=303)	NOT (n=69)	OTHERS (n=234)	P value
Vasopressor requirement #	160 (52.6)	51 (73.9)	109 (46.6)	<0.001
Dialysis requirement #	34 (11.2)	17 (24.6)	17 (7.3)	<0.001
Transfusion requirement #	77 (25.4)	32 (46.4)	45 (19.2)	<0.001

n (%) - #

D) Ventilatory requirements

Majority of the patients who got admitted to the ICU were for the respiratory support as depicted above (Fig 11). Among the study population, patients who required invasive ventilatory support during their course of admission in the ICU are analyzed further.

Table 13: Ventilatory requirement details

Variables	Overall (n=303)	NOT (n=69)	Without NOT (n=234)	P value
Invasive ventilation #	220 (72.6)	65 (94.2)	155 (66.2)	<0.001
Ventilation free days@	22.0 (19.0; 24.0)	20.0 (15.0; 22.75)	23.0 (20.0; 25.0)	<0.001

[n (%) - #, IQR- @]

- The requirement for ventilation was higher in patients with NOT (65 out of 69, 94.2%) as compared to the patients without NOT (155 out of 234, 66.2%) and showed a statistically significant p value (<0.001).

Transfusion Summary and associated risks

i. Packed cells – Transfusion summary

Out of the 77 patients who received transfusions during their course in hospital, 66 (Out of 303, 21.8%) patients required packed cells transfusion.

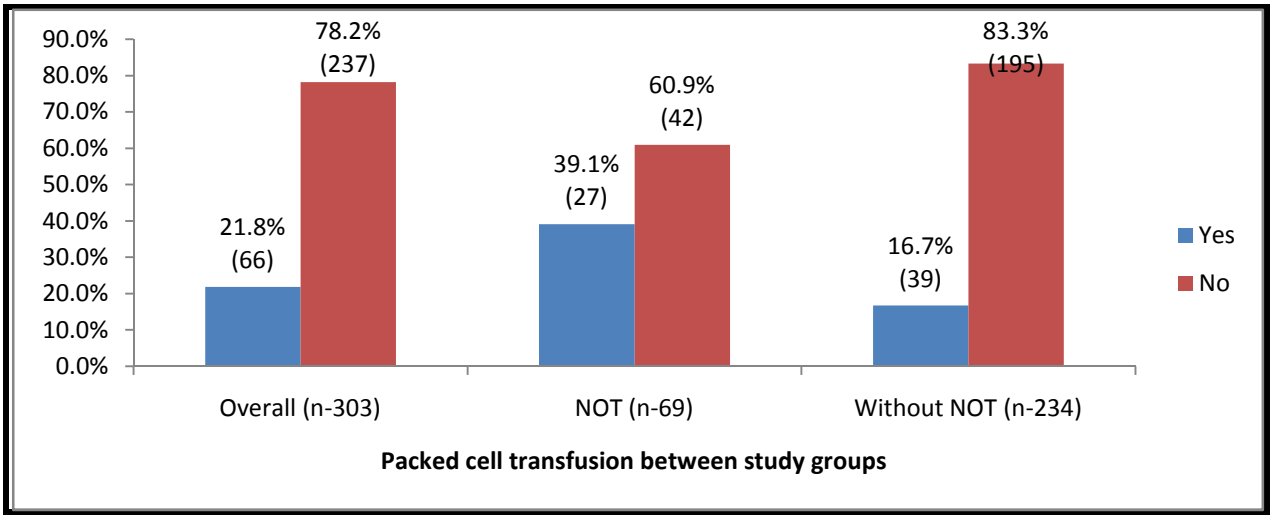

Figure 17 Packed cell requirements

- On comparing the packed cell transfusion requirement between the study groups (patients with and without NOT, 27/69; (39.1%) vs 39/234; (16.7%)) a statistically significant difference was observed (p value<0.001)
- Of the 27 patients requiring packed red cell transfusions with NOT, only 11 had bleeding manifestations and of the 39 patients without NOT only 11 had bleeding manifestations.

ii. Platelet transfusion summary

Platelet transfusion requirement was analyzed between the study groups. Of the 77 patients who required transfusions, 17 (22.08%) required platelet transfusions on at least one occasion.

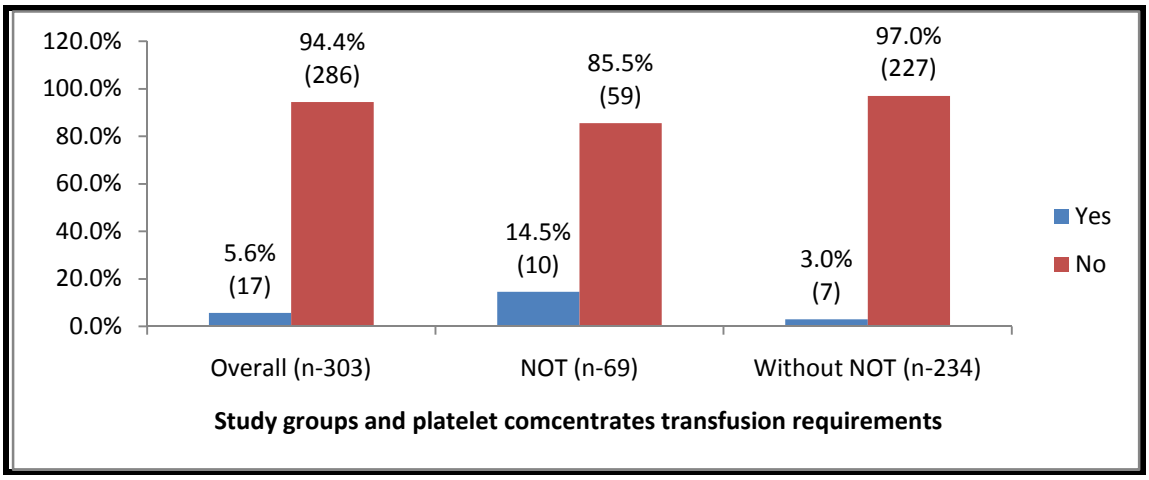

Figure 18 Platelet transfusion requirements

- In patients with NOT 10 (out of 69), 14.5%, required platelet transfusions, while in the patients without NOT 7 (out of 234), 3.0%, had received platelet transfusions.
- As the number of platelet transfusions were extremely limited statistical significance could not be assessed between the study groups (patients with and without NOT)
- Of the 17 patients who received platelet transfusions, 8 had bleeding manifestations.

- However on analyzing the bleeding manifestations and platelet requirement, 5 patients (out of the 10) had received platelet transfusion from the group NOT and 3 patients from the group without NOT had received platelet transfusion due to bleeding manifestations.

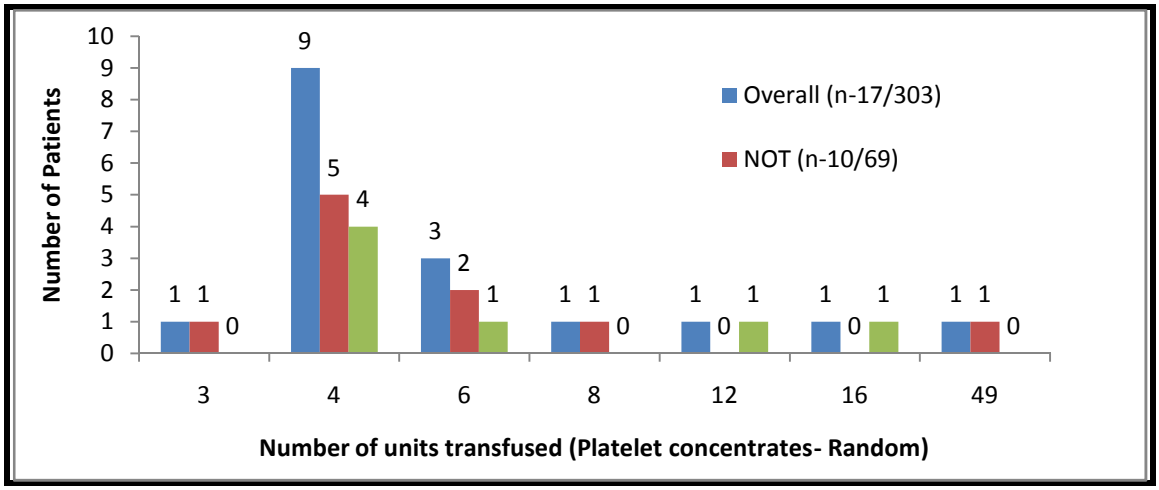

Figure 19 Overall platelet transfusions summary

To a maximum, 49 platelets were transfused to a patient who had severe bleeding manifestations secondary to DIC.

iii. Fresh frozen plasma (FFP) transfusion summary

18 patients received FFP transfusion during their hospital stay for either therapeutic or for prophylactic requirement.

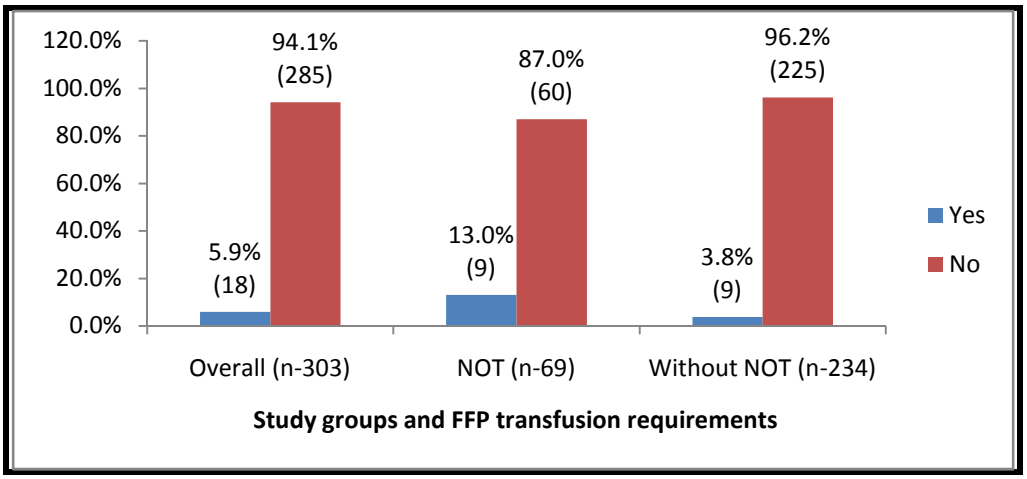

Figure 20 FFP transfusion requirements

- From the 18 patients (out of 303) who had received FFP transfusions, 9 patients (out of 69) are from the group NOT and the rest 9 (out of 234) belonged to the group without NOT.
- Statistical significance between the patients with and without NOT could not be ascertained due to the limited number of FFP transfusions.
- On analyzing the bleeding manifestations and FFP transfusion between the groups, 4 patients (out of 9) from the group NOT received FFP transfusion due to bleeding manifestations and 3 patients (out of 9) from the group without NOT had bleeding symptoms.

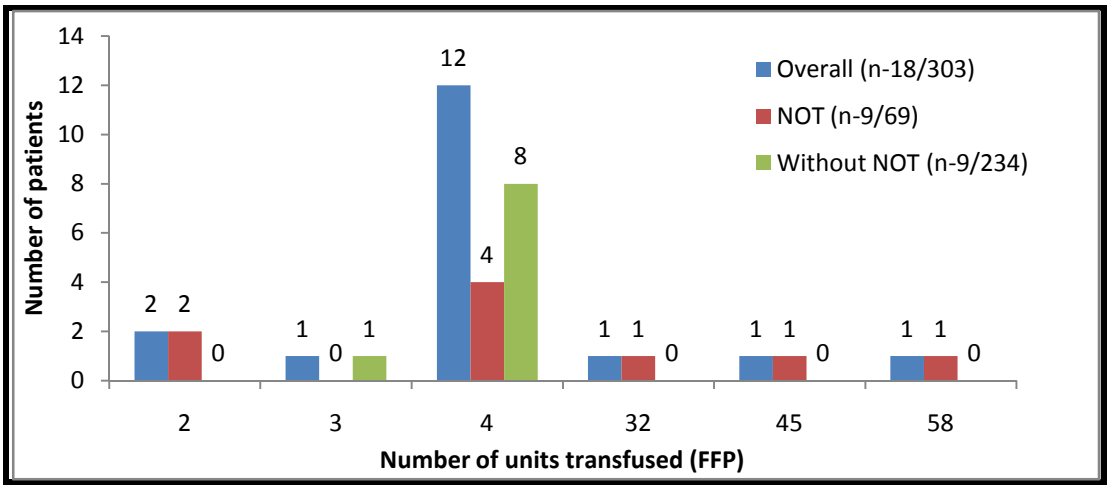

Figure 21 Overall FFP transfusions summary

- Of the 3 patients who had received the maximum number of FFP transfusions, 2 patients received FFP for therapeutic plasma exchange and one patient had received in view of severe DIC and associated coagulopathy.

iv. Cryoprecipitate transfusion summary

Out of 77 patients who received transfusions, cryoprecipitate was transfused in only 2 patients.

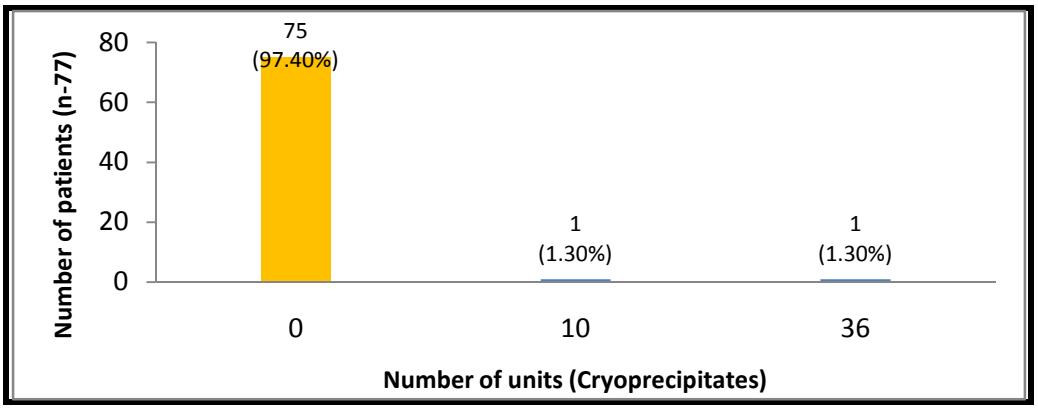

Figure 22 Overall cryoprecipitate transfusions summary

v. Bleeding manifestations in patients who had received transfusions

The overall bleeding manifestation had been analyzed in the study population.

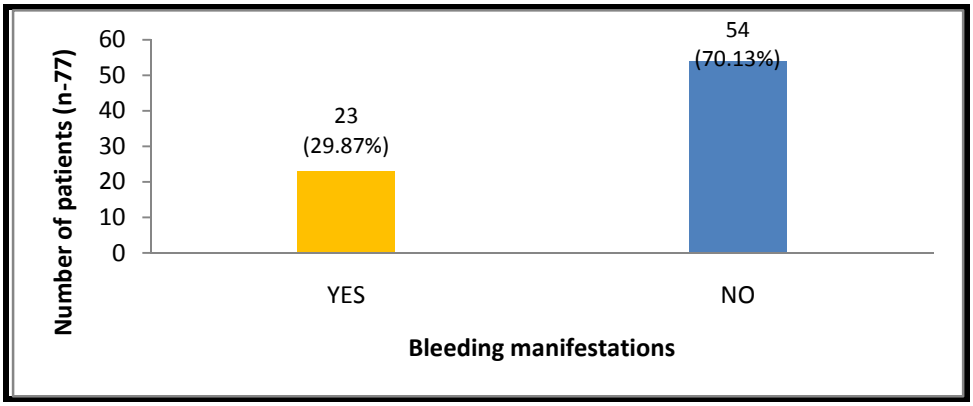

Figure 23 Summary of bleeding patients

- Of the 77 patients who received transfusions, 23 patients had bleeding manifestations.
- Majority of the patients required transfusions without any bleeding manifestations and as part of prophylactic management.

vi. Comparison of bleeding in patients with and without NOT

Out of the 77 patients required transfusions 23 (29.87%) patients had significant bleeding symptoms.

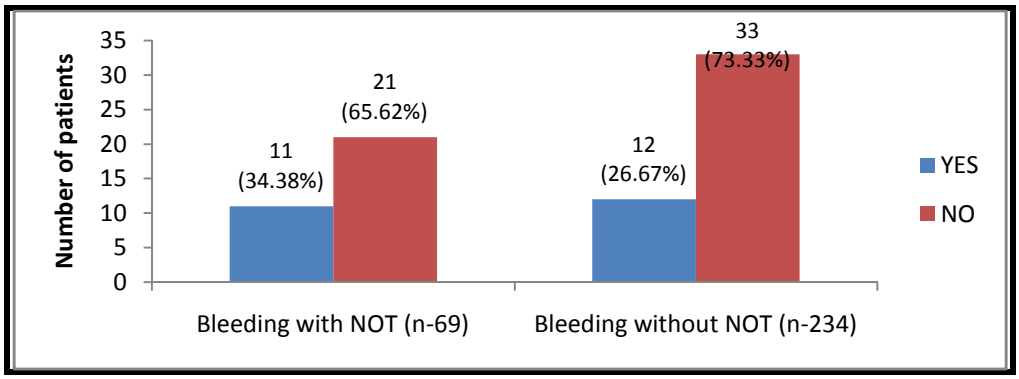

Figure 24 Comparison of bleeding risks

- In patients with NOT the bleeding risk is slightly higher 34.38% when compared with the patients without NOT (26.67%).
- The bleeding risks observed in patients without NOT is predominantly secondary to anticoagulant and antiplatelet therapy and a few remained secondary to procedure.

