"USE OF IMMATURE PLATELET FRACTION TO PREDICT TIME TO PLATELET RECOVERY IN PATIENTS WITH DENGUE INFECTION AND FOR OPTIMAL MANAGEMENT"

BY

REG NO: BG0122009

Dissertation

Submitted to

KAHER, Belagavi, Karnataka,

In partial fulfilment of the requirements for the degree of

M.D.

IN

GENERAL MEDICINE

DEPARTMENT OF GENERAL MEDICINE

JAWAHARLAL NEHRU MEDICAL COLLEGE,

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DECEMBER-2024 / JANUARY -2025

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Sub: Institutional Ethical Clearance for the study.

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LIST OF ABBREVIATIONS

Abbreviation	Full Form
DENV	Dengue Virus
IPF	Immature Platelet Fraction
WHO	World Health Organization
RNA	Ribonucleic Acid
NS1	Non-structural Protein 1
NS2A	Non-structural Protein 2A
NS2B	Non-structural Protein 2B
NS3	Non-structural Protein 3
NS4A	Non-structural Protein 4A
NS4B	Non-structural Protein 4B
NS5	Non-structural Protein 5
ADE	Antibody-Dependent Enhancement
DHF	Dengue Hemorrhagic Fever
DSS	Dengue Shock Syndrome
ER	Endoplasmic Reticulum

IgM	Immunoglobulin M
IgG	Immunoglobulin G
TNF	Tumor Necrosis Factor
IL-6	Interleukin-6
C3a	Complement Component 3a
C5a	Complement Component 5a
DF	Dengue Fever
TNF-α	Tumor Necrosis Factor-alpha
IFN-γ	Interferon-gamma
CRP	C-Reactive Protein
PCT	Procalcitonin
AST	Aspartate Aminotransferase
ALT	Alanine Aminotransferase
U/L	Units Per Liter
ITP	Immune Thrombocytopenic Purpura
DIC	Disseminated Intravascular Coagulation
TTP	Thrombotic Thrombocytopenic Purpura

HIV	Human Immunodeficiency Virus
CBC	Complete Blood Count
Hct	Hematocrit
IV	Intravenous
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
IBW	Ideal Body Weight
RBCs	Red Blood Cells
COVID-19	Coronavirus Disease 2019
PCV	Packed Cell Volume
RBC	Red Blood Cell
KLE	Karnataka Lingayat Education (as in KLE, Belgaum, India)
Hb	Hemoglobin

ABSTRACT

Introduction:

Dengue fever is a mosquito-borne viral infection, which has emerged as a significant global public health threat, with over 12 million cases reported in 2024. Severe dengue is characterised by thrombocytopenia and plasma leakage and can lead to life-threatening complications. This study aimed to evaluate the utility of the Immature Platelet Fraction as a predictive marker for platelet recovery time in dengue patients, thereby improving clinical management and reducing unnecessary interventions.

Methods:

A one-year observational study was conducted at a tertiary care center in Belgaum, India, involving 90 dengue patients aged >18 years with confirmed dengue infection. Daily platelet counts and IPF values were monitored, and correlations between these parameters were analyzed. Data were collected using a structured clinical data collection tool, and statistical analysis was performed using R version 4.2.1 and Microsoft Excel.

Results:

The majority of participants were young adults (18-30 years), with a male predominance (67.8%). Platelet counts showed a gradual increase from Day 1 (median: 59 x 10^9/L) to Day 7 (median: 114 x 10^9/L), while IPF levels fluctuated, peaking on Day 3 (median: 10.8%). A significant negative correlation between platelet counts and IPF was observed, strongest on Days 1, 2, and 5 (Spearman correlation: -0.55 to -0.84, $p < 0.001$). Higher IPF levels at admission were associated with faster platelet recovery. Transfusions were administered to 36.7% of participants, with 25.5% receiving random donor platelets. Also, 16 patients with low platelet counts and high IPF levels received transfusions despite not being candidates.

Conclusion:

IPF serves as a valuable predictor of platelet recovery in dengue patients, enabling timely and efficient clinical management. These findings highlight the importance of incorporating IPF into routine dengue care, particularly in high-risk populations.

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INTRODUCTION

Dengue fever, a mosquito-borne viral infection caused by the dengue virus (DENV), has emerged as a significant and growing public health threat worldwide. The incidence of dengue has surged over recent decades, largely driven by the expansion of vector habitats, urbanization, climate change, and population growth, creating ideal conditions for the multiplication of *Aedes* mosquitoes, particularly *Aedes aegypti*, the primary vector.[1]

In 2024, over 12 million cases of dengue have been reported in North, Central, and South America and the Caribbean.[2] Annually, 100 to 400 million infections are reported, and around half of the global population is currently at risk according to the World Health Organization.[1] In 2023, dengue cases reached an all-time high, impacting more than 80 countries across all WHO regions. Since early 2023, continuous transmission along with an unexpected surge in cases led to a record-breaking total of over 6.5 million reported infections and more than 7,300 deaths attributed to dengue.[1] Although most cases show mild to moderate symptoms, 5% of patients may progress to severe illness.[3]

Dengue disease typically progresses over a span of 2 to 7 days, transitioning through the febrile, critical, and recovery phases. In the febrile phase, patients have high fever, malaise, and general flu-like symptoms. The critical phase follows, marked by potential life-threatening complications such as plasma leakage, severe bleeding, and organ impairment. During this phase, a significant decrease in platelet count, or thrombocytopenia, often occurs, elevating the risk of bleeding and shock. The recovery phase then ensues, marked by reabsorption of leaked fluids and a gradual stabilization of the patient's health.[4,5]

Despite established WHO guidelines recommending outpatient management for many dengue patients, hospitalization may be warranted for those presenting with warning signs such as persistent vomiting, severe abdominal pain, or profound thrombocytopenia.[6] In thrombocytopenia, the platelet count is reduced, it is one of the most consistent hematologic findings in dengue and is commonly used as a marker of disease severity.[7] The mechanisms underlying dengue-related thrombocytopenia are complex, including impaired platelet production due to DENV infection of bone marrow progenitor cells, increased platelet destruction mediated by the immune response, and direct effects on platelet function.[8] Monitoring platelet counts is thus essential for assessing disease severity and guiding treatment decisions.