Therapeutic outcomes

A) Hospital Mortality and AKI details

All the patients were followed up during their entire hospital stay and the development of acute kidney injury and the adverse event of hospital mortality are documented and analyzed.

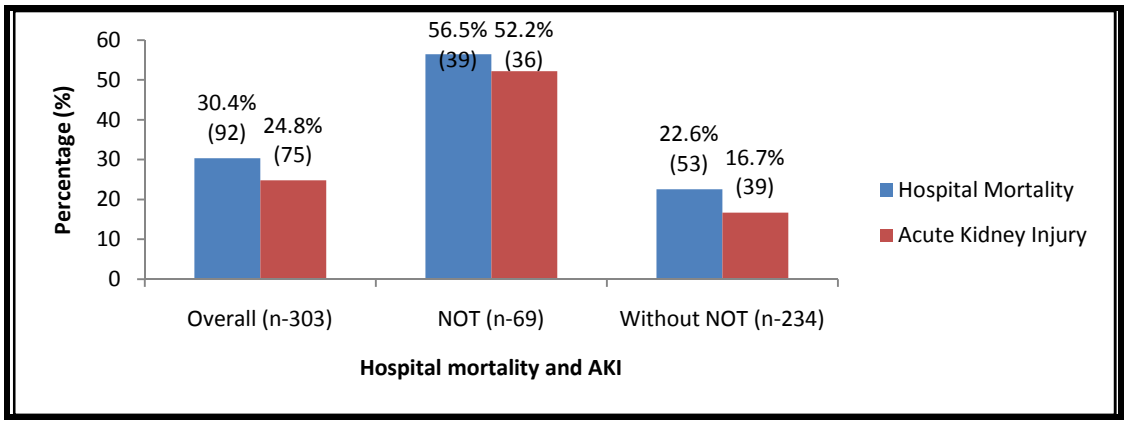

Figure 25 Hospital Mortality and AKI details

- On analyzing the hospital mortality between patients with and without NOT (39 (56.5%) versus 53 (22.6%)), a statistically significant p value was observed (p value <0.001).
- Similarly, 52.2% patients in the NOT group developed AKI, which on comparing with patients without NOT group (16.7%) showed a statistical significance (p value <0.001).

Table 14: Hospital mortality and AKI data

Variables	Overall (n=303)	NOT (n=69)	Without NOT (n=234)	P value
Acute kidney injury[#]	75 (24.8)	36 (52.2)	39 (16.7)	<0.001
Hospital mortality[#]	92(30.4)	39 (56.5)	53 (22.6)	<0.001

[n (%) - #

B) Length of stay in hospital and ICU

The ICU and hospital length of stay were analyzed for the entire study population which showed a statistical significance (p value <0.001) between the study groups (NOT vs without NOT)

Table 15: Length of stay in Hospital and ICU

Variables	Overall(n=303)	NOT(n=69)	OTHERS(n=234)	P value
ICU LOS [$@]	6.0 (4.0; 10.0)	10.0 (7.0; 14.5)	5.0 (4.0; 8.0)	<0.001
Hospital LOS [$@]	13.0 (8.0; 20.0)	17.0 (10.0; 28.5)	12.0 (8.0; 17.0)	<0.001

LOS- Length of stay, IQR- Inter-quartile range [IQR- @, Median- $]

Factors associated with hospital mortality

The univariate logistic regression analysis was performed on all 303 patients to evaluate the significance of factors that are associated with in-hospital mortality.

Table 16: Factors associated with hospital mortality

Variable	Univariate analysis		
	OR	**95% CI**	**P value**
Age	1.01	1.00-1.03	0.015
Sex	1.20	0.73-1.98	0.453
APACHE II	1.03	1.00-1.03	0.051
Predicted mortality rate	1.01	0.99-1.02	0.061
Platelets (/1000) [+]	0.99	0.99-1.00	0.060
Sr. Albumin [+]	0.37	0.24-0.55	<0.001*
Blood urea [+]	1.00	1.00-1.01	0.051
Ph [+]	1.32	0.28-6.15	0.721
NOT	4.44	2.52-7.81	<0.001*
Vasoactive drugs	3.95	2.29-6.82	<0.001*
AKI	3.30	1.91-5.71	<0.001
Dialysis	2.58	1.25-5.33	0.010
Transfusion requirement	2.47	1.44-4.23	0.001*

Invasive ventilation	10.20	3.97-26.22	<0.001*
ICU LOS	1.03	0.99-1.06	0.075
Hospital LOS	0.98	0.96-1.00	0.189

+Parameters at admission, *Considered for multivariate

The statistically significant variables observed in the univariate analysis are considered for the multivariate analysis.

Table 17: Multivariate analysis for factors associated with hospital mortality

Variable	Multivariate analysis		
	OR	**95%CI**	**P value**
Sr. albumin	0.42	0.26-0.65	<0.001
Vasoactive drugs	2.18	1.09-4.31	0.026
Invasive ventilation	6.02	1.97-18.3	0.002
NOT	**2.43**	1.21-4.91	0.013
Transfusion requirement	0.92	0.43-1.96	0.830

In the multivariate analysis, even after adjusting for the clinically significant variables (sr. albumin, vasoactive drugs, invasive ventilation, transfusion requirement), NOT had 2.3 times the risk for mortality (2.43, 1.21-4.91, $P = 0.013$).

Discussion

Thrombocytopenia is one of the commonest findings, frequently encountered in patients admitted to ICU. In an ICU setting thrombocytopenia prevails as a poor prognostic marker with regards to patient outcome. It is commonly associated with multi organ failure, thus making the management complicated (14). Patients admitted in ICU can present either with thrombocytopenia or can develop thrombocytopenia during their course of admission. The incidence of thrombocytopenia in ICU may vary based on the types of care provided (medical, surgical or mixed) (2). However NOT in an ICU patient indicates a complication (sepsis or liver impairment, etc.) which is worsening or evolving, thus making it clinically significant (2). Despite many literatures highlighting the significance of NOT in an ICU setting, there are only a few studies available in the Indian population. Against this background our study was performed.

The incidence of NOT in our study population is 22.8%. The study performed by Hui. Et al., 2011 (66) by analyzing the previous literatures shows the overall incidence of thrombocytopenia was 13-44.1%, which is comparable with our result. Another larger study done in UK involving 29 ICUs, by stanworth et al. (67) estimated that 12.4% of patients developed severe thrombocytopenia during their course of admission in ICU.

Our study was conducted in medical ICU. A similar study from Korea by lim et al., evaluated NOT in 186 patients (13). It was reported with an incidence of 37.1%. Another

Indian study by Mehta et al. evaluated NOT in a cohort of 500 patients admitted to a medical ICU and found 41 patients (8.2%) had pre-existing thrombocytopenia at the time of ICU admission and 149 patients (32.4%) developed thrombocytopenia during their ICU stay (NOT) (68). On comparing with these two studies, our incidence for NOT is slightly lower. The reason could be due to an early diagnosis of the cause for thrombocytopenia and treating the patients appropriately.

A study by Crowther et al. conducted in a mixed ICU setup (medical/surgical) analyzed 261 patients and found that in 121 (46%, 95% confidence interval [CI], 40%-53%) patients, there were thrombocytopenia (62 on ICU admission and 59 acquired during their ICU stay) (16). Of the 199 patients with normal platelet count at ICU admission, 59 (29.6%, 95% CI, 23.4%-36.5%) developed at least one platelet count of less than 150×10^9/L during their ICU admission. In a medical (19), medical-surgical (18), and medical-cardiac (69) ICU, thrombocytopenia acquired in the ICU has a reported incidence of 44.1%, 18.8%, and 14.3%, respectively. Thus the incidence of thrombocytopenia in ICU varies depending on the type of care provided (medical, surgical or mixed) and the platelet count threshold used for defining thrombocytopenia (150 or 100×10^9/l). It may also vary depending on the clinical presentations which are predominantly dealt in each ICU at different centers (e.g. cardiac surgery versus liver transplant units) (Stephan et al, 1999; Hui et al, 2011).

In our study, out of the 69 patients with NOT, 50 (72.5%) patients had thrombocytopenia associated with sepsis. Three patients (4.3%) had thrombocytopenia associated with DIC and four (5.80%) patients had drug-induced thrombocytopenia. Thus the predominant cause for thrombocytopenia remained as sepsis-associated thrombocytopenia. The cause for NOT could not be classified in 12 patients. The study by Lim et al. analyzed the causes for thrombocytopenia in 69 patients with NOT. It was found that Sepsis with DIC was the most frequent cause of NOT with 46 patients (66.7 %), followed by drug-induced thrombocytopenia (18.8%), HIT (2.9%), and liver disease (1.4%). Thus it could be ascertained that in sub tropical countries, the risk associated with sepsis remains a major burden in patient management.

A cohort study conducted at the Mayo Clinic Medical Center, evaluated 304 patients with sepsis and septic shock, found that 145 patients developed thrombocytopenia. Among them 37 patients (25.5%) had an overt DIC. Septic shock was present in 285 out of 304 patients (93.7%), and the most common source of sepsis was pneumonia. Drug-induced thrombocytopenia developed in 26 of 145 patients (17.9%), and all the cases were established to be secondary to antibiotics. Of the 145 patients who developed thrombocytopenia, ELISA to detect heparin-platelet factor 4 antibodies was performed in 49 patients. Two patients had equivocal test results but ruled out later that they did not have immune-mediated HIT. One patient had a positive test result and was diagnosed with immune-mediated HIT (70).

In our study, four patients had drug-induced thrombocytopenia. The drugs which are attributed to the cause for thrombocytopenia are a) Carbamazepine, b) Phenytoin, c) Rifampicin and d) Cyclophosphamide. Two patients on evaluation for heparin induced thrombocytopenia, had a high pre-test probability score, however on testing for anti-heparin/PF4 antibodies they demonstrated a negative test results. Thus we couldn't able to establish HIT as the causality for thrombocytopenia in any patients. The medications such as antiepileptics, antibiotics and immunosuppressant drugs which are commonly used in ICU remains the drugs which cause thrombocytopenia. For 12 patients the cause for NOT remained unclassifiable. The reason for this is due to the short duration of thrombocytopenia which recovered with adequate treatment. Another reason for this is due to the death of these patients before even complete evaluation was done. The cause of thrombocytopenia associated with sepsis remained higher, similar to the previous studies Lim et al. (66.7%) and Mehta et al. (59.7%). Few of the patients with sepsis progressed to develop DIC with severe coagulopathy and bleeding manifestations.

A meta-analysis of 15 studies (Martel et al.) evaluated the risk of HIT with prophylactic unfractionated versus LMW heparin in 7287 patients, most of the patients undergoing orthopedic surgery and found that the risks for developing HIT with Unfractionated heparin is 2.6 percent (95% CI 1.5-3.8 percent) and with LMW heparin is 0.2 percent (95% CI 0.1-0.4 percent) (71).

Comparing the studies by Lim et al. (2.9%) and Martel et al. (2.6%), in our study we were not able to diagnose HIT in any patients. The reason could be due to its overall low incidence rate and also due to the testing platform which was being used. In our study we have used gel agglutination assay which has a sensitivity of 80-100% with a low specificity when compared to the gold standard, serotonin release assay (79).

Of the entire study population (303 patients), 77 (25.4%) patients has received one or more blood/blood component transfusions. In the group of patients with NOT 32 patients (out of 69) required transfusions (46.40%) and in the group, without NOT, 45 patients (out of 234) required transfusions (19.20%). On comparing these two groups a statistically significant p value (p value < 0.001) is observed.

The study by Stanworth et al (2013) showed that up to 30% of critically ill patients receive a transfusion in ICU and the majority of which are for prophylaxis rather than treatment of bleeding, which is comparable with the present study.

In our study, of the 77 patients who required transfusions, 17 (22.08%) patients required platelet transfusions, 18 (23.37%) patients required FFP transfusions and only 2 patients required cryoprecipitate transfusions. 23 patients (29.87%) out of 77 had bleeding symptoms. Thus the majority of transfusions done were prophylactic in relation to ICU procedures. In the patients with NOT group, the bleeding risk remained slightly higher 34.38% when compared with the patients without NOT group (26.67%). The bleeding

risks observed in patients without NOT was predominantly found to be secondary to anticoagulant and antiplatelet therapy and a few remained secondary to ICU procedures.

It has been demonstrated from the study by Vasu et al. (2016), the overall platelet transfusion rate in ICU patients was 11.9% (213/1790) including 19.2% (178/927) in thrombocytopenic patients and 3.9% (34/863) in non-thrombocytopenic patients. In their study 213 patients required 480 units of platelets transfusions through 319 transfusion episodes among them a majority of 82.1% (262/319) of the transfusion episodes were therapeutic and 17.9% (58) were prophylactic (72). When compared, the platelet transfusion requirement in our study is slightly higher, which was limited by the number of patients studied.

Analyzing the vasopressor requirements in our study groups, 59 patients (73.90%) in the NOT group (69 patients) and 109 patients (46.60%) in the group without NOT (234 patients) required vasopressor supports. On comparing the two groups, a statistically significant p value (<0.001) is observed. Similarly, the dialysis requirement in the NOT group (17 out of 69 patients, 24.60%) when compared with the group without NOT (17 out of 234 patients, 7.30%) showed a statistical significance (p value- <0.001). Thus the vasopressor requirement and dialysis requirement in patients admitted to ICU, with associated NOT is higher. Also in our study, the mechanical ventilator support required for 94.2% patients in the NOT group and 66.2% in the patients without NOT group (p value <0.001).

On analyzing the hospital mortality between patients with and without NOT (39 (56.5%) versus 53 (22.6%)) there was a statistically significant p value is observed (p value <0.05). There is also a significant decrease in the ICU length of stay and the total days of hospitalization in patients with and without NOT. Thus in patients with NOT, the in hospital mortality is higher with an associated increase in the hospital length of stay when compared to the patients without NOT. 36 (52.2%) patients in the NOT group developed acute kidney injury during their admission.

The study by Mehta et al. showed a higher ICU mortality in patients with thrombocytopenia when compared to patients without thrombocytopenia (15.4 v. 8.7%, p=0.03). This finding is comparable to our study. The reason for this high mortality might be because of thrombocytopenic patients being much sicker than those who did not develop thrombocytopenia during their ICU stay. Thus, thrombocytopenia reflects the severity of the disease in the critically ill patients.

The univariate logistic regression analysis was performed on all the 303 patients to evaluate the significance of factors that are associated with in-hospital mortality. The variables such as age, APACHE II score, sr.albumin and blood urea showed a statistically significant p value (<0.05). The unadjusted odds ratio (OR) for NOT, with regards to the hospital mortality is 4.44 (95% CI, 2.52-7.81, $P < 0.001$). When adjusted for age, gender, SAPS 3, and ICU LOS (model 1), NOT significantly increased the odds ratio of hospital

mortality (4.70, 2.06- 10.70, $P < 0.001$). Even after adjusting for the clinically significant variables from univariate analysis (sr. albumin, vasoactive drugs, invasive ventilation, transfusion requirement), NOT remained a significant risk factor for mortality (2.43, 1.21-4.91, $P = 0.013$). This is comparable with the study by Lim et al and Mehta et al.

LIMITATIONS

1. The incidence of thrombocytopenia in this study is limited to a medical ICU. As from the literatures, the thrombocytopenia in ICU may vary based on the types of care provided (medical, surgical or mixed). Hence a concomitant evaluation in other ICU setups would have helped to substantiate the findings.
2. The evaluation of thrombocytopenia needed a robust work-up to arrive at a diagnosis. The evaluation in our study, to arrive at a diagnosis is based on the patients clinical evidence and limited investigations.
3. The cause for NOT in few patients remained as unclassified. Thus a more extensive and systematic approach would be appropriate to evaluate more.

CONCLUSION

- The incidence of NOT (22.8%) in our study population is comparable with that of other international studies.
- Sepsis-associated thrombocytopenia (72.50%) remained as the major cause for thrombocytopenia in patients with NOT, similar to the western literatures.
- Patients with NOT (46.40%) required significantly higher number of transfusions when compared to the patients who did not developed thrombocytopenia (19.20%). The risk for bleeding also found to be higher in patients with NOT.
- The outcome of in hospital mortality was significantly higher in patients with NOT. Even after adjusting for the clinically significant variables (sr. albumin, vasoactive drugs, invasive ventilation, transfusions requirement), the patients with NOT has 2.43 times the risk for mortality.
- Around 52.2% of patients with NOT, developed acute kidney injury during the hospital stay.
- From a therapeutic perspective, patients with NOT required much more vasopressor supports, dialysis and invasive ventilatory support with a significantly longer duration of hospitalization.
- Thus, it is evident that NOT in a patient during ICU stay has significant prognostic value in defining the outcomes (in terms of mortality) and planning transfusion requirements.

REFERENCES

1. Jonsson AB, Rygård SL, Russell L, Perner A, Møller MH. Bleeding and thrombosis in intensive care patients with thrombocytopenia-Protocol for a topical systematic review. Acta Anaesthesiol Scand. 2019 Feb;63(2):270–3.

2. Zarychanski R, Houston DS. Assessing thrombocytopenia in the intensive care unit: the past, present, and future. Hematol Am Soc Hematol Educ Program. 2017 Dec 8;2017(1):660–6.

3. Ali N, Auerbach HE. New-onset acute thrombocytopenia in hospitalized patients: pathophysiology and diagnostic approach. J Community Hosp Intern Med Perspect. 2017 Jul 13;7(3):157–67.

4. Greer JP. Wintrobe's Clinical Hematology. Lippincott Williams & Wilkins; 2008. 1360 p.

5. Holinstat M. Normal platelet function. Cancer Metastasis Rev. 2017;36(2):195–8.

6. Tomaiuolo M, Brass LF, Stalker TJ. Regulation of Platelet Activation and Coagulation and Its Role in Vascular Injury and Arterial Thrombosis. Interv Cardiol Clin. 2017 Jan 1;6(1):1–12.

7. Stalker TJ, Traxler EA, Wu J, Wannemacher KM, Cermignano SL, Voronov R, et al. Hierarchical organization in the hemostatic response and its relationship to the platelet-signaling network. Blood. 2013 Mar 7;121(10):1875–85.

8. The expansive role of oxylipins on platelet biology | SpringerLink [Internet]. [cited 2019 Apr 27]. Available from: https://link.springer.com/article/10.1007/s00109-017-1542-4

9. Coronary heart disease risk factors take a disproportional toll on women. - PubMed - NCBI [Internet]. [cited 2019 Apr 28]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25810295/

10. Sex differences in platelet toll-like receptors and their association with cardiovascular risk factors [Internet]. [cited 2019 Apr 28]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4376646/

11. Autophagy is induced upon platelet activation and is essential for hemostasis and thrombosis [Internet]. [cited 2019 Apr 28]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4559933/

12. Greinacher A, Selleng K. Thrombocytopenia in the Intensive Care Unit Patient. ASH Educ Program Book. 2010 Dec 4;2010(1):135–43.

13. Lim SY, Jeon EJ, Kim H-J, Jeon K, Um S-W, Koh W-J, et al. The Incidence, Causes, and Prognostic Significance of New-Onset Thrombocytopenia in Intensive

Care Units: A Prospective Cohort Study in a Korean Hospital. J Korean Med Sci. 2012 Nov;27(11):1418–23.

14. How do we approach thrombocytopenia in critically ill patients? - Thachil - 2017 - British Journal of Haematology - Wiley Online Library [Internet]. [cited 2019 Aug 4]. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.14482

15. Drews RE, Weinberger SE. Thrombocytopenic disorders in critically ill patients. Am J Respir Crit Care Med. 2000 Aug;162(2 Pt 1):347–51.

16. Crowther MA, Cook DJ, Meade MO, Griffith LE, Guyatt GH, Arnold DM, et al. Thrombocytopenia in medical-surgical critically ill patients: prevalence, incidence, and risk factors. J Crit Care. 2005 Dec;20(4):348–53.

17. Clinical review: Scoring systems in the critically ill | Critical Care | Full Text [Internet]. [cited 2019 Aug 12]. Available from: https://ccforum.biomedcentral.com/articles/10.1186/cc8204

18. Vanderschueren S, De Weerdt A, Malbrain M, Vankersschaever D, Frans E, Wilmer A, et al. Thrombocytopenia and prognosis in intensive care. Crit Care Med. 2000 Jun;28(6):1871–6.

19. Strauss R, Wehler M, Mehler K, Kreutzer D, Koebnick C, Hahn EG. Thrombocytopenia in patients in the medical intensive care unit: bleeding prevalence, transfusion requirements, and outcome. Crit Care Med. 2002 Aug;30(8):1765–71.

20. Leslie SD, Toy PT. Laboratory hemostatic abnormalities in massively transfused patients given red blood cells and crystalloid. Am J Clin Pathol. 1991 Dec;96(6):770–3.

21. Neame PB, Kelton JG, Walker IR, Stewart IO, Nossel HL, Hirsh J. Thrombocytopenia in septicemia: the role of disseminated intravascular coagulation. Blood. 1980 Jul;56(1):88–92.

22. Thachil J, Warkentin TE. How do we approach thrombocytopenia in critically ill patients? Br J Haematol. 2017;177(1):27–38.

23. Stone JH. HELLP syndrome: hemolysis, elevated liver enzymes, and low platelets. JAMA. 1998 Aug 12;280(6):559–62.

24. Alhamdi Y, Toh C-H. The role of extracellular histones in haematological disorders. Br J Haematol. 2016;173(5):805–11.

25. Cines DB, Bussel JB, Liebman HA, Luning Prak ET. The ITP syndrome: pathogenic and clinical diversity. Blood. 2009 Jun 25;113(26):6511–21.

26. Characterization of platelet-reactive antibodies in children with varicella-associated acute immune thrombocytopenic purpura (ITP) - Wright - 1996 - British Journal of Haematology - Wiley Online Library [Internet]. [cited 2019 Aug 15]. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1046/j.1365-2141.1996.d01-1872.x

27. Nugent D, McMillan R, Nichol JL, Slichter SJ. Pathogenesis of chronic immune thrombocytopenia: increased platelet destruction and/or decreased platelet production. Br J Haematol. 2009 Sep;146(6):585–96.

28. Thrombocytopenia in the Intensive Care Unit - Helena L. Wang, Claudine Aguilera, Kevin B. Knopf, Tze-Ming Benson Chen, David M. Maslove, Ware G. Kuschner, 2013 [Internet]. [cited 2019 Aug 15]. Available from: https://journals.sagepub.com/doi/abs/10.1177/0885066611431551?journalCode=jica

29. Dewitte A, Lepreux S, Villeneuve J, Rigothier C, Combe C, Ouattara A, et al. Blood platelets and sepsis pathophysiology: A new therapeutic prospect in critical ill patients? Ann Intensive Care [Internet]. 2017 Dec 1 [cited 2019 Aug 18];7. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5709271/

30. Morrell CN, Maggirwar SB. Recently recognized platelet agonists. Curr Opin Hematol. 2011 Sep;18(5):309–14.

31. Gawaz M, Vogel S. Platelets in tissue repair: control of apoptosis and interactions with regenerative cells. Blood. 2013 Oct 10;122(15):2550–4.

32. Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med. 2000 May 4;342(18):1334–49.

33. Middleton EA, Weyrich AS, Zimmerman GA. Platelets in Pulmonary Immune Responses and Inflammatory Lung Diseases. Physiol Rev. 2016;96(4):1211–59.

34. Brown KA, Brain SD, Pearson JD, Edgeworth JD, Lewis SM, Treacher DF. Neutrophils in development of multiple organ failure in sepsis. Lancet Lond Engl. 2006 Jul 8;368(9530):157–69.

35. De Backer D, Orbegozo Cortes D, Donadello K, Vincent J-L. Pathophysiology of microcirculatory dysfunction and the pathogenesis of septic shock. Virulence. 2014 Jan 1;5(1):73–9.

36. Tőkés-Füzesi M, Woth G, Ernyey B, Vermes I, Mühl D, Bogár L, et al. Microparticles and acute renal dysfunction in septic patients. J Crit Care. 2013 Apr;28(2):141–7.

37. Souza ACP, Yuen PST, Star RA. Microparticles: markers and mediators of sepsis-induced microvascular dysfunction, immunosuppression, and AKI. Kidney Int. 2015 Jun;87(6):1100–8.

38. Martin L, Koczera P, Zechendorf E, Schuerholz T. The Endothelial Glycocalyx: New Diagnostic and Therapeutic Approaches in Sepsis. BioMed Res Int. 2016;2016:3758278.

39. Ning S, Barty R, Liu Y, Heddle NM, Rochwerg B, Arnold DM. Platelet Transfusion Practices in the ICU: Data From a Large Transfusion Registry. Chest. 2016;150(3):516–23.

40. Greinacher A, Selleng S. How I evaluate and treat thrombocytopenia in the intensive care unit patient. Blood. 2016 Dec 29;128(26):3032–42.

41. De Blasi RA, Cardelli P, Costante A, Sandri M, Mercieri M, Arcioni R. Immature platelet fraction in predicting sepsis in critically ill patients. Intensive Care Med. 2013 Apr;39(4):636–43.

42. Levi M, Ten Cate H. Disseminated intravascular coagulation. N Engl J Med. 1999 Aug 19;341(8):586–92.

43. Thijs LG, de Boer JP, de Groot MC, Hack CE. Coagulation disorders in septic shock. Intensive Care Med. 1993;19 Suppl 1:S8-15.

44. Gando S, Kameue T, Nanzaki S, Nakanishi Y. Disseminated intravascular coagulation is a frequent complication of systemic inflammatory response syndrome. Thromb Haemost. 1996 Feb;75(2):224–8.

45. Roumen RM, Hendriks T, van der Ven-Jongekrijg J, Nieuwenhuijzen GA, Sauerwein RW, van der Meer JW, et al. Cytokine patterns in patients after major vascular surgery, hemorrhagic shock, and severe blunt trauma. Relation with subsequent adult respiratory distress syndrome and multiple organ failure. Ann Surg. 1993 Dec;218(6):769–76.

46. Weiner CP. The Obstetric Patient and Disseminated Intravascular Coagulation. Clin Perinatol. 1986 Dec 1;13(4):705–17.

47. Toh C-H, Alhamdi Y, Abrams ST. Current Pathological and Laboratory Considerations in the Diagnosis of Disseminated Intravascular Coagulation. Ann Lab Med. 2016 Nov;36(6):505–12.

48. Bakhtiari K, Meijers JCM, de Jonge E, Levi M. Prospective validation of the International Society of Thrombosis and Haemostasis scoring system for disseminated intravascular coagulation. Crit Care Med. 2004 Dec;32(12):2416–21.

49. Sivula M, Tallgren M, Pettilä V. Modified score for disseminated intravascular coagulation in the critically ill. Intensive Care Med. 2005 Sep;31(9):1209–14.

50. Cauchie P, Cauchie C, Boudjeltia KZ, Carlier E, Deschepper N, Govaerts D, et al. Diagnosis and prognosis of overt disseminated intravascular coagulation in a general hospital -- meaning of the ISTH score system, fibrin monomers, and lipoprotein-C-reactive protein complex formation. Am J Hematol. 2006 Jun;81(6):414–9.

51. Colman RW, Rubin RN. Disseminated intravascular coagulation due to malignancy. Semin Oncol. 1990 Apr;17(2):172–86.

52. Aster RH, Curtis BR, McFarland JG, Bougie DW. DRUG-INDUCED IMMUNE THROMBOCYTOPENIA: PATHOGENESIS, DIAGNOSIS AND MANAGEMENT. J Thromb Haemost JTH. 2009 Jun;7(6):911–8.

53. Reese JA, Li X, Hauben M, Aster RH, Bougie DW, Curtis BR, et al. Identifying drugs that cause acute thrombocytopenia: an analysis using 3 distinct methods. Blood. 2010 Sep 23;116(12):2127–33.

54. Priziola JL, Smythe MA, Dager WE. Drug-induced thrombocytopenia in critically ill patients. Crit Care Med [Internet]. 2010 Jun [cited 2019 Sep 9];38. Available from: insights.ovid.com

55. Aster RH, Curtis BR, McFarland JG, Bougie DW. DRUG-INDUCED IMMUNE THROMBOCYTOPENIA: PATHOGENESIS, DIAGNOSIS AND MANAGEMENT. J Thromb Haemost JTH. 2009 Jun;7(6):911–8.

56. George JN. Drug-Induced Thrombocytopenia: A Systematic Review of Published Case Reports. Ann Intern Med. 1998 Dec 1;129(11_Part_1):886.

57. Wazny LD, Ariano RE. Evaluation and Management of Drug-Induced Thrombocytopenia in the Acutely Ill Patient. Pharmacother J Hum Pharmacol Drug Ther. 2000;20(3):292–307.

58. Sakr Y. Heparin-induced thrombocytopenia in the ICU: an overview. Crit Care. 2011;15(2):211.

59. Greinacher A, Eichler P, Lietz T, Warkentin TE. Replacement of unfractionated heparin by low-molecular-weight heparin for postorthopedic surgery antithrombotic

prophylaxis lowers the overall risk of symptomatic thrombosis because of a lower frequency of heparin-induced thrombocytopenia. Blood. 2005 Oct 15;106(8):2921–2.

60. Greinacher A, Farner B, Kroll H, Kohlmann T, Warkentin TE, Eichler P. Clinical features of heparin-induced thrombocytopenia including risk factors for thrombosis. A retrospective analysis of 408 patients. Thromb Haemost. 2005 Jul;94(1):132–5.

61. Linkins L-A, Warkentin TE. The approach to heparin-induced thrombocytopenia. Semin Respir Crit Care Med. 2008 Feb;29(1):66–74.

62. George JN, Nester CM. Syndromes of Thrombotic Microangiopathy. N Engl J Med. 2014 Aug 14;371(7):654–66.

63. Sekhon SS, Roy V. Thrombocytopenia in adults: A practical approach to evaluation and management. South Med J. 2006 May;99(5):491–8; quiz 499–500, 533.

64. Arnold DM, Nazi I, Warkentin TE, Smith JW, Toltl LJ, George JN, et al. Approach to the diagnosis and management of drug-induced immune thrombocytopenia. Transfus Med Rev. 2013 Jul;27(3):137–45.

65. Ferreira JA, Johnson DW. The incidence of thrombocytopenia associated with continuous renal replacement therapy in critically ill patients. Ren Fail. 2015 Aug;37(7):1232–6.

66. pubmeddev, al HP et. The frequency and clinical significance of thrombocytopenia complicating critical illness: a systematic review. - PubMed - NCBI [Internet]. [cited 2019 Sep 23]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/21071526

67. Stanworth SJ, Walsh TS, Prescott RJ, Lee RJ, Watson DM, Wyncoll DLA, et al. Thrombocytopenia and platelet transfusion in UK critical care: a multicenter observational study. Transfusion (Paris). 2013 May;53(5):1050–8.

68. Mehta C, George J v, Mehta Y, Ali MT, Singh MK. Incidence and risk factors for thrombocytopenia in the intensive care units of a tertiary hospital in northern India. South Afr J Crit Care. 2016 Jul 26;32(1):28.

69. Shalansky SJ, Verma AK, Levine M, Spinelli JJ, Dodek PM. Risk markers for thrombocytopenia in critically ill patients: a prospective analysis. Pharmacotherapy. 2002 Jul;22(7):803–13.

70. Venkata C, Kashyap R, Farmer JC, Afessa B. Thrombocytopenia in adult patients with sepsis: incidence, risk factors, and its association with clinical outcome. J Intensive Care [Internet]. 2013 Dec 30 [cited 2019 Sep 24];1(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4373028/

71. Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. Blood. 2005 Oct 15;106(8):2710–5.

72. Thrombocytopenia and guideline-evaluated appropriateness of platelet transfusion in a tertiary care intensive care unit - Vasu - 2016 - ISBT Science Series - Wiley Online Library [Internet]. [cited 2019 Sep 24]. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/voxs.12286

73. Akca S, Haji-Michael P, de Mendonça A, Suter P, Levi M, Vincent JL. Time course of platelet counts in critically ill patients. Crit Care Med. 2002 Apr;30(4):753–6.

74. Baughman RP, Lower EE, Flessa HC, Tollerud DJ. Thrombocytopenia in the intensive care unit. Chest. 1993 Oct;104(4):1243–7.

75. Colman RW, Rubin RN. Disseminated intravascular coagulation due to malignancy. Semin Oncol. 1990 Apr;17(2):172–86.

76. Levi M. Diagnosis and treatment of disseminated intravascular coagulation. Int J Lab Hematol. 2014 Jun;36(3):228–36.

77. Venugopal A. Disseminated intravascular coagulation. Indian J Anaesth. 2014 Sep 1;58(5):603.

78. Gando S, Kameue T, Nanzaki S, Nakanishi Y. Disseminated intravascular coagulation is a frequent complication of systemic inflammatory response syndrome. Thromb Haemost. 1996 Feb;75(2):224–8.

79. Warkentin TE. Heparin-induced thrombocytopenia: diagnosis and management. Circulation. 2004 Nov 2;110(18):e454-458.

80. Warkentin T. Heparin-Induced Thrombocytopenia in Critically Ill Patients. Semin Thromb Hemost. 2015 Feb;41(01):049–60.

81. Vincent J-L, editor. Intensive Care Medicine [Internet]. New York, NY: Springer New York; 2006 [cited 2019 Sep 21]. Available from: http://link.springer.com/10.1007/0-387-35096-9

82. Pene F, Vigneau C, Auburtin M, Moreau D, Zahar J-R, Coste J, et al. Outcome of severe adult thrombotic microangiopathies in the intensive care unit. Intensive Care Med. 2005 Jan;31(1):71–8.

83. Yaguchi A, Lobo FLM, Vincent J-L, Pradier O. Platelet function in sepsis. J Thromb Haemost JTH. 2004 Dec;2(12):2096–102.