One promising marker that has emerged in recent years is the Immature Platelet Fraction (IPF). The IPF measures the proportion of newly formed platelets, or reticulated platelets, which reflect the rate of thrombopoiesis.[9] As an indicator of bone marrow response to thrombocytopenia, IPF reflects the regenerative capacity of the bone marrow in response to platelet loss. Elevated IPF levels may signify an impending recovery in platelet counts, providing an earlier indication of platelet normalization than traditional platelet counts.[10–12]

Given the rising incidence and associated mortality, the potential of IPF to serve as an early indicator of platelet recovery has significant implications for clinical management, potentially reducing the need for invasive or costly interventions and improving patient outcomes. The objective of this thesis is to investigate the use of IPF as a prognostic tool in predicting time to platelet recovery in patients with dengue infection. By exploring IPF in relation to traditional biomarkers such as platelet count, hematocrit levels, and liver function markers, this research aims to establish IPF's predictive value and practicality in the clinical setting. Thrombocytopenia in dengue

patients can cause fall in platelet count, often leading to platelet transfusions, though current guidelines recommend transfusions only for those with severe bleeding episodes. Prophylactic platelet transfusion lacks evidence of benefit and can pose risks, including immunization reactions, immunosuppression, and infection transmission. Knowing the time to platelet recovery through IPF assessments could help avoid unnecessary transfusions and improve patient management. Ultimately, this study contributes to dengue management by developing refined diagnostic and treatment strategies that help healthcare providers deliver timely, efficient, and effective care, thereby mitigating the disease's burden and reducing dengue-associated mortality.

AIMS AND OBJECTIVES

- To Predict Time to Platelet Recovery by Using Immature Platelet Fraction in Dengue Patients.

REVIEW OF LITERATURE

Overview of dengue virus and its transmission

Dengue is a viral infection transmitted to humans through the bite of infected mosquitoes.[1] DENV is an enveloped, positive-sense RNA virus in the flavivirus family, which includes West Nile virus, yellow fever virus, Japanese encephalitis virus, hepatitis C virus, and tick-borne encephalitis virus. These viruses are transmitted to humans by arthropod vectors such as mosquitoes and ticks.[13]

Dengue Viral Structure:

There are four serotypes, DENV-1, DENV-2, DENV-3, and DENV-4. The dengue virus is a spherical particle with a lipopolysaccharide envelope, measuring about 50 nm in diameter when immature and 60 nm when mature. Its 11 kb genome features a single open reading frame that encodes three structural proteins: capsid (C), membrane (M), and envelope (E). Additionally, the virus produces seven non-structural proteins: NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5. The viral particle consists of an RNA genome encased by C proteins that form the inner core.[14]

The surface proteins E and M help to differentiate between immature and mature dengue viruses. The immature virus is often described as "spiky" because M proteins, which are linked to a precursor membrane protein (pr), form heterodimers with E proteins, creating spike-like projections on the surface. In mature virions, furin cleaves the soluble pr from the M protein, resulting in the M proteins being attached to the viral membrane while the pr protein is excluded.[15]

Mosquito Transmission of Dengue Virus

DENV is mainly transmitted to humans through the bites of infected *Aedes aegypti* mosquitoes, with *Aedes albopictus* as a secondary vector. *Aedes aegypti* is particularly adapted to human environments, thriving in tropical and subtropical regions. Known for its black and white markings, *A. aegypti* is a small mosquito that breeds prolifically in artificial containers such as buckets, flower pots, and discarded tires around human dwellings. This close association with human habitation increases mosquito populations and, consequently, the risk of DENV transmission.[16]

Adult *A. aegypti* mosquitoes prefer resting indoors and primarily feed on humans during daylight, showing peak activity around dawn and dusk. However, feeding can occur throughout the day, making this mosquito particularly effective in transmitting DENV. Unlike many other mosquito species, *A. aegypti* can bite multiple hosts in a single feeding session, which allows the virus to be spread to several people in one blood meal. This unique feeding behavior amplifies the potential for rapid viral dissemination within a community.[17–19]

When a naïve *A. aegypti* mosquito feeds on a human infected with DENV, it ingests the virus along with the blood through its proboscis. The virus then travels through the esophagus and into the midgut of the mosquito, where it must overcome a variety of barriers. Dengue viral particles are resistant to the mosquito's stomach enzymes and penetrate the stomach lining, infecting midgut epithelial cells. Once inside these cells, DENV undergoes rapid replication and spreads throughout the mosquito's body via the hemocoel (the mosquito's circulatory system). The virus then reaches and infects the salivary glands, where it concentrates, completing the incubation process within the mosquito in five to seven days.[14]

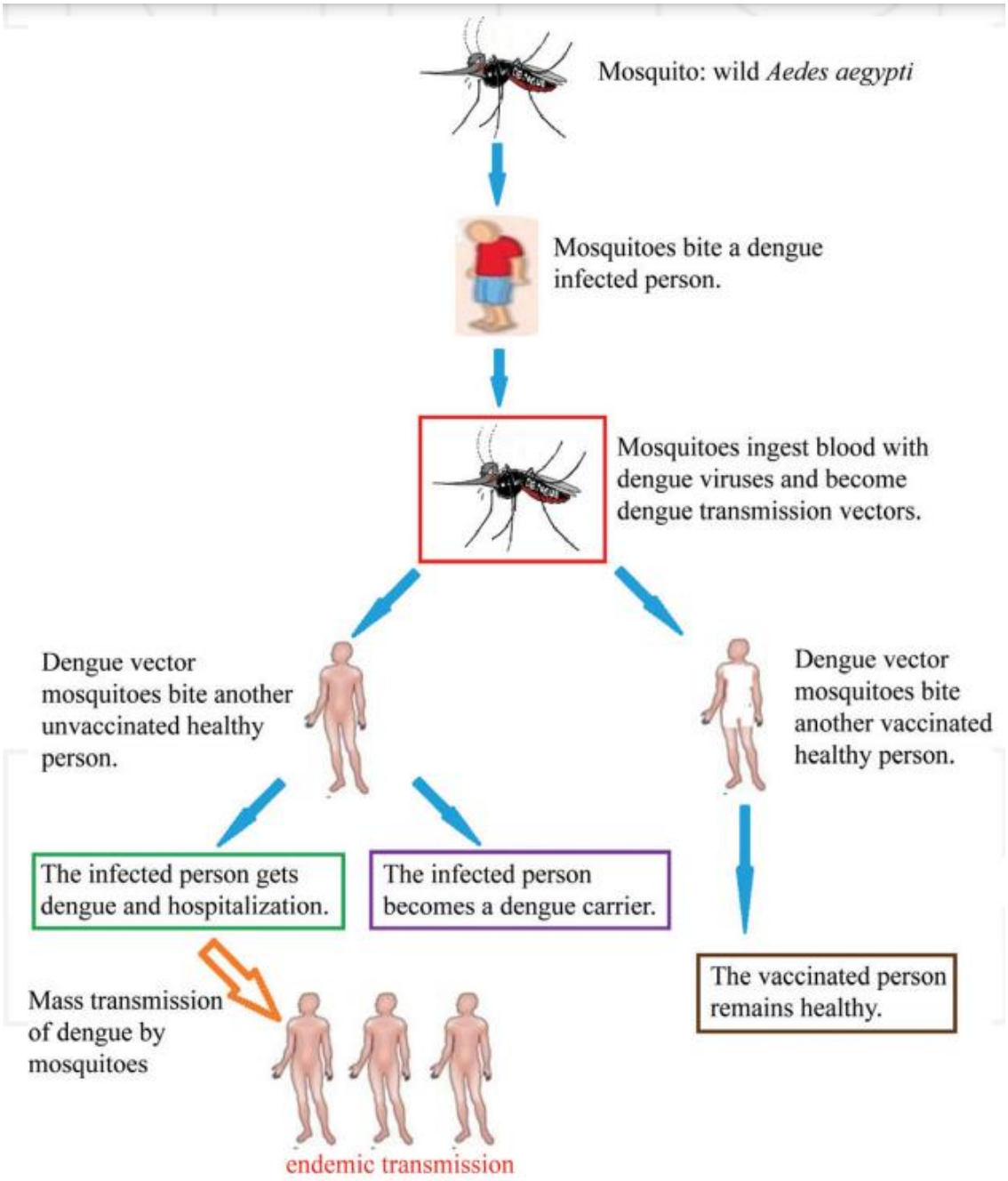


Figure 1: Dengue transmission[20]

At this stage, the mosquito is now infectious and can transmit DENV to a human host through its saliva during subsequent blood meals. When an infected mosquito bites a human, DENV is introduced into the bloodstream, beginning an incubation phase within the human host that typically lasts three to fourteen days. During this period, the virus replicates and spreads within the host's body. Clinical

symptoms of dengue, including fever, headache, muscle pain, and joint pain, may appear after the incubation period, indicating the onset of dengue fever.[21]

This mosquito-human cycle is a significant driver of dengue transmission in densely populated areas with inadequate sanitation and numerous mosquito breeding sites. Because *A. aegypti* mosquitoes are closely integrated into human environments, preventing dengue outbreaks involves concerted efforts in mosquito control and public health interventions.

Pathophysiology

Infection with any of the four DENV serotypes presents similar symptoms, though the severity can vary based on the serotype, viral strain, immune status, host age, and genetic background.[22] Macrophages, monocytes, and dendritic cells enter through cell receptor-mediated endocytosis. Following transmission from an infected *Aedes aegypti* mosquito, these cells are targeted by DENV. Inside the host cells, viral RNA undergoes replication, with new virions assembling in the endoplasmic reticulum (ER) and Golgi apparatus. During a secondary infection with a different serotype, a phenomenon known as antibody-dependent enhancement (ADE) can occur, where non-neutralizing antibodies from a previous infection facilitate viral entry and replication. This increases the risk for severe manifestations, including Dengue Haemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS), through intensified immune responses and vascular permeability, resulting in plasma leakage and shock.[23]

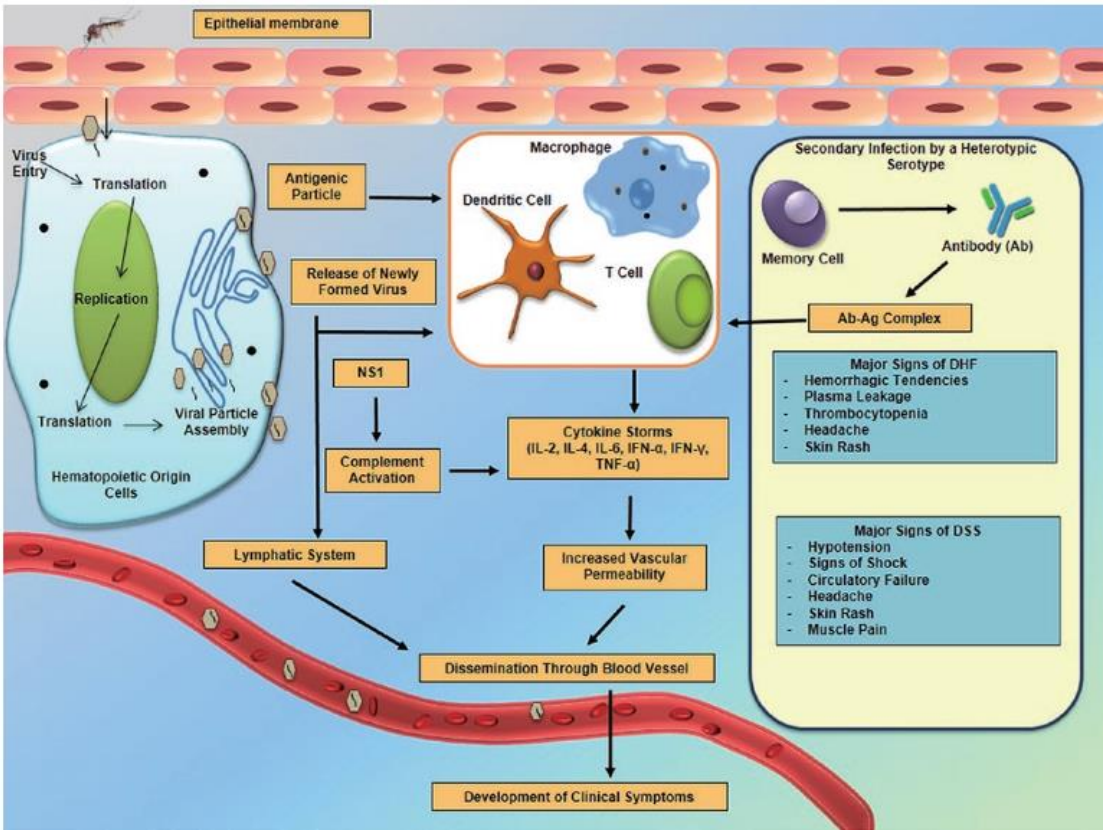


Figure 2: Entry, dissemination and responses of dengue virus in humans[24]