84. Squizzato A, Hunt BJ, Kinasewitz GT, Wada H, Ten Cate H, Thachil J, et al. Supportive management strategies for disseminated intravascular coagulation. An international consensus. Thromb Haemost. 2016 02;115(5):896–904.

ANNEXURE

Table 2: The 4T's scoring system

Scores	2	1	0
Thrombocytopenia	>50% platelet fall to nadir ≥20	30 - 50% platelet fall or nadir 10 – 19	<30% platelet fall or nadir <10
Timing* of onset of platelet fall (or other sequelae of HIT)	Days 5 - 10, or ≤day 1 with recent heparin (past 30 days)	>day 10 or timing unclear; or <day 1 with recent heparin (past 31 - 100 days)	<day 4 (no recent heparin)
Thrombosis or other sequelae	Proven new thrombosis, skin necrosis, or acute systemic reaction after intravenous unfractionated heparin bolus	Progressive or recurrent thrombosis, erythematous skin lesions or suspected thrombosis (not proven)	None
Other cause(s) of platelet fall	None evident	Possible	Definite
HIT: The 'Four Ts' (2, 1 or 0 for each of four categories: maximum possible score = 8). Pretest probability score: 6 - 8 indicates high; 4 - 5 intermediate; and 0 - 3 low. First day of immunizing heparin exposure considered day 0.			

Table 3: Mechanisms and causes for thrombocytopenia in ICU

Mechanisms	Causes
Pseudo-thrombocytopenia	a) Clotted blood sample b) EDTA-induced ex vivo platelet clumping c) Platelet resetting/satellitism with leukocytes d) Macrothrombocytes (rare, patients with hereditary giant platelet disorders) e) GPIIb/IIIa inhibitor induced pseudothrombocytopenia
Hemodilution	a) Infusion of fluids b) Transfusion of red blood cell concentrates and plasma
Increased platelet consumption	a) Sepsis, septic shock (bacteremia, fungemia) b) Malaria (in endemic regions) c) Major bleeding d) Acute disseminated intravascular coagulopathy (shock, burns, trauma, infection, acute promyelocytic leukemia and obstetrical complications) e) Chronic disseminated intravascular coagulopathy (large hemangioma, large aortic aneurysm, malignancy) f) Thrombotic microvascular disorders (TTP/HUS) g) Hemophagocytosis h) Hyperfibrinolysis (liver cirrhosis, metastatic

	prostate/ovarial carcinoma) i) Extracorporeal circulation with large surface exposure (extracorporeal lung assist, hemofiltration) j) Intravascular devices (cardiac assist devices, intra-aortic ballon pump) k) Severe pulmonary embolism/severe thrombosis
Increased platelet destruction	a) Severe infections (sepsis, hemorrhagic fever [Dengue virus], cross reacting antibodies) b) Heparin-induced thrombocytopenia c) Auto-immune thrombocytopenia d) Drug-induced thrombocytopenia e) Active and passive posttransfusion purpura (platelet alloantibodies)
Decreased platelet production	a) Severe infection (bacterial toxins) b) Toxic effects on bone marrow (intoxications, drugs) c) Bone marrow infiltrative diseases d) Leukemia and myelodysplasia e) Chronic liver disease f) Chronic ethanol abuse with folate deficiency g) Post stem cells transplantation with delayed engraftment and radiation
Increased platelet sequestration	a) Hypersplenism b) Hypothermia

Table 4: ISTH scoring system for DIC (47)

1. In a patient with an underlying disorder that is associated with overt DIC, obtain results from the global coagulation tests (prothrombin time, platelet count, fibrinogen, and a fibrin-related marker).
2. Score the test results: • Platelet count (≥100: 0, <100: 1, <50: 2) • Elevated levels of a fibrin-related marker, e.g., D-dimer, fibrin degradation products (no increase=0, moderate increase=2, strong increase=3) • Prolonged prothrombin time (<3 seconds: 0, ≥3 but <6 seconds: 1, ≥6 seconds: 2) • Fibrinogen level (≥1 g/L: 0, <1 g/L: 1)
3. Calculate the score: • ≥5 compatible with overt DIC: repeat scoring daily • <5 suggestive of non overt DIC: repeat next 1-2 days daily

Table 6: Mechanisms of immune mediated drug induced thrombocytopenia (55)

Mechanism	Description	Prototype Drugs
Hapten-dependent	Drug (hapten) binds covalently to platelet membrane glycoprotein producing a neoepitope recognized by antibody	Penicillin, cephalosporins
Drug-glycoprotein complex (quinine-type)	Drug interacts noncovalently with platelet membrane glycoprotein; antibody bonds	Quinine, quinidine, NSAIDs
Auto-antibody	Drug induces an autoantibody that reacts with a platelet surface glycoprotein in the absence of the drug	Gold salts, procainamide
Ligand-induced binding site (fiban-type)	Drug binds to platelet GPIIb/IIIa complex inducing conformational change and formation of a neoepitope recognized by antibody	Eptifibatide, tirofiban, lotrafiban
Drug-specific antibody	Drug consists of chimeric Fab fragments against GPIIIa with a murine component that is recognized by antibody	Abciximab
Immune complex	Drug reacts with PF4 to produce an antigenic complex against which antibodies react; resulting immune complexes bind to platelet Fc receptors resulting in platelet activation	UH, LMWH

Table 7: Criteria and Level of Evidence for Establishing a Causative Relationship in Drug-Induced Thrombocytopenic Purpura (56)

Criterion and Level of Evidence and description	
1	Therapy with the candidate drug preceded thrombocytopenia, and recovery from thrombocytopenia was complete and sustained after discontinuation of therapy.
2	The candidate drug was the only drug used before the onset of thrombocytopenia, or other drugs were continued or reintroduced after discontinuation of therapy with the candidate drug, with a sustained normal platelet count.
3	Other causes of thrombocytopenia were ruled out.
4	Re-exposure to the candidate drug resulted in recurrent thrombocytopenia
Level of evidence	
A	Definite — criteria 1, 2, 3, and 4 are met.
B	Probable — criteria 1, 2, and 3 are met.
C	Possible — criterion 1 is met.
D	Unlikely — criterion 1 is not met.

IRB Approval

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

July 30, 2018

Dr. Raja Vasanth,
PG Registrar,
Department of Transfusion Medicine,
Christian Medical College,
Vellore – 632 002.

Sub: **Fluid Research Grant: New Proposal:**
Incidence and causes of new onset thrombocytopenia in medical intensive care unit in a tertiary referral centre in South India.
Dr. Raja Vasanth. S, PG Registrar, Emp. 31393, Transfusion Medicine and Immunohaematology, Dr. Dolly Daniel, Professor, Emp. No.11674, Dr. Sukesh Chandran Nair Professor Emp. No. 13758, Dr. Nitty S. Mathews Assistant Professor, Emp. No.20774, Dr. Tulasi Geevar Assistant Professor, Emp. No.20883, Department of Transfusion Medicine and Immunohaematology, Dr. Binila Chacko Physician Emp. No.28471, Critical care Unit, Dr. Alice Joan Mathuram Professor Emp. No.28529, Dr. Thambu David Professor, Dr. Sowmya Sathyendra Professor, Dr. O.C. Abraham, Professor, Dr. Ramya Professor, Dept. of Medicine. Thenmozhi. M Associate research officer, Emp. No.32347, Biostatistics, Dr. Abhishek. S Senior Resident, Emp. No.81616, Critical Care Unit, Mr. Amalraj Senior Demonstrator, Mr. Surender Singh Senior Demonstrator, Emp. No.01826, Department of Transfusion Medicine and immunohaematology.

Ref: IRB Min. No. 11290 [OBSERVE] dated 04.04.2018

Dear Dr. Raja Vasanth,
I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Biju George, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS., MD., DM.
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc: Dr. Dolly Daniel, Dept. of Transfusion Medicine, CMC, Vellore

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

July 30, 2018

Dr. Raja Vasanth,
PG Registrar,
Department of Transfusion Medicine,
Christian Medical College,
Vellore – 632 002.

Sub: **Fluid Research Grant: New Proposal:**
Incidence and causes of new onset thrombocytopenia in medical intensive care unit in a tertiary referral centre in South India.
Dr. Raja Vasanth. S, PG Registrar, Emp. 31393, Transfusion Medicine and Immunohaematology, Dr. Dolly Daniel, Professor, Emp. No.11674, Dr. Sukesh Chandran Nair Professor Emp. No. 13758, Dr. Nitty S. Mathews Assistant Professor, Emp. No.20774, Dr. Tulasi Geevar Assistant Professor, Emp. No.20883, Department of Transfusion Medicine and Immunohaematology, Dr. Binila Chacko Physician Emp. No.28471, Critical care Unit, Dr. Alice Joan Mathuram Professor Emp. No.28529, Dr. Thambu David Professor, Dr. Sowmya Sathyendra Professor, Dr. O.C. Abraham, Professor, Dr. Ramya Professor, Dept. of Medicine. Thenmozhi. M Associate research officer, Emp. No.32347, Biostatistics, Dr. Abhishek. S Senior Resident, Emp. No.81616, Critical Care Unit, Mr. Amalraj Senior Demonstrator, Mr. Surender Singh Senior Demonstrator, Emp. No.01826, Department of Transfusion Medicine and immunohaematology.

Ref: IRB Min. No. 11290 [OBSERVE] dated 04.04.2018

Dear Dr. Raja Vasanth,

The Institutional Review Board (**Blue**, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Incidence and causes of new onset thrombocytopenia in medical intensive care unit in a tertiary referral centre in South India" on April 04th 2018.

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

The Committee reviewed the following documents:

1. IRB application format
2. Consent Form (English, Hinidi)
3. Information Sheet (English, Hinidi, Telugu)
4. Proforma
5. Signature Page
6. Cvs. Of Drs. Abhishek, Binila Chacko, Tulasi Geevar, Dolly, Nitty Mathews, Alice, OC Abraham, Ramya, Sowmya, Surendra Singh, Sukesh Chandra Nair and Ms. Thenmozhi.
7. No. of documents 1- 6.

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on April 04th 2018 in the New IRB Room, Bagayam, Christian Medical College, Vellore 632 004.

Name	Qualification	Designation	Affiliation
Dr. Biju George	MBBS, MD, DM	Professor, Haematology, Research), Additional Vice Principal , Deputy Chairperson (Research Committee), Member Secretary (Ethics Committee), IRB, CMC, Vellore	Internal, Clinician
Rev. Joseph Devaraj	BSc, BD	Chaplaincy Department, CMC, Vellore	Internal, Social Scientist
Dr. B. J. Prashantham	MA(Counseling Psychology), MA(Theology), Dr. Min(Clinical Counselling)	Chairperson, Ethics Committee, IRB. Director, Christian Counseling Centre, Vellore	External, Social Scientist
Dr. Anuradha Rose	MBBS, MD, MHSC (Bioethics)	Associate Professor, Community Health, CMC, Vellore	Internal, Clinician
Dr. Thomas V Paul	MBBS, MD, DNB, PhD	Professor,Endocrinology, CMC, Vellore	Internal, Clinician
Mr. C. Sampath	BSc, BL	Advocate, Vellore	External, Legal Expert

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Dr. Jayaprakash Muliyil	BSc, MBBS, MD, MPH, Dr PH (Epid), DMHC	Retired Professor, CMC, Vellore	External, Scientist &Epidemiologist
Ms. Grace Rebekha	M.Sc., (Biostatistics)	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M. Phil, BL.	Sr. Legal Officer, CMC, Vellore	Internal, Legal Expert
Dr. Ratna Prabha	MBBS, MD (Pharma)	Associate Professor, Clinical Pharmacology, CMC, Vellore	Internal, Pharmacologist
Mrs. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay Person
Mrs. Sheela Durai	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Dr. Vivek Mathew	MD (Gen. Med.) DM (Neuro) Dip. NB (Neuro)	Professor, Neurology, CMC, Vellore	Internal, Clinician
Dr. Santhanam Sridhar	MBBS, DCH, DNB	Professor, Neonatology, CMC, Vellore	Internal, Clinician
Dr. Barney Isaac	M.B.,B.S. D.N.B (Respiratory Diseases)	Associate Professor, Pulmonary Medicine, CMC, Vellore	Internal, Clinician
Dr. John Antony Jude Prakash	MBBS, MD	Professor, Clinical Microbiology, CMC, Vellore.	Internal, Clinician.
Dr. Ajith Sivadasan	MD, DM	Professor, Neurological Sciences, CMC, Vellore	Internal, Clinician
Mrs. Sophia Vijayananthan	MSc Nursing	Addl. Deputy Dean CMC, Vellore	Internal, Nurse
Dr. Asha Solomon	MSc Nursing	Associate Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of Withdrawals for the study entitled: "Incidence and causes of new onset thrombocytopenia in medical intensive care unit in a tertiary referral centre in South India" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in).

Fluid Grant Allocation:

A sum of 1,00,000/- INR (Rupees One Lakh Only) will be granted for 2 years. 50,000/- INR (Rupees Fifty Thousand only) will be granted for 12 months as an Ist Installment. The rest of the 50,000/- INR (Rupees Fifty thousand only) each will be released at the end of the first year as 2 nd Installment.

Yours sincerely,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS., MD., DM.,
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