The immune response in primary infection is typically slower, with immunoglobulin M (IgM) antibodies appearing first, followed by immunoglobulin G (IgG). In secondary infections, IgG levels surge rapidly, while IgM remains low, often exacerbating ADE.[25] Key immune mediators, such as cytokines and complement factors (e.g., TNF, IL-6, C3a, and C5a), further amplify inflammation and contribute to increased vascular permeability, correlating with disease severity.[26]

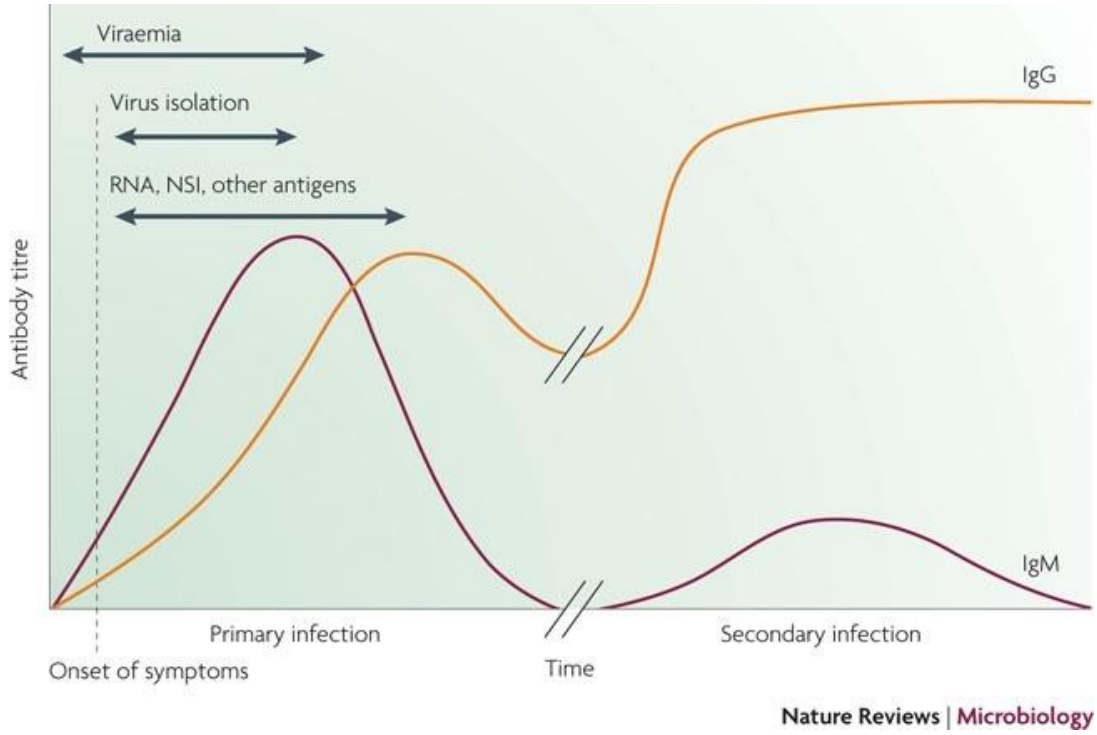


Figure 3: Response to Primary and Secondary Dengue Infection[27]

a) **Dengue Fever**

Infection with the dengue virus causes symptoms starting with fever, it is also accompanied by joint pain, along with headache, body aches, rash, fatigue, nausea, and vomiting.[28] Other symptoms experienced by infected individuals are loss of appetite, digestive issues, respiratory discomfort, sore throat, and altered taste. Fever usually lasts for 2 to 7 days with temperature between 102°F to 105°F and signs like pharyngitis, conjunctivitis, and swollen lymph nodes. Many patients also develop a rash, which is sometimes followed by another rash spreading to the extremities. When the fever resolves, petechiae and intense itching may appear.[29] Dengue fever can lead to bleeding symptoms, including petechiae, purpura, gastrointestinal bleeding, bleeding gums, heavy menstrual flow, nosebleeds, bloody urine, and jaundice.[13] Although rarely fatal, dengue fever has an acute phase lasting three to seven days,

followed by a recovery phase that can last weeks, with residual symptoms of weakness and depression.[1]

a) **Dengue Hemorrhagic Fever**

DHF occurs more frequently in young children and is associated with a more virulent DENV strain, which increases the likelihood of severe disease with high viral loads.[22] The risk of DHF is particularly elevated in cases of secondary DENV infection with a different serotype, partly due to antibody-dependent enhancement (ADE). Certain host factors, including female sex, blood type AB, specific human leukocyte antigen alleles, and genetic variations also increase DHF risk.[30–33] Factors like race and certain polymorphisms in the vitamin D receptor and Fcγ receptor genes are linked to lower DHF risk in secondary infections.[34–36] DHF often begins with typical DENV infection symptoms, including sudden fever lasting two to seven days, before plasma leakage symptoms emerge as a defining feature. After fever subsides,the critical phase starts, marked by circulatory failure, hemorrhagic symptoms, thrombocytopenia (low platelet count), and hemoconcentration (increased red blood cells). Hemorrhagic signs may include skin hemorrhages, petechiae and purpura on the torso and limbs, nosebleeds, gastrointestinal bleeding, bleeding gums, and dark vomit or stools associated with blood oxidation.[37,38]

a) **Dengue Shock Syndrome**

DSS is characterized by an initial fever and general symptoms, followed by a sudden worsening. As the fever resolves, the skin may appear cool, blotchy, and congested, with additional signs such as bluish discoloration around the mouth, weak and rapid pulse, restlessness, and abdominal pain. These symptoms can quickly escalate into shock due to plasma leakage.[1,39] DSS symptoms overlap with those of

DHF and, without prompt intervention, may lead to fatality. Early antishock treatment can improve recovery chances if administered quickly once DSS symptoms appear.[39,40]

Signs and symptom

According to WHO, most people with dengue experience mild or no symptoms and recover within 1–2 weeks. If symptoms do appear, they usually start 4–10 days after infection and last between 2–7 days. Common symptoms include:[1]

1. High fever (around 40°C or 104°F)
2. Intense headache
3. Pain behind the eyes
4. Muscle and joint aches
5. Nausea
6. Vomiting
7. Swollen glands
8. Skin rash

People infected with dengue for a second time have a higher risk of developing severe symptoms. Severe dengue symptoms typically emerge after the fever subsides and may include:

Severe stomach pain

Persistent vomiting

Rapid or labored breathing

Bleeding from the gums or nose

Extreme fatigue

Restlessness

Blood in vomit or stool

Intense thirst

Pale, cool skin

Weakness

Treatment and it's complications

Dengue illness can typically be divided into three distinct phases: the febrile, critical, and recovery phases.[4]

Table 1: Dengue Illness Phases

Phase	**Clinical Manifestations**	**Challenges**
Febrile Phase	-For 2–7 days -Sudden high-grade fever, facial flushing, erythematous skin rash, body aches, muscle, and joint pain, headache -Mild bleeding symptoms (e.g., petechiae, mucosal bleeding) -Liver tenderness and progressive leukopenia	- Risk of dehydration - High fever can lead to neurological issues or febrile seizures
Critical Phase	- Lasts 24–48 hours - Begins around the time fever subsides - leukopenia, thrombocytopenia - Plasma leakage - Elevated hematocrit, which may decrease in cases of severe bleeding - Hypovolemic or cardiogenic shock due to myocardial dysfunction - Severe organ impairment, metabolic acidosis, and potential for disseminated intravascular coagulation	- High risk of shock and severe organ damage
Recovery Phase	- For 48–72 hours - Fluid reabsorption in the extravascular compartment - Improvement in overall well-being and appetite - Increased urination, rash and generalized itching - Bradycardia	- Risk of fluid overload if excessive fluids were administered - Potential for pulmonary edema and congestive heart failure

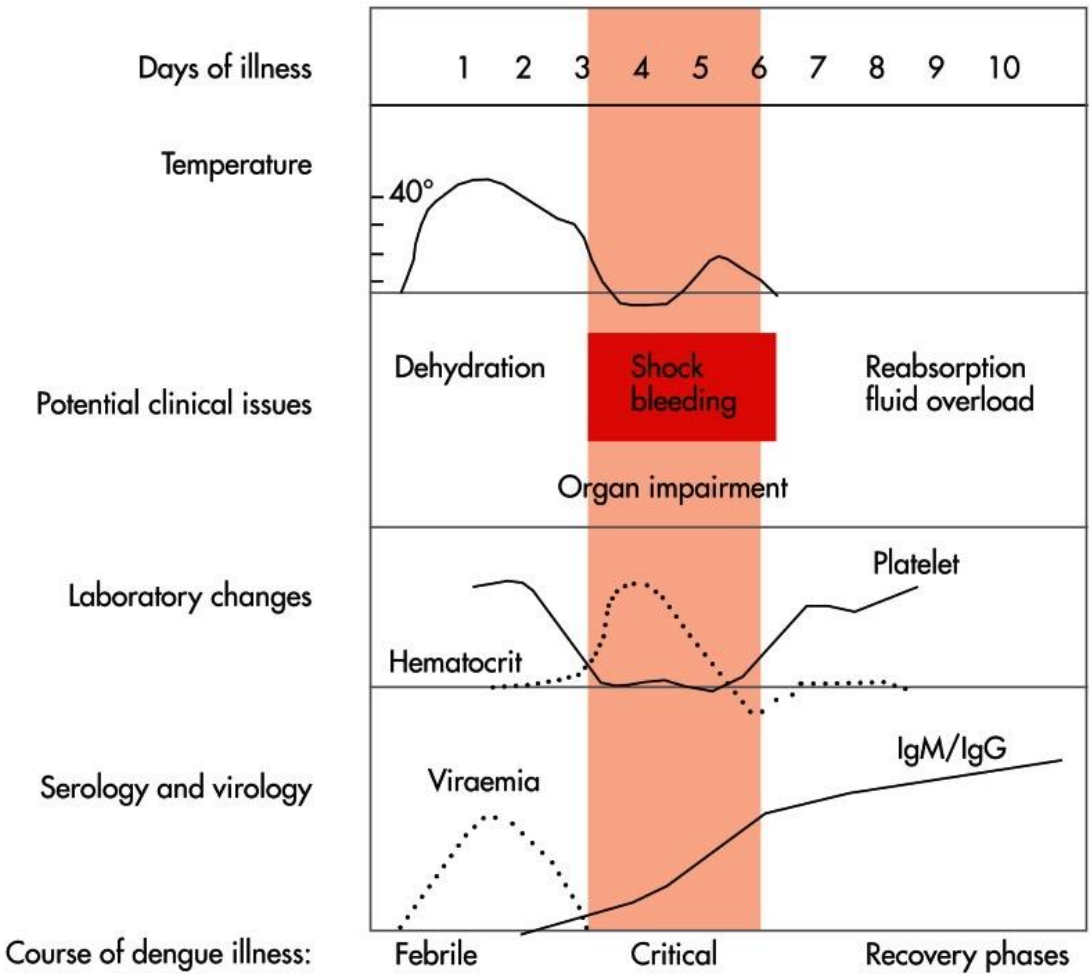


Figure 4: Course of Illness[4]

Classification for Management

Patients with dengue can be categorized into three management groups based on symptoms and severity: those who may be managed at home (Group A), those requiring hospital-based care (Group B), and those needing urgent emergency care (Group C).[42]

Management of Mild Dengue Patients (Group A):[42]

1. Patients and family members should be informed about the warning signs: Severe abdominal pain, persistent vomiting, red spots/patches on the skin, bleeding from nose, gums, or vomiting blood, black tarry stools, drowsiness, irritability, pale/cold/clammy skin, difficulty breathing
2. Encourage adequate oral fluid intake, avoid carbonated drinks, and monitor for over-hydration in infants and young children.
3. Ensure the patient takes adequate bed rest.
4. Maintain body temperature below 100°F; use paracetamol (10 mg/kg/dose, every 6 hours; max 4 gm/day for adults), and avoid aspirin or NSAIDs.
5. For high-grade fever unresponsive to paracetamol, use tepid sponging or lukewarm showers/baths.
6. Regular monitoring for disease progression from mild to moderate/severe.
7. Clinical examination, CBC, and hematocrit tests should be conducted as needed based on the patient's condition.