IRB Min. No. 11290 [OBSERVE] dated 04.04.2018

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

Data Spread Sheets

Sl no	AG	SEX	ENROLLED D	ICU	APA	PREI	ICU HO	HO	DI/	VAS	MEC	VEN	VEC	AKI	TRA	RC	PR	FF	CRY	TH	NOT	CA	DI/	HT	MA	NEI	CAF	CRF	CLD	HB	AI	ADMN	P	TB	T.PR	ALB	URE	CRE	PH	PT	INR	APTT	FIBR
1	62	1	03/10/2018	1	11	13	18	29	1	2	1	1	18	10	2	1	1	0	0	0	2	1	1	2	2	2	2	2	2	12.5	160000	2.1	7.4	3.8	21	1	7.5	12.5	1.15	52.2		
2	74	2	03/10/2018	1	16	24	3	11	2	2	2	2			2	1	2	0	0	0	1	2		1	1	2	2	1	2	2	7.7	514000	0.4	7.3	4.2	48	2	7.3					
3	41	2	03/10/2018	1	10	11	6	11	2	2	2	2			2	1	1	0	0	0	2	2		1	1	2	2	2	2	2	7.7	200000	0.8	7.1	3	28	1	7.4					
4	47	2	03/10/2018	2	11	13	5	11	2	2	1	2			2	1	1	0	0	0	1	2		1	2	2	1	1	2	2	7.4	407000				28	1	7.5					
5	50	1	05/10/2018	1	27	61	15	25	2	2	1	1	17	11	2	2	0	0	0	0		1	1	2	2	2	2	2	2	16.5	162000				36	1	7.5	11.5	1.06	29.9		
6	57	1	05/10/2018	1	11	13	8	18	1	2	1	1	5	23	2	1	1	0	0	0	2	2		1	1	2	2	2	2	8.4	322000	1	6.9	1.9	39	1	7.5					
7	34	1	05/10/2018	1	8	8.7	6	35	1	2	2	2			2	2	0	0	0	0		1	5	2	2	2	2	2	2	16.3	155000	0.2	5.8	3.2	28	1	7.3	11.6	1.06	41.2		
8	32	1	05/10/2018	1	13	17	28	28	1	2	1	1	27	1	2	2	0	0	0	0		1	1	2	2	2	1	2	2	10.1	233000				81	1	7.5	12	1.11	31.3		
9	65	1	05/10/2018	3	31	73	5	5	1	2	1	1	3	25	1	2	0	0	0	0		1	1	1	1	2	2	2	2	13.6	202000	1	6.5	3.1	58	4	7.2	12.6	1.17	41.5	467	
10	43	1	05/10/2018	1	17	26	8	22	2	2	1	1	6	22	2	1	0	6	4	0	1	2		1	2	2	2	2	2	9.9	273000	0.2			111	4	7.5					
11	55	2	05/10/2018	3	12	15	11	25	2	2	1	1	4	24	2	2						2		2	2	2	2	2	2	11.4	221000				40	1	7					
12	45	2	08/10/2018	1	8	8.7	5	9	2	2	2	2			2	2						2		2	2	2	2	2	2	10.4	156000				46	1	7.4					
13	55	2	11/10/2018	2	22	42	5	11	2	2	1	2			2	2						2		1	2	2	2	2	2	13.4	174000	2.4	6.3	3.5	25	2	7.3					
14	60	1	08/10/2018	1	16	24	3	15	1	2	1	1	2	26	2	2						2		2	1	2	1	2	2	8.1	222000	2.5	4.9	1.9	21	1	7.3					
15	47	1	09/10/2018	3	19	32	5	5	2	2	1	2			1	2						2		2	2	2	2	2	2	12.6	324000	1.6	7.8	3.2	41	3	7.4					
16	59	2	11/10/2018	2	22	42	6	7	1	1	1	1	4	24	1	1	1	8	4	0	1	1	2	1	1	2	2	2	2	12.8	170000	1	6.2	3	55	2	7.5	12.8	1.18	44	139	
17	45	2	11/10/2018	1	16	24	18	18	1	2	1	1	8	20	2	1	1	0	0	0	2	2		2	2	2	2	2	2	13	305000	0.5	7.5	2.9	73	1	7.3					
18	49	1	08/10/2018	1	5	5.8	14	15	1	2	1	1	15	13	2	2						1	1	1	1	2	2	2	2	13.6	150000	1.5	4.8	2.4	76	1	7.3	13.3	1.23	34.1		
19	60	1	11/10/2018	1	9	9.9	7	23	2	2	1	1	6	22	2	2						2		2	1	2	2	2	2	14.4	182000	0.8	5.2	3.1	25	1	7.4					
20	28	2	15/10/2018	3	26	57	5	13	2	1	1	1	4	24	2	2						2		2	2	2	2	2	2	9.3	261000	0.2	5.8	2.4	37	5	7.4					
21	65	2	17/10/2018	2	40	51	7	14	2	2	2	2			2	2						2		2	1	2	2	2	2	10.4	241000	0.9	7.7	3.6	122	2	7.4					
22	60	1	15/10/2018	1	12	15	4	10	2	2	2	2			2	2						2		2	1	2	2	1	2	2	9.6	375000				52	1	7.5					
23	60	2	11/10/2018	1	13	17	13	13	1	2	1	1	13	15	1	2						1	1	2	2	2	2	2	2	12.5	224000	0.2	6.5	2.7	64	2	7.4	11.7	1.07	36.7		
24	30	1	22/10/2018	1	10	11	6	42	2	2	2	1	5	23	2	2						2		2	2	2	2	2	2	15.5	256000				62	1	7.4					
25	48	1	11/10/2018	1	22	42	47	71	2	2	1	1	49	21	2	2						2		2	2	2	2	2	2	9.6	287000				57	1	7.5					
26	54	2	17/10/2018	2	14	19	12	16	2	2	1	1	5	23	1	2						2		1	2	2	2	2	2	11.6	160000	0.9	7.3	2.9	33	1	7.1					
27	58	1	19/10/2018	3	8	8.7	9	16	2	2	2	2			2	2						1	5	2	1	2	2	2	2	14.9	245000				57	2	7.4	11.6	1.06	27.1		
28	60	1	22/10/2018	2	11	13	21	66	2	2	1	1	16	12	1	1	0	6	2	0	2	1	1	1	1	2	2	1	2	2	9.3	373000	1.5	6.5	2.4	36	6	7.4	12	1.1	47.1		
29	57	2	22/10/2018	1	14	19	13	38	2	2	1	1	12	16	2	2						1	1	1	1	2	2	2	2	11.6	194000	1.2	6.5	2.6	52	1	7.4	10.3	0.94	37		
30	43	2	22/10/2018	1	6	6.7	8	9	1	2	2	1	8	20	2	2						1	0	1	1	2	2	2	2	10.8	196000	0.2	5.8	3.4	51	1	7.2	10.4	0.95	32.4		
31	58	1	27/10/2018	3	19	32	5	14	2	2	2	1	4	24	2	1	1	0	0	0	2	2		1	2	2	2	2	2	7.7	705000				35	1	7.2					
32	51	1	27/10/2018	3	14	19	6	28	2	2	1	2			2	2						2		1	2	2	2	1	2	2	12.9	196000	0.5	6.7	2.4	57	1	7.2					
33	41	1	29/10/2018	3	7	7.6	3	6	2	2	1	2			2	2						2		2	2	2	2	2	2	17.1	238000	0.8	8.1	5.1	16	1	7.3					
34	30	1	29/10/2018	2	6	6.7	4	7	2	2	2	2			2	2						2		2	2	2	2	2	2	13.7	346000	0.7	8.4	4.4	42	1	7.4					
35	45	2	30/10/2018	1	9	9.9	7	7	1	2	1	1	7	21	1	1	3	0	0	0	1	1	2	2	2	2	2	2	2	11.8	231000	1.2	7.8	3.1	18	1	7.4	48.8	4.68	90.5		
36	64	1	31/10/2018	1	18	29	4	45	2	2	1	1	4	24	2	2						2		2	1	2	1	2	2	2	13.8	309000	2.7	6.6	3.7	22	0	7.3					
37	46	2	31/10/2018	1	15	21	4	8	2	2	2	2			2	2						2		1	1	2	2	2	2	2	7.2	351000	0.2	7.5	3.7	24	0	7.5					

Sl no	AG	SEX	NROLLED D	ICU	APA	PRE	ICU HO	HO	DI/	VAS	MEC	VEN	VEC	AKI	TRA	RC	PR	FF	CRY	TH	NOT	CA	DI/	HT	MA	NEI	CAF	CRF	CLD	HB	AI	ADMN	P	TB	T.PR	ALB	URE	CRE	PH	PT	INR	APTT	FIBRI
38	44	2	30/10/2018	1	12	15	12	12	1	2	1	1	8	20	2	2						2		2	2	2	2	1	2	2	12.1	421000	0.8	6.3	2.8	40	1	7.6					
39	65	1	04/11/2018	3	22	42	9	19	2	1	1	1	3	25	1	1	3	0	0	0	2	1	3	2	2	2	2	2	2	2	7.4	202000	1.4	5	1.4	258	7	7.3	10.5	0.96	38		
40	69	2	09/11/2018	1	14	15	4	8	2	2	2	2			1	2						2		1	1	2	2	2	2	2	14.8	271000	0.5	7.1	3.6	28	1	7					
41	51	2	09/11/2018	3	20	36	12	30	1	2	1	1	11	17	2	1	2	4	0	0	1	1	6	2	2	2	2	1	2	2	9.3	193000	3.4	4.1	2.1	96	1	7.3	11.7	1.08	50.7		
42	70	2	09/11/2018	2	19	32	5	15	2	2	1	2			2	2						2		1	1	2	2	1	2	2	11.1	220000				2	1	7.4					
43	46	2	09/11/2018	2	14	19	9	19	2	2	2	2			2	2						2		1	2	2	2	2	2	2	9.4	898000	0.2	6.3	3	18	0	7.5					
44	22	2	09/11/2018	1	14	19	3	8	2	2	2	1	3	25	2	2						2		2	2	2	2	2	2	2	10.4	284000	0.5	7.8	4.9	38	1	7.5					
45	76	2	09/11/2018	1			3	3	1	2	1	1	3	25	1	2						2		1	1	2	2	1	2	2	11.4	443000				38	1	7.2					
46	59	1	12/11/2018	1	14	19	5	10	2	2	2	2			2	2						2		1	2	2	2	2	2	2	16.5	192000				78	1	7.3					
47	28	1	12/11/2018	1	10	11	10	30	2	2	2	2			2	2						2		1	1	2	2	1	2	2	11.5	252000	1.5	5.2	3.3	63	1	7.3					
48	24	2	12/11/2018	1	10	11	4	26	2	2	2	1	3	25	2	2						2		2	2	2	2	2	2	2	9.7	183000				29	1	7.5					
49	27	2	12/11/2018	3	14	19	18	30	1	1	1	1	16	19	1	1	28	#	45	36	1	1	2	2	2	2	2	2	2	2	8.9	423000	1.2	5.1	2.3	61	2	7.3	16.2	1.57	71.4	121	
50	26	2	15/11/2018	2	3	4.4	4	11	2	2	2	2			2	2						2		2	2	2	2	2	2	2	13	315000				34	1	7.5					
51	75	2	16/11/2018	1	26	57	3	8	1	2	1	1	3	25	2	2						2		1	1	2	2	2	2	2	11.9	172000				2	2	7.4					
52	44	2	18/11/2018	1	12	15	5	14	2	2	2	2			2	2						2		2	2	2	2	2	2	2	13.9	156000	0.4	6.4	3.3		1	7.4					
53	74	2	18/11/2018	1	9	9.9	9	20	2	2	2	2			2	2						2		2	2	2	2	2	2	2	14.5	230000	1.0	6.8	2.3	33	1	7.4					
54	76	1	18/11/2018	2	21	39	9	29	1	2	1	1	8	20	1	2						1	1	2	2	2	2	2	2	2	7.9	314000	1	5.4	2.3	44	1	7.4	15.1	1.41	43.9		
55	16	2	19/11/2018	1	11	13	6	11	2	2	2	1	5	23	2	2						2		2	2	2	2	2	2	2	9.6	150000				21	1	7.4					
56	57	2	18/11/2018	2	8	8.7	4	8	2	2	1	2			2	2						2		1	2	2	2	2	2	2	13	242000	0.4	6.1	3.1	112	1	7.4					
57	50	1	19/11/2018	2	14	19	4	8	2	2	2	2			2	2						2		1	1	2	2	2	2	2	10.6	207000	0.5	6.3	2.9	33	1	7.5					
58	47	2	19/11/2018	1	22	42	3	5	2	2	2	1	3	25	2	2						2		2	2	2	2	2	2	2	12.8	241000	0.5	7.3	3.6	27	1	7.5					
59	61	1	21/11/2018	1	8	9.9	3	7	2	2	1	1	3	25	2	2						2		2	1	2	2	2	2	2	10.5	333000	0.4	6.4	3.2		1	7.5					
60	19	1	26/11/2018	2	15	21	3	7	2	2	1	2			2	2						2		1	2	2	2	2	2	2	15.1	172000	0.5	6.5	2.8	69	2	7.3					
61	20	1	21/11/2018	1	11	13	7	11	1	2	2	1	7	21	2	2						2		2	2	2	2	2	2	2	13.9	293000					1	7.4					
62	45	1	21/11/2018	1	5	5.7	9	17	2	2	1	1	8	20	2	2						2		2	2	2	2	2	2	2	14.8	178000					1	7.4					
63	35	2	23/11/2018	1	9	9.9	7	11	1	2	2	1	6	22	2	2						2		2	2	2	2	2	2	2	12.2	361000	0.5	7.5	3.7	24	1	7.4					
64	55	2	26/11/2018	1	32	76	6	14	2	1	2	1	5	23	1	1	2	0	0	0	2	2		1	1	2	2	2	1	2	6.8	290000	0.4	5.9	2.9	290	10	7.3					
65	73	1	26/11/2018	3	13	17	11	22	1	2	1	1	4	24	1	1	1	0	0	0	1	2		2	1	2	2	2	2	2	9.3	315000	0.7	6.8	2.3	47	2	7.5					
66	67	1	26/11/2018	1	22	42	53	68	1	1	1	1	53	35	1	1	6	4	0	0	1	1	1	1	1	2	2	2	2	2	11.6	160000	0.2	7.1	3.3	126	7	7.2	9.4	0.86	46.3	157	
67	62	2	26/11/2018	1	20	36	14	40	2	2	2	1	13	15	2	1	2	0	0	0	2	2		1	1	2	2	2	2	2	9.4	223000	0.4	7.3	3.5	40	1	7.5					
68	79	1	26/11/2018	1	17	26	10	25	2	2	1	1	9	19	2	2						1	1	1	1	2	2	2	2	2	17.4	172000	0.7	7.7	3.8	112	2	7.1	11.9	1.09	35.4		
69	59	1	28/11/2018	1	12	15	7	7	1	2	1	1	6	22	2	2						2		2	2	2	2	2	2	2	14.3	204000	1.4	6.5	3.1	36	1	7.3					
70	75	1	03/12/2018	2	17	26	7	11	1	2	2	2			2	2						2		1	1	2	2	2	2	2	12.6	256000	1.1	6.7	2.9	36	1	7.3					
71	21	2	03/12/2018	1	5	5.8	7	10	2	2	2	1	5	23	2	2						2		2	2	2	2	2	2	2	13.6	247000				22	1	7.4					
72	23	1	04/12/2018	1	17	26	10	27	1	1	2	1	7	21	1	1	1	0	0	0	2	1	1	2	2	2	2	2	2	2	9.2	171000	0.8	5.8	2.3	71	6	7.2	12.1	1.11	49.9		
73	52	2	03/12/2018	2	9	9.9	5	13	2	2	2	2			1	1	2	0	0	0	1	2		1	1	2	2	2	2	2	9.4	615000	0.5	7	3.8	35	1	7.4					
74	80	2	04/12/2018	1	15	21	9	22	2	2	2	1	7	21	2	2						2		2	2	2	2	2	2	2	8.9	497000	0.6	6.9	3.2	31	1	7.5					

1	SI no	AG	SEX	ENROLLED D	ICU	APA	PREI	ICU	HOS	HO	DIA	VAS	MEC	VEN	VFE	AKI	TRA	RC	PR	FFI	CRY	TH	NOT	CAL	DIA	HTI	MA	NEI	CAF	CRF	CLD	HB	AI	ADMN P	TB	T.PR	ALB	URE	CRE	PH	PT	INR	APTT	FIBR
77	76	65	2	04/12/2018	2			3	10	2	2	1	2			2	2						2		1	2	2	2	2	2	2	12.2	279000	0.4	7.9	3.6	42	3	7.2				
78	77	54	1	06/12/2018	3	22	42	8	14	1	1	1	1	7	21	1	1	3	0	0	0	1	1	1	1	1	2	2	2	1	2	7.2	152000	0.2	4.5	1.2	225	6	7.5	39.2	3.74	86	
79	78	75	1	07/12/2018	2			3	9	2	2	2	2			2	2						2		1	1	2	2	2	2	2	13.8	258000	0.2	7.2	4.1	27	1	7.4				
80	79	31	2	06/12/2018	1	9	9.9	16	54	2	2	1	1	16	12	2	1	0	0	4	0	2	1	1	2	2	2	2	2	2	2	12	200000				15	0	7.4	13.2	1.22	40.3	290
81	80	45	2	05/12/2018	2	17	26	5	9	1	1	1	1	9	19	2	2						2		1	2	2	2	2	2	2	14.2	399000	2.9	6.9	3	63	4	7.3				
82	81	73	1	13/12/2018	1	15	21	8	9	1	2	1	1	8	20	2	1	2	0	0	0	1	2		2	1	2	2	2	2	2	8.2	266000	0.6	6.9	3.1	23	1	7.3				
83	82	46	1	09/12/2018	2	6	6.7	6	24	2	2	2	2			2	2						2		1	2	2	2	2	2	2	11.7	259000	1.6	7.4	3.5	51	2	7.4				
84	83	69	1	10/12/2018	2	11	13	3	9	2	2	2	2			2	2						2		2	1	2	2	2	2	2	13.4	275000	2.1	7.3	3.4	22	1					
85	84	26	1	12/12/2018	1	12	15	3	21	2	2	2	1	5	23	2	2						2		2	2	2	2	2	2	2	12.7	257000	2.6	9.5	4.6	35	1	7.4				
86	85	48	1	12/12/2018	1	21	39	9	13	2	2	1	1	7	21	2	1	1	0	0	0	2	2		1	2	2	2	2	2	2	8.7	412000	0.9	5.8	2.9	13	0	7.3				
87	86	65	1	15/12/2018	2	11	13	5	17	2	2	1	2			2	1	0	0	2	0	2	1	6	2	2	2	2	2	2	2	12.2	205000	1.1	6.4	2.1	35	1	7.4	12.6	1.16	37.7	201
88	87	67	1	13/12/2018	1	19	32	5	12	2	2	2	1	5	23	2	2						2		1	1	2	2	1	2	2	11.3	215000	0.6	5.8	3.2	64	2	7.2				
89	88	62	2	16/12/2018	2	10	11	4	6	2	2	2	2			2	2						2		1	1	2	2	2	2	2	12	307000	0.9	6.4	3.4	47	1	7.3				
90	89	76	2	16/12/2018	1	17	26	4	22	2	2	2	2			2	1	2	0	3	0	1	2		1	1	2	2	1	2	2	6.5	367000	0.5	5.8	3.3	26	1	7.5				
91	90	55	2	18/12/2018	1	12	15	4	4	1	2	2	1	3	25	1	2						2		1	1	2	2	2	2	2	11.5	287000	0.3	7.9	3.3	86	2	7.2				
92	91	44	1	12/12/2018	1	21	39	30	30	1	2	1	1	30	-2	2	1	1	0	4	0	2	2		2	2	2	2	2	2	2	13.4	158000	0.5	5.9	3.3	43	1	7.4				
93	92	31	2	16/12/2018	1	12	15	7	13	2	2	2	1	3	25	2	2						2		2	2	2	1	2	2	2	12	307000	0.9	6.4	3.4	47	1	7.5				
94	93	52	2	15/12/2018	1	13	17	11	31	2	2	1	1	9	19	1	1	1	0	0	0	2	1	1	1	2	1	2	1	2	2	12.9	266000	0.5	6.4	3.6	23	1	6.9	11.6	1.07	33.2	
95	94	66	1	21/12/2018	1	14	19	5	13	2	2	2	1	3	25	2	2						2		1	1	2	1	2	2	2	10.8	218000				36	1	7.2				
96	95	47	1	21/12/2018	1	8	8.7	12	36	2	2	1	1	2	26	1	1	0	4	4	0	2	2		1	2	2	2	2	2	2	10	370000				30	1	7.5				
97	96	54	1	23/12/2018	1	6	6.7	4	4	1	2	2	1	3	25	2	2						2		1	2	2	2	2	2	2	12.7	178000	0.9	7.9	2	80	1	7.2				
98	97	58	2	22/12/2018	1	24	50	3	3	1	2	2	1	2	26	2	2						2		1	2	2	2	2	2	2	13.2	441000	0.7	7.1	3.7	88	1	7				
99	98	24	1	20/12/2018	1	4	5.1	12	22	2	2	1	1	12	16	2	2						1	1	2	2	2	2	2	2	2	12.2	180000	0.5	5.9	2.9	33	1	7.4	14.6	1.35	29	
100	99	58	2	23/12/2018	2	17	25	6	6	1	1	1	1	6	22	2	2						1	1	1	1	2	1	2	2	2	10.4	272000	0.3	4.5	2.8	34	1	6.8	12.9	1.19	30.4	165
101	100	86	1	27/12/2018	4	25	54	5	13	2	1	2	2			2	2						2		1	1	2	2	1	1	2	10.1	366000	0.3	6.1	2.7	107	6	7.3				
102	101	40	1	27/12/2018	1	28	61	7	7	1	2	1	1	7	21	1	2						1	1	2	2	2	2	2	2	2	13.7	210000	0.9	6.2	2.3	48	2	7.2	18.3	1.71	33.6	670
103	102	54	1	27/12/2018	1	16	24	17	26	2	2	2	1	16	12	2	2						2		2	2	2	2	2	2	2	14.9	306000	0.5	6.1	3.9	15	1	7.5				
104	103	34	1	27/12/2018	1	10	11	10	17	2	2	1	1	10	18	2	2						2		2	2	2	2	2	2	2	16.8	297000	0.6	8.8	5	30	1	7.4				
105	104	76	1	29/12/2018	1	25	54	15	26	2	2	1	2			2	1	2	0	0	0	2	2		2	2	2	2	2	2	2	6.3	342000	0.5	7	2.9	73	2	7.3				
106	105	79	1	29/12/2018	1	10	11	5	9	2	2	2	2			2	2						2		1	1	2	2	1	2	2	12.1	206000	1	7.6	3.9	64	1	7.3				
107	106	45	1	01/01/2019	1	2	3.8	1	5	2	2	2	1	3	25	2	2						2		2	2	2	2	2	2	2	14.8	219000	0.6	7.8	4.3	31	1	7.4				
108	107	73	2	31/12/2018	1	15	21	4	8	2	2	2	2			2	2						2		1	2	2	2	1	2	2	15.8	459000	0.7	6.8	2.9	40	1	7.4				
109	108	53	2	03/01/2019	1	8	8.7	5	9	2	2	2	1	4	24	2	2						2		1	1	1	2	2	2	2	12.3	318000	0.3	8.3	4.3	26	1	7.5				
110	109	65	1	05/01/2019	1	24	50	7	18	1	2	1	1	6	22	2	1	1	0	0	0	2	2		2	2	2	2	2	2	2	9.3	453000	0.3	7.6	1.6	119	2	7.2				
111	110	69	2	05/01/2019	2	42	93	12	13	1	1	1	1	12	16	1	1	1	0	0	0	1	1	6	1	1	2	2	1	1	2	6.9	295000				205	6	7.1	10.5	0.96	27.7	
112	111	42	2	06/01/2019	1	16	24	3	8	2	2	2	2			2	2						2		2	2	2	2	2	2	2	10.7	268000	0.3	9.9	3.4	65	3	7.3				
113	112	69	2	06/01/2019	1	27	61	1	5	1	2	1	1	3	25	1	2						1	6	2	2	2	2	1	1	2	2	8.4	342000				33	2	6.8	13	1.2	44.2	