Management of Moderate Dengue Patients (Group B):[42]

1. Patients with warning signs or high-risk groups should be admitted for in-hospital management. Perform baseline hematocrit (Hct) before starting fluid therapy, but do not delay hydration if Hct results are unavailable.
2. Encourage oral fluids, if not tolerated, start IV fluid therapy with 0.9% Normal Saline or Ringer's Lactate. Use ideal body weight for fluid calculations in obese/overweight patients. Initial IV fluid: 7-10 mL/kg of crystalloid solution over 1 hour.
3. Evaluate clinical improvement hourly and gradually reduce IV fluids based on improvement, followed by stopping IV fluids after 24-48 hours, depending on clinical status.
4. In case of no improvement after IV Fluids, again evaluate hematocrit, and if Hct > 45%, give a second bolus (10 mL/kg crystalloid) over 1 hour. If no improvement, manage as Group C (severe dengue). If Hct < 45%, suspect severe bleeding and plan for blood transfusion.
5. Monitor vital signs until the patient is out of the critical phase.
6. Patients showing rapid recovery and not in the critical period can be sent home within 12-24 hours.

Management of Severe Dengue Patients (Group C):[42]

1. Patients with severe dengue, including severe plasma leakage, severe haemorrhages, severe organ impairment, and severe metabolic abnormalities, require urgent admission to a hospital with blood transfusion facilities. Severe dengue characteristics include

2. These patients should be given IV fluid resuscitation, using crystalloid solutions to maintain circulation during plasma leakage (24-48 hours).
3. Monitor vital signs every 5-30 minutes. Use ideal body weight (IBW) for fluid calculations in overweight/obese patients.
4. Management of Compensated Shock: Start IV crystalloids at 10-20 mL/kg/hour for 1 hour. Reassess vital signs, capillary refill, Hct, and urine output. If improved, gradually reduce fluids; if no improvement, check Hct. If Hct > 45%, give a second bolus if Hct decreases (<40% in children/adult females, <45% in adult males), suspect bleeding and transfuse whole blood (10 mL/kg) or packed RBCs (5 mL/kg).
5. Management of Decompensated Shock: Give IV crystalloid/colloid bolus (20 mL/kg over 15 minutes). If improved, continue with 10 mL/kg/hour for 1 hour, then gradually reduce fluids as above. If shock persists, check Hct. If Hct > 45%, repeat bolus (10-20 mL/kg over 15-30 minutes). If Hct decreases, transfuse blood immediately.
6. Monitor vital signs, urine output, Hct, blood glucose, renal/liver/coagulation profiles and maintain a fluid balance sheet.

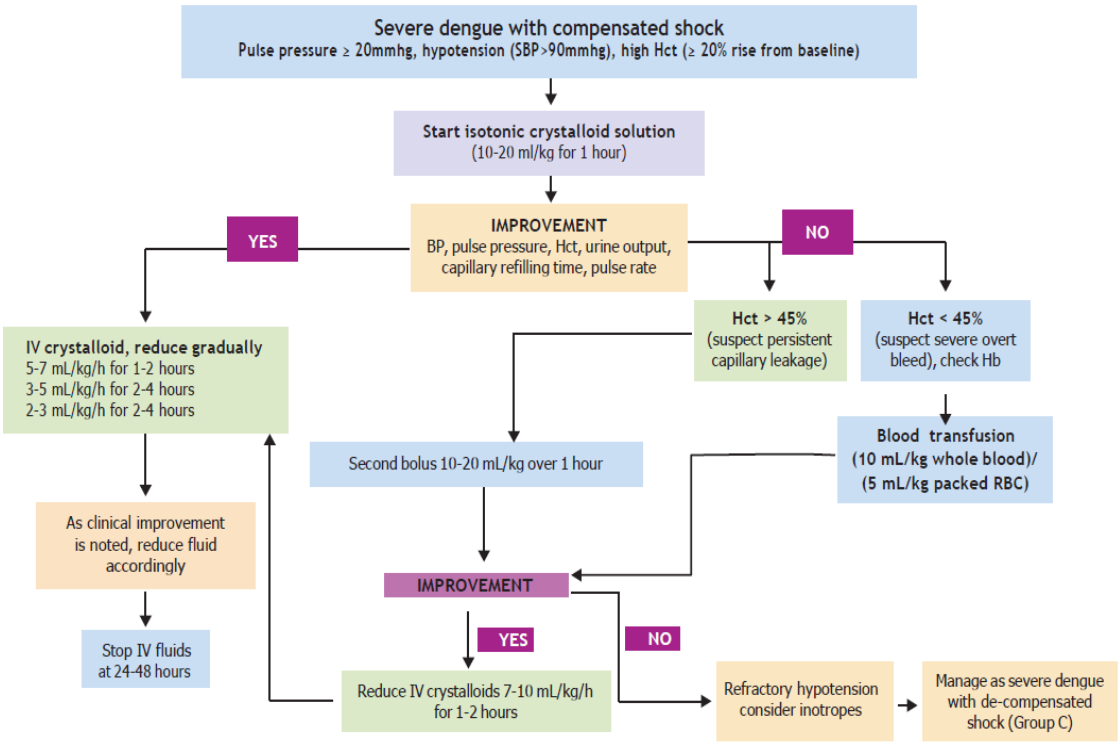


Figure 5: Management of Compensated Shock in Dengue Patients[42]

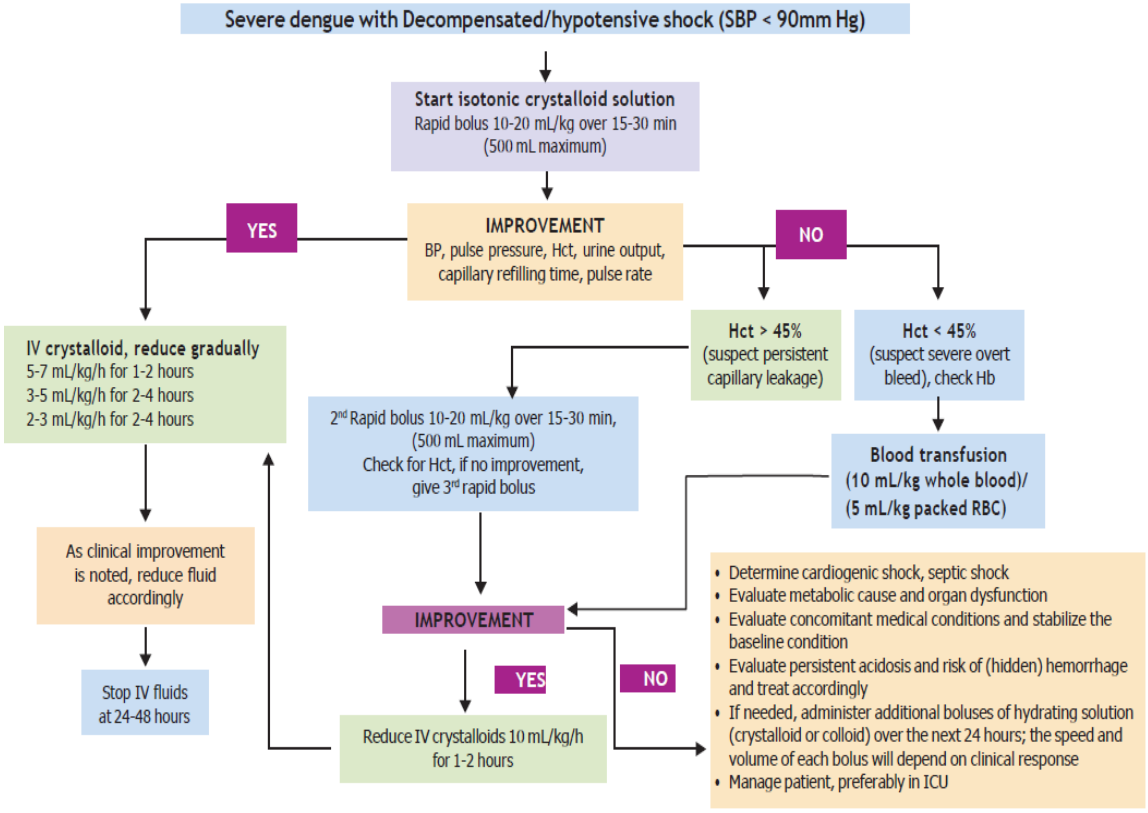


Figure 6: Managing Uncompensated Shock in Dengue Patients[42]

Incidence and Mortality

In 2019, there were 56.7 million new cases of dengue globally, with a near-equal distribution between genders: 48% were males, and 52% were females. Dengue-related deaths totalled 36,055 that year, with 18,993 deaths among males and 17,032 among females. From 1990 to 2019, dengue cases almost doubled, rising from 30.7 million to 56.9 million, and deaths also increased from 28,151 to 36,055 over the same period.[43]

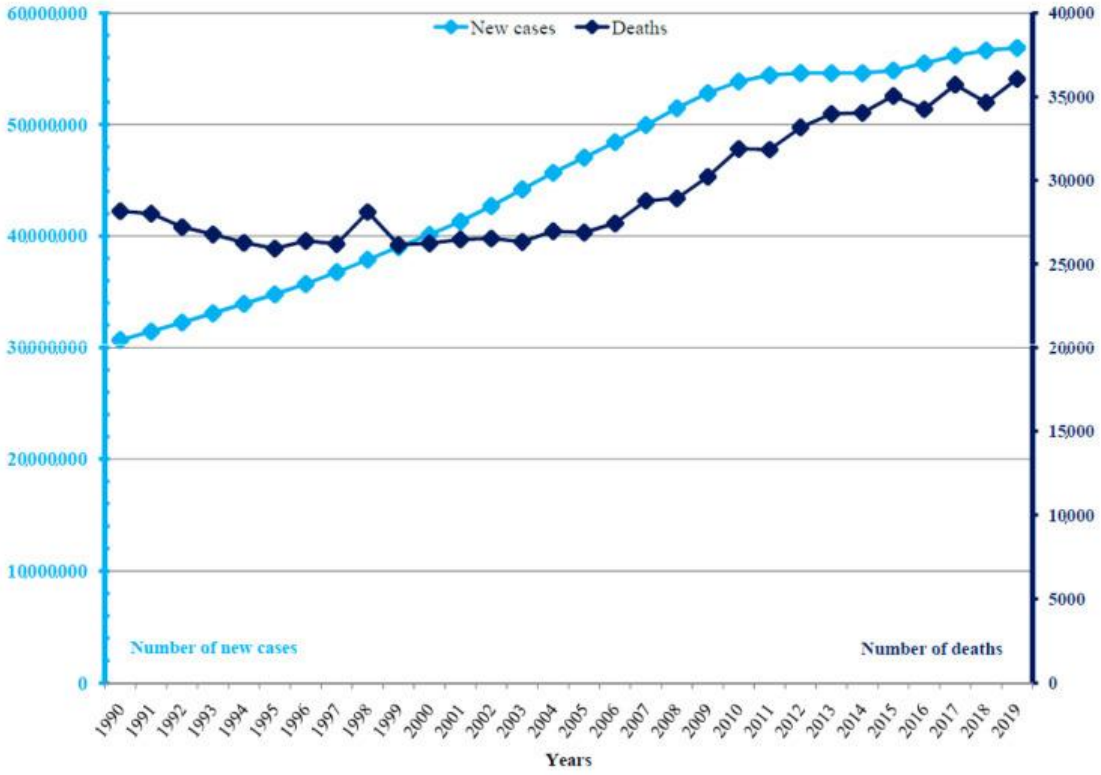


Figure 7: Incidence and Mortality of Dengue[43]

India:

Dengue has become a recurring epidemic in many parts of Southeast Asia, and its severity is increasing due to environmental changes. According to recent data, India reported 110,473 dengue cases between January and October 2022, a figure comparable to the 101,192 cases recorded in 2018. However, the number of cases in previous years was considerably higher: 188,401 in 2017, 157,315 in 2019, and 193,245 in 2021. The onset of the COVID-19 wave in India in 2020 led to a 56-60% decrease in dengue incidence, with only 44,585 cases reported. Between 1951-1960 and 2012-2021, the number of months conducive to Aedes aegypti dengue transmission in India increased by 1.69% annually, reaching 5.6 months. Endemic areas face the risk of a dual pandemic, where the concurrent burden of dengue and COVID-19 could overwhelm healthcare systems, complicating diagnosis due to the overlap in clinical and laboratory markers.[44]