1	SI no	AG	SEX	ENROLLED D	ICU	APA	PREI	ICU	HOS	HO	DIA	VAS	MEC	VEN	VFE	AKI	TRA	RC	PR	FFI	CRY	TH	NOT	CAL	DIA	HTI	MA	NEI	CAF	CRF	CLD	HB	AI	ADMN P	TB	T.PR	ALB	URE	CRE	PH	PT	INR	APTT	FIBR
114	113	56	2	06/01/2019	1	20	36	5	7	2	2	1	1	4	24	2	2						2		1	1	2	2	2	2	2	10.4	195000	0.4	6.1	3.6	26	1	6.9				
115	114	54	2	10/01/2019	1	18	29	8	8	1	2	2	1	7	21	1	1	1	0	0	0	2	2		1	1	2	2	1	2	2	11.1	315000	0.7	6.1	2.3	93	2	7.4				
116	115	52	2	10/01/2019	1	7	7.6	3	8	2	2	2	2			2	2						2		1	1	2	2	2	2	2	10.7	327000				18	1	7.4				
117	116	42	1	09/01/2019	1	10	11	12	19	1	2	1	1	13	15	2	2						1	6	2	1	2	2	2	2	2	14.4	203000	1.2	6.2	3.6	39	2	7.4	12	1.1	36	
118	117	60	2	11/01/2019	1			3	3	1	2	1	1	2	26	2	2						2		1	1	2	2	2	2	2	10.8	228000	0.2	7.5	3.9	41	1	7.5				
119	118	21	1	12/01/2019	1	15	21	7	8	1	1	2	1	5	23	1	1	2	0	0	0	2	1	1	2	2	2	2	2	2	2	6.3	263000	0.3	5.3	2	111	2	7.3	9.7	0.89	33.2	
120	119	60	1	12/01/2019	1	15	21	4	23	2	2	1	1	4	24	2	1	0	0	0	0	2	2		1	1	2	2	2	2	2	19.4	258000	1.7	5.1	2.9	30	1	7.3				
121	120	53	1	12/01/2019	2	8	8.7	5	5	2	2	1	2			2	2						2		2	2	2	2	2	2	2	12.5	283000	0.9	6.7	3.9	37	1	7.5				
122	121	58	1	14/01/2019	1	17	26	8	12	2	2	2	1	9	19	2	2						2		2	2	2	2	2	2	2	11.9	179000	0.7	6.2	2.3	151	3	7.3				
123	122	19	2	06/01/2019	1	26	57	3	6	2	2	1	1	2	26	2	2						2		2	2	2	2	2	2	2	13.3	315000	0.3	8	4.9	30	1	7.1				
124	123	43	2	18/01/2019	1	20	36	5	17	2	2	2	2			2	2						2		2	1	2	2	2	2	2	10.2	208000	0.2	5	1.3	112	5	7.3				
125	124	21	1	14/01/2019	1	4	5.1	6	17	2	2	2	2			2	2						2		2	2	2	2	2	2	2	14	212000				34	1	7.4				
126	125	59	1	15/01/2019	3	15	21	7	15	2	2	1	1	4	24	2	2						2		1	2	2	2	2	2	2	14.8	456000	0.8	8	4		1	7.1				
127	126	44	2	17/01/2019	1	26	57	5	13	2	2	2	1	4	24	2	2						2		1	1	2	2	2	2	2	8.8	335000	0.2	4.8	2.5	11	1	7				
128	127	58	2	18/01/2019	1	33	79	4	7	2	1	2	1	9	25	2	2						2		1	1	2	2	2	1	2	8.8	338000	0.2	6.3	3.6	112	5	7.1				
129	128	70	2	17/01/2019	2	14	18	3	17	2	2	2	2			2	2						2		1	1	2	2	2	2	2	15	318000	0.5	6.8	3.4	19	1	7.1				
130	129	56	1	19/01/2019	1	8	8.7	9	12	2	2	1	1	7	21	2	2						2		2	2	2	2	2	2	2	14.6	239000	0.4	8.2	4.5	28	1	7.3				
131	130	40	1	21/01/2019	1	10	11	10	24	2	2	2	1	6	22	2	1	0	#	0	0	2	2		2	1	2	2	2	2	2	14.1	213000	1.2	6.3	3.8	20	1	7.4				
132	131	18	1	21/01/2019	1	7	7.6	7	17	2	2	1	1	6	22	2	2						2		2	2	2	2	2	2	2	12.6	211000				26	1	7.4				
133	132	19	1	21/01/2019	1	5	5.8	32	46	2	2	1	1	15	13	2	1	2	0	0	0	2	2		2	2	2	2	2	2	2	12.9	442000	0.6	8.6	4.6	143	2	7.4				
134	133	56	1	22/01/2019	1	15	21	15	16	1	1	1	1	14	14	2	1	2	0	0	0	2	2		1	1	2	2	2	1	2	10.4	156000				171	10	7.4				
135	134	55	1	22/01/2019	2	16	24	4	15	2	2	1	1	4	24	2	2						2		2	2	2	2	2	2	2	16.0	334000	0.4	6.4	3.6	34	1	6.8				
136	135	57	2	22/01/2019	1	14	19	9	13	2	2	2	2			2	2						2		1	2	2	2	2	2	2	11.8	348000				78	1	7.4				
137	136	58	2	23/01/2019	2	15	21	12	17	2	2	1	1	10	18	2	2						2		1	1	2	2	2	2	2	10.2	532000	0.8	6.5	2.9	39	1	7				
138	137	38	1	25/01/2019	1	3	4.4	11	29	2	2	1	1	10	18	1	2						2		2	2	2	2	2	2	2	12.7	202000				31	1	7.4				
139	138	55	2	24/01/2019	2	18	29	5	8	1	2	1	2			1	2						2		1	1	2	2	2	2	2	9.3	230000				67	2	7.4				
140	139	66	2	28/01/2019	3	23	46	29	43	2	1	1	1	22	6	1	1	4	0	4	0	2	1	1	1	1	2	2	1	2	2	10.1	174000	0.5	7.5	3.2	100	4	6.9	11.7	1.07	38.6	
141	140	43	1	28/01/2019	4	19	32	13	23	1	1	2	1	4	24	1	1	4	0	0	0	1	1	1	1	1	2	2	2	2	2	5.0	262000	1.1	5.9	1.8	186	8	7.5	10.8	0.99	34.1	
142	141	74	2	29/01/2019	4	20	36	6	12	2	1	2	1	2	26	1	1	2	0	0	0	2	1	1	2	2	2	2	2	2	2	8.7	352000				174	6	7.4	14.9	1.38	45.2	
143	142	50	2	29/01/2019	3	15	21	3	32	2	2	1	1	3	25	2	1	3	0	0	0	2	2		2	2	2	2	2	2	2	6.0	247000	0.4	5	2	19	1	7.5				
144	143	55	2	29/01/2019	1	18	29	12	17	1	2	1	1	11	17	2	2						2		1	1	2	2	2	2	2	7.7	323000	3.8	5.3	2.3	77	1	7.3				
145	144	53	1	31/01/2019	2	27	61	3	8	2	2	1	1	2	26	2	2						2		2	2	2	2	2	2	2	14.1	224000	0.8	6.6	3.9	32	1	6.8				
146	145	30	1	29/01/2019	3	11	13	3	5	1	2	1	1	1	27	2	1	6	0	0	0	1	2		2	2	2	1	2	2	2	2.7	293000	5.5	5.6	3.4	67	1	7.2				
147	146	61	2	01/02/2019	1	18	29	3	6	2	2	2	1	2	26	2	2						2		2	1	2	2	2	2	2	11.5	205000	0.5	7.1	3.2	14	1	7.1				
148	147	30	1	01/02/2019	1	17	26	12	14	2	2	2	1	10	18	2	1	3	0	0	0	1	2		2	2	2	2	2	2	2	17.2	365000	0.9	7.8	4.8	40	1	7.3				
149	148	43	1	04/02/2019	1	3	4.4	5	13	2	2	2	1	1	27	2	2						2		2	2	2	2	2	2	2	14.7	205000	1.3	6.6	3.5	28	1	7.4				
150	149	28	1	04/02/2019	1	5	5.8	10	20	2	2	2	1	11	17	2	2						1	1	2	2	2	2	2	2	2	16.6	229000	1.1	7.2	4.6	26	1	7.3	10.4	0.95	29.2	

1	SI no	AG	SEX	ENROLLED	DIGU	APA	PRE	LIGU	HOI	HO	DIE	VAS	MEC	VEN	VEI	AKI	TRA	RC/	PRE	FEC	RYT	HN	NOT	CAI	DIA	HTI	MAN	NEU	CAI	CRE	CLO	HB	ALA	DMN	PLT	B	T.PR	ALB	URE	CRE	PH	PT	INR	APTT	FIBR
151	150	81	2	02/02/2019	2			3	7	2	2	2	2			2	2						2		2	1	2	2	2	2	2	10.6	231000					1	7.5				
152	151	48	2	02/02/2019	1	24	50	6	15	2	2	2	1	5	23	1	2						2		1	1	2	2	2	2	2	9.5	685000	0.6	6.2	2.9	124	7	7				
153	152	50	1	04/02/2019	1	16	24	3	4	1	2	1	1	3	25	2	2						1	1	2	1	2	2	2	2	2	14.3	304000				89	1	7.3				
154	153	21	2	04/02/2019	1	8	8.7	4	7	2	2	1	1	2	26	2	2						2		2	2	2	2	2	2	2	10.4	239000				11	1	7.5				
155	154	34	2	05/02/2019	1	10	11	4	9	2	2	2	1	4	24	2	2						2		2	2	2	2	2	2	2	15.2	374000	0.6	5.4	3	20	1	7.3				
156	155	48	2	07/02/2019	1	16	24	7	27	2	2	1	1	5	23	2	1	1	0	0	0	2	2		2	2	1	2	2	2	2	8.3	152000	0.4	5.9	2.8	9	1	7.4				
157	156	60	1	07/02/2019	1	18	29	20	20	1	1	1	1	14	14	1	2						2		1	1	2	2	2	2	2	12.5	243000				74	2	7.4				
158	157	55	1	08/02/2019	1	9	9.9	8	19	2	2	2	1	6	22	1	2						2		1	2	2	2	2	2	2	13.8	308000				27	1	7.4				
159	158	25	2	09/02/2019	1	1	3.3	7	10	2	2	1	1	5	23	2	2						2		2	2	2	2	2	2	2	10.5	264000	1.6	7.2	4.4	20	1	7.5				
160	159	40	2	09/02/2019	2	6	6.7	3	7	2	2	2	1	2		2	2						2		2	2	2	2	2	2	2	10.0	301000	0.2	7.1	4	31	1	7.4				
161	160	72	1	13/02/2019	1	32	76	11	19	2	1	1	1	7	21	1	1	1	0	0	0	2	2		1	1	2	2	1	2	2	7.9	251000				57	3	7.3				
162	161	56	2	14/02/2019	1	11	13	5	7	2	2	2	2			1	2						2		1	1	2	2	2	1	2	8.5	264000	0.5	6.1	3.9	45	2	7.3				
163	162	50	1	14/02/2019	1	13	17	19	20	1	2	1	1	19	9	1	1	2	0	0	0	2	1	1	2	2	2	2	2	2	2	10.3	361000	0.5	5.4	3.3	119	2	7.5	12.5	1.15	33.2	
164	163	24	1	11/02/2019	2	2	3.8	3	4	2	2	2	2			1	2						2		2	2	2	2	2	2	2	14.1	302000	0.4	7.1	4.6	18	1	7.5				
165	164	20	1	15/02/2019	1	18	29	11	25	2	1	2	2			1	1	1	0	0	0	1	2		2	2	2	2	2	2	2	9.1	250000				134	9	7.4				
166	165	25	1	17/02/2019	1	23	46	5	10	2	2	2	1	3	25	2	2						2		2	2	2	2	2	2	2	20.8	335000	2	7.9	4	36	1	7.2				
167	166	26	2	18/02/2019	3	6	6.7	15	15	1	2	1	1	13	15	1	1	1	0	0	0	2	1	1	2	2	2	2	2	2	2	13.3	152000	1.6	5.3	3	23	1	7.1	26.8	2.53	45.8	183
168	167	83	1	20/02/2019	3	20	36	7	7	1	2	1	1	6	22	1	2						2		1	2	2	2	2	2	2	15.1	365000				40	2	7.2				
169	168	50	1	17/02/2019	1	12	15	5	9	2	2	1	1	4	24	2	2						2		1	2	2	1	2	2	2	16.3	223000	0.3	8.3	4.7	38	1	7.2				
170	169	77	2	15/02/2019	1	25	54	17	17	1	2	1	1	10	18	2	1	1	0	0	0	2	1	1	1	1	2	2	2	2	2	7.2	356000	0.4	5.3	2	53	2	7.4	12.1	1.11	30	
171	170	24	1	20/02/2019	3	21	39	4	5	2	2	1	1	2	25	2	2						2		2	2	2	2	2	2	2	17.7	295000	1.7	7	4.1	21	1	7.3				
172	171	65	1	21/02/2019	1	30	70	8	22	2	2	2	1	9	19	1	2						2		1	1	2	1	2	1	2	11.8	289000	0.7	5.7	3.3	73	3	6.9				
173	172	29	2	24/02/2019	2	10	11	3	6	2	2	2	2			2	2						2		2	2	2	1	2	2	2	11.4	271000	0.4	5.6	3.6	18	1	7.4				
174	173	49	2	25/02/2019	3	23	46	11	21	2	2	1	1	12	16	2	2						2	1	2	2	2	2	2	2	2	13.4	197000	1.3	5.3	3.2	48	2	7.1	11	1.01	27.8	
175	174	52	1	25/02/2019	1	12	15	5	16	2	2	2	1	4	24	2	2						2		1	2	2	2	2	2	2	10.4	267000				26	1	7.4				
176	175	32	1	25/02/2019	2	11	13	3	12	2	2	1	2			2	2						2		2	2	2	2	2	2	2	10.5	858000				53	1	7.4				
177	176	38	1	27/02/2019	1	21	39	5	12	2	2	2	1	5	23	2	2						2		2	2	2	2	2	2	2	8.5	445000				74	0	7.5				
178	177	56	1	27/02/2019	1	21	39	10	13	2	2	2	1	8	20	2	2						1	6	1	2	2	2	2	2	2	17.1	224000	0.4	7.5	4.4	21	2	7.1	13	1.2	25.6	
179	178	45	1	28/02/2019	1	12	15	3	9	2	2	2	2			2	2						2		1	1	2	2	2	2	2	12.2	320000	0.9	8.4	3.5	102	2	7.5				
180	179	61	2	25/02/2019	1	18	29	4	27	2	1	2	2			1	2						2		2	1	2	2	2	2	2	9.7	172000				125	8	7.2				
181	180	30	1	01/03/2019	1	11	13	5	14	2	2	1	1	5	23	2	2						2		2	1	2	2	2	2	2	17.1	373000	1.5	8.5	4.6	38	1	7.5				
182	181	66	1	28/02/2019	2	20	36	4	8	2	2	1	2			1	2						1	1	1	1	2	2	1	2	2	13	168000	3.3	7.4	3.8	105	3	7.1	15.5	1.44	41.1	
183	182	23	2	28/02/2019	3	10	11	5	11	2	2	1	1	4	24	2	1	1	4	0	0	2	1	3	2	2	2	1	2	2	2	8.5	174000	1.8	5.9	3.1	19	1	7.6	10.9	1	25.6	
184	183	40	2	05/03/2019	2	1	3.3	3	3	2	2	2	2			2	2						2		2	2	2	2	2	2	2	12.8	212000	0.6	7.8	4.1	25	1	7.4				
185	184	55	1	04/03/2019	1	17	26	5	11	2	2	2	1	8	20	2	2						2		2	1	2	1	2	2	2	8.5	241000	0.4	6	2.1	17	1	7.5				
186	185	25	2	07/03/2019	3	6	6.7	9	9	2	2	2	1	7	21	2	2						1	1	2	2	2	2	2	2	2	10.8	211000	0.5	7.2	4.1	9	1	7.5	11.1	1.02	28.3	
187	186	63	1	14/01/2019	2	11	13	8	12	2	2	1	1	7	21	2	2						2		1	1	2	2	1	2	2	11.3	395000	0.6	6.2	3.3	16	1	7.3				

1	SI no	AG	SEX	ENROLLED	DIGU	APA	PRE	LIGU	HOI	HO	DIE	VAS	MEC	VEN	VEI	AKI	TRA	RC/	PRE	FEC	RYT	HN	NOT	CAI	DIA	HTI	MAN	NEU	CAI	CRE	CLO	HB	ALA	DMN	PLT	B	T.PR	ALB	URE	CRE	PH	PT	INR	APTT	FIBR
188	187	60	2	07/03/2019	1	34	81	8	13	2	2	1	1	7	21	1	2						1	1	1	2	2	2	2	2	2	9.5	160000	1.6	5.4	3.7	100	3	7.2	13.2	1.22	28	
189	188	62	1	07/03/2019	1	20	36	6	9	2	2	2	1	5	23	1	2						2		2	1	2	2	2	2	2	15	198000	0.5	7.4	4.4	55	2	7.2				
190	189	45	1	05/03/2019	1	6	6.7	3	6	2	2	2	1	3	25	2	2						2		2	2	2	2	2	2	2	14.3	274000	0.2	6.9	4.5	32	1	7.3				
191	190	65	1	11/03/2019	2	26	57	4	4	1	2	1	1	4	24	2	1	1	0	0	0	2	2		1	2	2	2	2	2	2	5.9	501000	3.6	5.6	2.6	95	2	7.1				
192	191	54	1	05/03/2019	1	10	11	11	23	2	2	2	1	10	18	2	2						1	1	2	2	2	2	1	2	2	11.9	279000	0.9	5.9	3.5	38	1	7.4	12.6	1.17	40.9	
193	192	61	2	05/03/2019	3	20	36	11	14	2	1	2	1	8	20	1	1	0	0	4	0	2	2		1	1	2	2	2	1	2	12.1	217000	0.6	7.4	3.7	164	5	7.1				
194	193	64	1	12/03/2019	1	14	19	5	11	2	2	2	1	4	24	2	2						2		1	2	2	2	2	2	2	13.7	327000	0.3	6.2	3.2	72	1	7.4				
195	194	49	1	14/03/2019	1	11	13	8	10	1	2	2	1	7	21	1	2						1	1	2	2	2	2	2	2	2	11.2	166000				12	1	7.5	9.5	0.87	33.5	
196	195	37	2	14/03/2019	1	21	39	5	8	2	2	2	1	4	24	2	2						2		2	2	2	1	2	2	2	8.2	190000	0.3	5.8	2.8		0	7.5				
197	196	58	1	15/03/2019	2	32	76	8	8	1	1	1	1	7	21	1	1	1	0	0	0	2	1	1	2	2	2	2	1	1	2	6.2	208000	1.9	5.1	2.3	49	3	7.4	14.7	1.36	54.9	348
198	197	70	1	15/03/2019	1	9	9.9	3	7	2	2	1	1	2	26	2	2						2		1	1	2	2	1	2	2	15.6	198000	0.6	5.5	4.1	16	1	7.3				
199	198	69	2	16/03/2019	1	23	46	15	39	1	2	1	1	15	13	2	2						2		2	2	2	2	2	2	2	11.2	293000	0.8	5.9	2.7	52	2	7.4				
200	199	82	1	17/03/2019	1	13	17	4	9	2	2	1	1	2	26	1	2						2		2	2	2	2	2	2	2	16.5	366000	0.6	6.2	3.2	36	1	7.2				
201	200	55	2	18/03/2019	2	8	8.7	11	28	2	2	1	1	14	14	2	2						2		2	2	2	2	2	2	2	11.5	275000	1.2	6.7	3.5	57	1	7.4				
202	201	62	1	18/03/2019	2	10	11	3	45	2	2	2	2			2	1	2	0	0	0	2	2		1	1	2	2	2	2	2	11.1	343000				55	2	7.5				
203	202	34	1	20/03/2019	1	20	36	15	17	2	2	1	1	15	13	2	2						2		2	2	2	2	2	2	2	13	267000	0.8	7	3.9	25	1	7.5				
204	203	51	2	20/03/2019	2	20	36	10	46	2	2	1	1	10	9	2	1	1	0	0	0	1	1	1	2	2	2	2	2	2	2	9.2	310000	0.5	5.2	2.4	20	1	7.4	11	1.01	51.5	
205	204	48	2	19/03/2019	1	14	19	5	5	1	2	1	1	5	23	1	2						2		2	2	2	2	2	2	2	13	280000	0.2	7.8	4.3	49	2	7.1				
206	205	52	2	20/03/2019	1	14	19	##	6	2	2	2	1	12	16	2	1	2	0	0	0	2	2		2	2	2	2	2	2	2	7.3	342000	1.5	6.9	2.8	82	1	7.5				
207	206	55	2	20/10/3201	1	20	36	5	12	2	2	2	1	3	25	2	2						2		1	1	2	2	2	2	2	9.4	226000				24	1	7.3				
208	207	28	1	23/03/2019	2	17	26	10	22	2	2	2	2			2	2						2		2	1	2	2	2	2	2	14.1	550000	0.5	6.4	4.9	19	1	7.2				
209	208	54	2	23/03/2019	1	11	13	21	27	1	2	1	1	19	9	2	1	4	4	4	10	1	2		1	1	2	1	2	2	2	10.1	339000				27	1	7.5				
210	209	46	1	23/03/2019	1	25	54	5	6	1	1	1	1	4	24	1	2						2		1	2	2	2	1	2	2	12.6	236000	0.2	5.9	3.4	119	7	7				
211	210	72	1	20/03/2019	1	14	19	5	15	2	2	2	1	5	23	2	2						2		1	1	2	2	2	2	2	11.6	190000				43	1	7.4				
212	211	76	1	25/03/2019	1	22	42	15	41	1	2	1	1	11	17	1	1	1	0	0	0	2	1	1	1	2	2	1	2	2	2	12.5	470000	0.7	6.5	3.2	80	3	7.4	12.5	1.15	27.1	
213	212	49	1	20/03/2019	1	7	7.6	14	22	2	2	1	1	14	14	2	2						2		2	2	2	2	2	2	2	12.3	345000	0.3	5.1	4.6	23	1	7.2				
214	213	25	2	31/03/2019	1	6	6.7	7	13	2	2	2	1	8	20	2	2						2		2	2	2	2	2	2	2	10	213000	0.8	6.4	3.2	17	1	7.4				
215	214	62	1	01/04/2019	2	30	70	3	7	2	2	1	2			1	2						2		2	2	2	2	2	2	2	10.0	316000	0.2	5.6	2.8	90	8	7.1				
216	215	78	2	01/04/2019	3	19	32	5	10	1	2	2	1	4	24	1	2						1	1	1	1	2	2	1	2	2	11.1	219000	1.3	5.2	3	35	1	7.2	10.9	1	34	
217	216	78	2	05/04/2019	1	11	13	5	13	2	2	2	2			2	2						2		1	1	2	2	2	2	2	12.3	354000	0.3	5.8	3.1	70	1	7.2				
218	217	25	2	05/04/2019	1	7	7.6	5	23	2	2	2	1	5	23	2	2						2		2	2	2	2	2	2	2	10	484000	0.5	7.4	3.4	24	1	7.4				
219	218	57	1	06/04/2019	1	9	9.9	14	14	1	2	1	1	9	19	2	2						2		2	2	2	2	2	2	2	13.8	224000	0.8	5.6	3.7	33	1	7.3				
220	219	34	1	07/04/2019	1	19	32	12	47	2	1	1	1	3	25	1	1	0	3	0	0	2	1	1	2	2	2	2	2	2	2	13.5	256000	0.2	5.7	2.8	72	2	6.8	10.2	0.93	27.9	
221	220	35	2	07/04/2019	1	4	5.1	5	8	2	2	2	1	5	23	2	2						2		2	2	2	2	2	2	2	11.1	191000	0.2	6.9	4.3	22	0	7.4				
222	221	67	1	07/04/2019	1	24	50	5	15	2	2	2	1	6	22	2	2						2		2	1	2	2	2	2	2	8.5	210000	0.4	5.2	3.3	27	1	7.2				
223	222	75	1	08/04/2019	1	22	42	5	15	2	2	2	1	3	25	2	1	2	0	4	0	2	2		2	2	2	2	2	2	2	9.1	252000	0.7	6.5	2.2	69	2	7.4				
224	223	80	1	11/04/2019	1	21	39	12	32	2	2	1	1	10	18	2	1	1	0	0	0	2	2		1	1	2	2	2	2	2	10.6	260000	1.1	6.3	2.9	56	1	7.6				

1	Sl no	AG	SEX	ENROLLED D	ICU	APA	PRE	ICU	HOS	HO	DIA	VAS	MEC	VEN	VFE	AKI	TRA	RC	PR	FFI	CRY	TH	NOT	CAI	DIA	HTI	MA	NEI	CAF	CRF	CLO	HB	AI	ADMIN P	TB	T.PR	ALBU	URE	CRE	PH	PT	INR	APTT	FIBR
225	224	68	1	11/04/2019	1	30	85	13	17	2	1	1	1	13	15	1	1	2	4	4	0	2	2	1	2	2	1	2	2	2	12.2	284000	0.3	8	3.7	168	9	7				
226	225	40	1	11/04/2019	3	21	50	5	8	1	2	1	1	4	24	2	1	1	0	0	0	2	2	2	2	2	2	2	2	2	6.6	320000	0.7	5.1	1.4	14	0	7.3				
227	226	36	1	12/04/2019	1	2	5.8	6	11	2	2	2	1	5	23	2	2						2	2	2	2	2	2	2	2	17	294000	0.7	6.8	3.7	21	1	7.4				
228	227	56	1	15/04/2019	2	18	29	3	8	2	2	1	2			1	2						2	1	1	2	2	2	2	2	14.2	332000	0.9	7.3	3.6	83	4	7.1				
229	228	54	2	15/04/2019	1	30	70	9	9	1	2	1	1	8	20	2	2						2	1	1	2	2	2	2	2	11.8	264000	0.8	6.4	2.5	25	1	7.3				
230	229	62	1	16/04/2019	1	21	39	3	5	1	2	2	1	3	25	2	2						2	1	1	2	1	1	2	2	9.4	152000	0.6	5	2.1	16	1	7.3				
231	230	75	2	16/04/2019	2	25	54	7	13	2	2	1	1	5	23	2	2						2	2	2	2	2	2	2	2	8.8	284000	0.3	6.3	3.7	33	1	7.5				
232	231	77	2	16/04/2019	1	21	39	3	23	2	2	1	2			2	2						2	2	1	2	2	2	2	2	13.1	241000	0.3	7.5	4.1	37	1	7.4				
233	232	91	2	18/04/2019	2	21	39	3	13	2	2	2	2			2	1	2	0	0	0	2	2	1	1	2	1	1	1	2	11.6	322000				122	4	7.5				
234	233	23	1	19/04/2019	4	13	17	4	12	2	1	2	2			1	2						2	2	2	2	2	2	2	2	15.1	240000	1.8	7	3.7	102	6	7.4				
235	234	48	2	18/04/2019	1	26	57	15	26	2	2	2	1	14	14	2	2						2	1	2	2	2	2	2	2	13.8	184000	0.2	7.2	4.1	29	1	7.2				
236	235	53	1	20/04/2019	1	6	8.7	4	4	1	2	1	1	4	24	2	2						2	1	1	2	2	1	2	2	13.5	300000				42	1	7.6				
237	236	58	1	21/04/2019	1	17	26	8	13	2	2	1	1	7	21	2	2						1	1	2	2	2	2	2	2	14.7	224000	0.2	7.2	4.2	17	1	7.4	11.6	1.07	35.8	
238	237	50	2	24/04/2019	1	15	21	6	54	1	2	1	1	1	25	2	2						2	1	2	2	2	2	2	2	11	300000	0.5	6.6	3.7	26	0	7.4				
239	238	49	2	27/04/2019	1	10	11	4	9	2	2	2	2			2	2						2	2	2	2	2	1	2	2	15	237000	3.3	7.9	4.1	22	1	7.4				
240	239	22	2	29/04/2019	2	5	5.8	5	8	2	2	2	2			2	2						2	2	2	2	2	2	2	2	12	261000	0.5	7.5	4.2	44	1	7.4				
241	240	31	1	11/04/2019	3	40	91	28	60	2	1	1	1	23	0	1	1	3	0	0	0	2	2	2	2	2	2	2	2	2	9.4	315000	0.4	6.6	2.8	180	5	7.2				
242	241	38	2	22/04/2019	3	15	21	18	62	2	1	2	1			1	1	5	0	32	0	1	1	3	2	2	2	2	2	2	7.5	204000				130	4	7.5	11.2	1.03	33.5	
243	242	80	1	23/04/2019	1	8	8.7	10	28	2	2	1	1	10	18	2	2						1	1	2	2	2	1	2	2	15	222000	0.7	7.4	4.8	30	1	7.3	10.5	0.96	35.2	
244	243	45	1	26/04/2019	1	21	39	10	15	2	2	1	1	9	19	2	2						2	2	2	2	2	2	2	2	12.1	241000	0.2	6.9	3.8	34	1	7.3				
245	244	61	1	16/04/2019	1	15	21	15	21	1	1	1	1	11	17	1	1	4	4	56	0	1	1	1	2	1	2	1	2	2	7.2	196000	0.8	6.2	3.2	133	4	7.2	12.6	1.16	26.4	
246	245	52	1	28/04/2019	1	26	57	3	10	2	2	2	2			2	2						2	1	1	2	2	2	1	2	9.3	180000	0.6	6.5	3.2	88	6	7.3				
247	246	50	1	01/05/2019	22	6	8.7	3	5	2	2	2	2			2	2						2	2	1	2	2	2	2	2	12.2	167000	0.9	5.9	3.8	23	1	7.4				
248	247	76	2	01/05/2019	1	15	21	12	17	1	2	1	1	7	21	2	2						1	6	1	2	2	2	2	2	11.4	213000	0.7	7	2.6		1	7.3	11.7	1.07	39.1	
249	248	38	2	30/04/2019	1	8	8.7	4	7	2	2	2	2			2	2						2	2	2	2	2	2	2	2	12.2	161000	0.2	7.6	3.4	21	1	7.5				
250	249	60	1	01/05/2019	2	17	26	4	13	2	2	1	1	4	24	2	2						2	1	2	2	2	2	2	2	11.6	584000	0.4	9.8	3.6	38	1	7.4				
251	250	27	1	04/05/2019	2	25	54	5	14	2	2	2	1	3	25	1	2						2	2	2	2	2	2	2	2	10	200000	0.4	5.6	2.2	113	10	7.2				
252	251	57	1	04/05/2019	1	10	11	3	5	1	2	1	1	3	25	2	2						2	1	1	2	2	1	2	2	9.6	152000					1	7.4				
253	252	24	1	03/05/2019	3	12	15	4	6	2	2	1	1	4	24	2	2						2	2	2	2	2	2	2	2	12.9	218000	1.3	5.5	2.2	51	1	7.4				
254	253	69	1	04/05/2019	1	33	42	9	10	1	2	1	1	9	19	2	2						2	1	1	2	1	2	2	2	9.8	221000	0.5	7.5	2.3	18	0	7.5				
255	254	72	2	04/05/2019	1	18	29	4	14	2	2	2	1	3	25	2	2						2	1	1	2	2	2	2	2	11.5	292000	1	7	3.6	52	1	7.3				
256	255	71	2	07/05/2019	3	16	29	6	8	2	2	1	1	4	24	2	2						1	6	1	1	2	2	1	2	2	10.8	264000	1	6.3	3.7	24	1	7.3	11.5	1.05	26.2	
257	256	54	2	07/05/2019	2	22	42	7	17	2	2	1	1	4	24	2	1	3	0	0	0	2	2	1	1	2	2	1	2	2	8.1	575000	0.2	7.2	3.2	49	2	7				
258	257	56	1	07/05/2019	1	10	11	6	8	2	2	2	1	6	22	1	2						1	1	1	2	2	2	2	2	14.9	222000	2.1	7	3.6	46	2	7.4	11.4	1.05	29.6	
259	258	59	2	07/05/2019	2	17	26	3	11	2	2	1	2			1	2						2	1	2	2	2	1	2	2	10.6	340000	1.6	7	4.2	27	1	7.1				
260	259	68	1	08/05/2019	1	17	26	6	9	1	2	2	1	6	22	2	2						2	1	1	2	2	2	2	2	13	276000	0.7	7.2	4.3	18	1	7.1				
261	260	41	2	08/05/2019	1	12	15	5	7	2	2	2	1	3	25	2	2						2	2	2	2	2	2	2	2	9.7	395000	0.9	7.3	3.9	14	1	7.4				