Pathophysiology of thrombocytopenia in dengue

Thrombocytopenia has long been a key indicator of clinical severity in dengue, as outlined in WHO guidelines.[28,45] It is defined as a rapid decline in platelet count or a count below 150,000 per microliter of blood.[46] Studies on platelet kinetics in DHF and dengue fever show a significant drop in platelet count by the 4th day of illness. Previous research has documented a mild to moderate decrease in platelet counts between the 3rd and 7th days in adult cases of DHF without shock, with levels returning to normal by the 8th or 9th day.[47–49] In adults, platelet counts below 5×10^9/L and a packed cell volume greater than 50% are closely linked to bleeding. However, one study involving 245 dengue patients found no correlation between platelet count and clinical bleeding, with 81 non-bleeding patients showing counts

below 20 × 10^9/L.[50] Another study of 225 patients suggested that bleeding is more common in those with platelet counts under 20 × 10^9/L.[51]

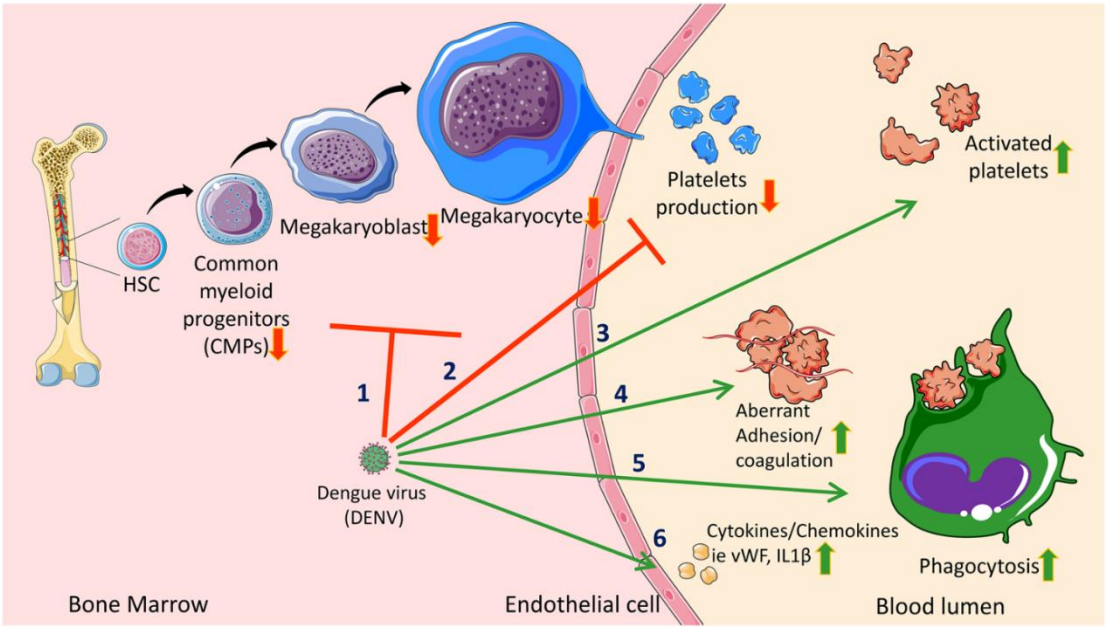


Figure 8: Dengue virus (DENV)-induced thrombocytopenia[8]

Dengue virus (DENV)-induced thrombocytopenia occurs through several interconnected mechanisms that impair platelet production and function. First, DENV affects megakaryopoiesis by infecting megakaryocytes and their progenitor cells, leading to apoptosis and preventing proper maturation of megakaryocytes, thereby reducing platelet output. Additionally, DENV disrupts thrombopoiesis by decreasing the number of megakaryocytes and interfering with platelet formation.[52–54] In secondary DENV infections, platelet activation is heightened through the antibody-dependent enhancement (ADE) process, where IgG antibodies interact with Fc receptors on platelets, exacerbating platelet dysfunction.[55,56] DENV infection also leads to increased platelet activation, further contributing to platelet hyper-reactivity.[57] Infected platelets, along with nearby endothelial cells, release a variety of cytokines, chemokines, and other pro-inflammatory factors, fueling systemic

inflammation and amplifying platelet activation. Moreover, DENV directly infects platelets, causing platelet apoptosis and leading to their loss from circulation. The combined effects of ADE, increased platelet activation, and the secretion of inflammatory mediators promote platelet aggregation and coagulation, which are eventually cleared from the bloodstream by phagocytic cells. These complex interactions between DENV and platelet function highlight the multifaceted nature of thrombocytopenia in dengue infection.[58]

Prognostic Tools for Platelet Recovery and Disease Progression in Dengue

Various prognostic tools and markers have been developed and studied to aid in predicting platelet recovery and disease progression. These tools help clinicians in identifying patients at higher risk of complications, such as hemorrhage or shock, and managing them effectively.

1. **Platelet Count**

A rapid decline in platelet count or a platelet count less than 150,000 per microliter is considered indicative of clinical severity.[7] However, platelet count alone cannot always predict the severity or outcome of the disease, as it is influenced by multiple factors, including bone marrow suppression, platelet consumption, and destruction during the infection.[52]

In dengue, platelet counts usually begin to drop around the 3rd to 4th day of illness and may reach their lowest point by day 5–6. A rapid recovery of platelet count after this low point is associated with a favorable outcome. Patients whose platelet counts fail to recover by day 6–7 or who continue to exhibit severe thrombocytopenia are at higher risk for developing complications such as bleeding or shock.[59]

2. **Haematocrit (Packed Cell Volume)**

A key clinical feature distinguishing DHF from Dengue Fever (DF) is plasma leakage. Hemoconcentration, indicated by a 20% increase in hematocrit, is commonly used to identify plasma leakage. However, hematocrit levels can be influenced by factors beyond plasma leakage, including fever, dehydration, and bleeding.[60,61]