1	Sl no	AG	SEX	ENROLLED D	ICU	APA	PRE	ICU	HOS	HO	DIA	VAS	MEC	VEN	VFE	AKI	TRA	RC	PR	FFI	CRY	TH	NOT	CAI	DIA	HTI	MA	NEI	CAF	CRF	CLO	HB	AI	ADMIN P	TB	T.PR	ALBU	URE	CRE	PH	PT	INR	APTT	FIB
262	261	60	1	08/05/2019	1	25	57	10	16	2	2	1	7	21	2	1	1	0	0	0	2	1	6	1	2	2	2	2	2	1	8.5	150000	1	8.7	3	27	1	7.3	11.7	1.08	37.9	
263	262	21	2	09/05/2019	1	12	15	10	15	2	2	2	1	8	20	2	2						2		2	2	2	2	2	2	12.1	300000	0.5	8.2	4.2	24	1	7.5				
264	263	65	2	09/05/2019	1	20	36	4	4	2	2	1	1	4	24	2	2						2		2	1	2	2	2	2	14.4	288000	0.5	8.8	4.1	28	1	7.3				
265	264	70	1	10/05/2019	1	17	26	8	14	2	2	2	1	7	21	2	2						2		1	1	2	2	2	2	11.9	513000	0.9	8.1	3.5	65	1	7.3				
266	265	70	1	09/05/2019	1	25	54	7	18	2	2	2	1	5	23	1	2						1	1	1	1	2	2	2	2	12.1	108000	0.5	7.9	3.3	85	5	7.1	10.5	0.96	37.3	
267	266	50	1	12/05/2019	1	17	26	3	7	2	2	2	2			2	2						2		2	2	2	2	2	2	9	424000	0.9	6.6	3.2	22	1	7.5				
268	267	54	2	13/05/2019	3	25	54	5	8	2	2	2	1	3	25	2	2						1	1	2	1	2	2	2	2	2	10.6	156000	0.3	6.4	3.2	50	2	6.8	11	1.01	30.2	
269	268	40	1	13/05/2019	1	22	42	3	7	2	2	2	2			1	2						2		1	1	2	2	2	1	2	9.4	237000	2	7.1	4	110	6	7.4				
270	269	68	1	13/05/2019	1	17	26	4	14	2	2	2	1	4	24	2	1	2	4	0	0	1	2		2	1	2	2	2	2	2	10.4	107000				109	3	7.0				
271	270	52	2	13/05/2019	1	10	11	3	3	2	2	2	1	3	25	2	2						2		2	1	2	2	2	2	2	14.8	350000	1.2	9	4.9	21	1	7.6				
272	271	43	1	13/05/2019	1	25	57	5	30	2	2	1	1	5	23	2	2						2		2	2	2	2	2	2	2	16.2	301000	0.2	8.9	4.6	25	1	7.1				
273	272	51	1	13/05/2019	1	14	19	22	29	1	2	1	1	24	4	2	1	0	6	4	0	2	1	1	2	2	2	1	2	2	2	15.1	216000	1	8.4	4.3	62	2	7.5	14.2	1.31	30.4	
274	273	23	2	15/05/2019	1	13	17	5	7	2	2	2	1	3	25	2	2						2		2	2	2	1	2	2	2	13.4	275000	0.3	6.9	3.8	13	1	7.4				
275	274	44	2	14/05/2019	1	10	11	3	6	2	2	2	2			2	2						2		2	2	2	2	2	2	10.3	259000	0.3	7.6	4.3	23	1	7.4				
276	275	21	2	13/05/2019	1	20	36	10	16	2	2	2	1	7	21	2	2						2		2	2	2	2	2	2	10.5	277000	0.2	6.2	3.5	15	1	7.3				
277	276	58	1	16/05/2019	1	17	26	9	42	2	2	2	2			2	2						2		2	1	2	2	2	2	10.7	245000					1	7.4				
278	277	72	1	16/05/2019	1	17	26	3	9	2	2	2	2			2	2						2		1	2	2	2	2	2	10.7	458000	0.5	8	4.2	13	1	7.4				
279	278	25	1	17/05/2019	1	10	11	15	33	2	2	1	1	15	13	2	2						1	1	2	2	2	2	2	2	11.5	175000	0.7	5.5	3.1	24	1	7.4	10.2	0.93	32.9	
280	279	35	1	15/05/2019	1	18	29	3	56	1	2	2	1	3	25	2	1	0	0	4	0	2	2		2	2	2	2	2	2	16.4	253000	0.2	6.4	3.7	13	1	7.4				
281	280	45	1	17/05/2019	1	17	26	7	14	2	2	1	2			2	2						2		2	2	2	2	2	2	10.7	352000	0.2	7.3	3.5	38	1	7.2				
282	281	57	1	17/05/2019	1	8	8.7	3	3	1	2	2	1	3	25	2	2						2		2	2	2	2	2	2	9.4	253000	1.5	5.6	2.2	160	2	7.5				
283	282	75	2	18/05/2019	1	21	39	13	14	1	2	1	1	14	14	1	2						2		1	1	2	2	2	2	10.2	179000	0.3	7	4.1	41	2	7.2				
284	283	50	1	21/05/2019	1	27	61	4	15	2	1	2	1	3	25	1	2						2		1	1	2	2	1	2	10.8	241000	2.2	6.5	2.7	126	10	7.2				
285	284	48	1	22/05/2019	1	24	50	5	11	2	2	1	1	5	23	2	2						2		2	2	2	2	2	2	15.4	520000	0.2	8.5	5.2	21	1	7				
286	285	86	2	23/05/2019	2	17	26	3	8	2	2	2	2			2	2						2		2	2	2	2	2	2	10.8	377000				54	2	7.3				
287	286	73	1	24/05/2019	1	20	67	15	16	1	2	1	1	15	13	2	2						2		2	2	2	2	2	2	14.5	251000	0.5	5.9	2.9	18	1	7.2				
288	287	44	2	25/05/2019	1	29	26	9	20	2	2	1	1	6	22	2	1	3	0	0	0	2	2		1	2	2	2	2	2	5.8	698000	0.8	5.4	2.1	41	1	7				
289	288	65	2	25/05/2019	2	33	79	5	10	2	2	1	1	4	24	1	2						2		1	1	2	2	2	2	10.3	387000	0.5	5.4	3	54	3	7.2				
290	289	62	1	25/05/2019	1	10	32	4	23	2	2	2	2			2	2						2		1	2	2	2	2	2	10.0	229000	0.4	6.7	3.3	33	4	7.1				
291	290	67	1	26/05/2019	1	30	70	5	9	2	1	1	2			1	2						2		1	1	2	2	2	2	8.8	197000	0.4	5.4	2.7	149	10	7.2				
292	291	60	1	28/05/2019	1	8	8.7	5	12	2	2	2	2			2	2						2		1	1	2	1	2	2	2	11.4	206000	0.4	6.1	3.1	40	1	7.5				
293	292	54	2	29/05/2019	1	16	24	6	19	2	2	1	1	5	23	1	2						1	3	2	1	2	2	2	2	1	13.2	164000	0.5	7.4	4.1	18	1	7.2	10.5	1.02	27.5	
294	293	54	2	29/05/2019	1	18	29	5	6	1	2	1	1	7	21	2	2						2		2	2	2	2	2	2	14.5	154000	1.1	7.1	4	45	1	7.5				
295	294	39	2	28/05/2019	1	20	36	5	7	2	2	1	1	6	22	2	2						2		2	2	2	2	2	2	13.4	194000	0.9	7.6	3.8	35	1	7.5				
296	295	32	1	31/05/2019	1	13	70	13	14	1	2	1	1	13	15	2	2						1	1	2	2	2	2	2	2	13.3	216000	1.5	5.8	3.3	28	2	7.0	12.6	1.16	29.5	
297	296	64	1	31/05/2019	1	30	70	8	15	2	2	1	1	4	24	2	2						2		2	2	2	2	2	2	12.5	156000	1	5.6	3.3	37	1	7.3				
298	297	52	1	31/05/2019	1	21	39	4	6	1	2	1	1	5	23	2	2						2		1	2	2	2	2	2	9	189000	0.4	7.2	2.7	34	1	7.4				

1	Sl no	AG	SEX	ENROLLED D	ICU	APA	PRE	ICU	HOS	HO	DIA	VAS	MEC	VEN	VFE	AKI	TRA	RC	PR	FFI	CRY	TH	NOT	CAI	DIA	HTI	MA	NEI	CAF	CRF	CLO	HB	AI	ADMIN P	TB	T.PR	ALBU	URE	CRE	PH	PT	INR	APTT	FIBR
299	298	52	2	31/05/2019	1	17	26	7	19	1	2	1	1	3	25	1	1	1	0	0	0	2	1	1	1	2	2	2	2	2	8	151000	1.1	5.2	2.6			7.5	12.1	1.11	45.6	455
300	299	72	2	01/06/2019	1	16	24	8	8	1	1	1	1	8	20	1	2						1	1	1	1	2	2	2	2	12.7	360000	1	7.7	4.2	14	1	7.3	11.9	1.1	35.6	
301	300	62	1	01/06/2019	3	16	24	7	13	2	2	1	1	5	23	2	2						2		1	1	2	1	1	2	13.9	374000	0.6	5.8	3.1	23	1	7				
302	301	72	1	02/06/2019	2	15	21	14	14	1	2	1	1	12	16	1	1	1	0	0	0	2	1	1	1	1	2	2	2	2	15.3	236000	1.7	5.8	3.3	58	1	7.4	10	0.92	43	
303	302	83	2	02/06/2019	1	30	70	4	4	1	2	1	2			2	2						2		2	2	2	2	2	2	14.4	285000	0.4	7.2	3.7	17	1	7.3				
304	303	63	1	02/06/2019	1	11	13	7	13	2	2	2	2			2	2						2		2	1	2	2	2	2	8.8	313000	0.6	7.7	3.4	37	1	7.3				

Clinical Proforma

CLINICAL PROFORMA
DEPARTMENT OF TRANSFUSION MEDICINE AND IMMUNOHAEMATOLOGY

INCIDENCE AND CAUSES OF NEW ONSET THROMBOCYTOPENIA IN MEDICAL INTENSIVE CARE UNIT IN A TERTIARY REFERRAL CENTRE IN SOUTH INDIA

PRELIMINARY DETAILS:

Unique ID :

Hospital No :

Name :

Age :

Sex : Male / Female Date of enrollment:

	Date	Reason
Admission In ICU		
Discharge from ICU		
DAMA/Referral from ICU		
Death in ICU		
Total hospitalized days		

PRIMARY REASON FOR ICU ADMISSION:

PRESENT ICU ADMISSION		
Respiratory		
Cardiovascular		
Gastrointestinal		
Neurologic diseases		
Malignancy		
Genitourinary		
Poisoning		
Infections		
OTHERS		

PREEXSITING COMORBIDITES:

Comorbidities	Tick	Duration
Diabetes Mellitus		
Hypertension		
Malignancy		
Neurologic disease		
Cardiac disease		
Chronic renal failure		
Liver disorders		
OTHERS		

CLINICAL PROFORMA
DEPARTMENT OF TRANSFUSION MEDICINE AND IMMUNOHAEMATOLOGY

INVESTIGATIONS:

	On admission	Day 3	Day 3 – 5 (Any one day)	Day 5 – 10 (Any one day)	Day 10 – 14 (Any one day)	Comments – If any
Hemoglobin						
WBC						
Diff. count (N/L)						
Platelets						
MPV						
IPF						
TB/DB						
T.P/Albumin						
SGOT/SGPT						
ALP						
UREA/CREAT						
PH						
PT/INR						
APTT						
PROCAL						
FIBRINOGEN						
D-DIMER						
ADAM TS13						

CULTURE DETAILS:

Culture specimen	Tick	Organisms grown
Blood		
Urine		
Sputum		
Pus		
Cavity fluids (Ascitic, CSF, Pleural)		
Others (If any)		

CLINICAL PROFORMA
DEPARTMENT OF TRANSFUSION MEDICINE AND IMMUNOHAEMATOLOGY

	REQUIREMENT: YES / NO	NO OF DAYS
CRRT/DIALYSIS		
VASOPRESSOR REQUIREMENT		
MECHANICAL VENTILATION		

TRANSFUSION DETAILS:

Blood & products	**Packed cells/ Rejuvenated cells**	**PRC – RDP/SDP**	**FFP**	**CRYO PRECIPITATE**	**CRYO SUPERNATANT**
No of units transfused in the present admission					
Reason for transfusions – Therapeutic/Prophylactic					

ONLY IN PATIENTS WITH NOT

SPECIAL TESTS:

1	HIT SCREENING test: PF4/heparin antibodies	POSITIVE / NEGATIVE	**Value:**
2	IMAGING / DOPPLER STUDIES: (CT/MRI/DOPPLER/ECHO: If done)	Thrombosis	
		Bleeding	

SPECIFIC TREATMENT RECEIVED IN NOT PATIENTS ONLY:

Therapy	YES/NO	No of days
Plasma exchange		
IVIG		

CLINICAL PROFORMA
DEPARTMENT OF TRANSFUSION MEDICINE AND IMMUNOHAEMATOLOGY

DRUG DETAILS:

DRUGS		Total no of days	Day – Onset of thrombocytopenia	Day – Discontinuation of medicine	Recovery – of thrombocytopenia	
					Yes/No	If Yes days
Heparin	UH					
	LMWH					
Amphotericin B						
Septran						
Carbapenems						
Cephalosporins						
Vancomycin						
Linezolid						
Piperacillin						
Ampicillin						
Rifampicin						
Ethambutol						
Abciximab						
Amiadarone						
Digoxin						
Methyldopa						
Phenytoin						
Valproic acid						
Carbamazepine						
Quinine						
Quinidine						
Ibuprofen/Naproxen						

THE 4T SCORING SYSTEM OF HIT: (Circle)

Scores	2	1	0
Thrombocytopenia	>50% platelet fall	30 - 50% platelet fall	<30% platelet fall
Timing* of onset of platelet fall (or other sequelae of HIT)	Days 5 - 10, or ≤ day 1 with recent heparin (past 30 days)	>day 10 or timing unclear or <day 1 with recent heparin (past 31 - 100 days)	<day 4 (no recent heparin)
Thrombosis or other sequelae	Proven new thrombosis, skin necrosis, or acute systemic reaction after IV unfractionated heparin bolus	Progressive or recurrent thrombosis, erythematous skin lesions or suspected thrombosis (not proven)	None
Other cause(s) of platelet fall	None evident	Possible	Definite
HIT: The 'Four Ts' (2, 1 or 0 for each of four categories: maximum possible score = 8). Pretest probability score: 6 - 8 indicates high; 4 - 5 intermediate; and 0 - 3 low. First day of immunising heparin exposure considered day 0.			

Total Pretest ProbabilityScore:

Consent Form

CHRISTIAN MEDICAL COLLEGE, VELLORE
INFORMED CONSENT

STUDY TITLE: Incidence and causes of new onset thrombocytopenia in medical intensive care unit in a tertiary referral centre in South India.

Study Number:

Subject's Name:

Date of birth/Age:

1) I confirm that I have read and understood the information sheet dated for the above study and have had the opportunity to ask questions.
2) I understood that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
3) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purposes.
4) I am willing to give 5-10ml of blood for testing purposes which is mentioned in the information sheet.
5) Overall, I agree to take part in the above study.

Signature (or Thumb impression) of the subject/ legally acceptable

Signatory's Name: Signature:

Or

Date:

Signature of the investigator: **Date:**

Study Investigator's Name:

Signature/ thumb impression of the witness: **Date:**

Name & Address of the witness: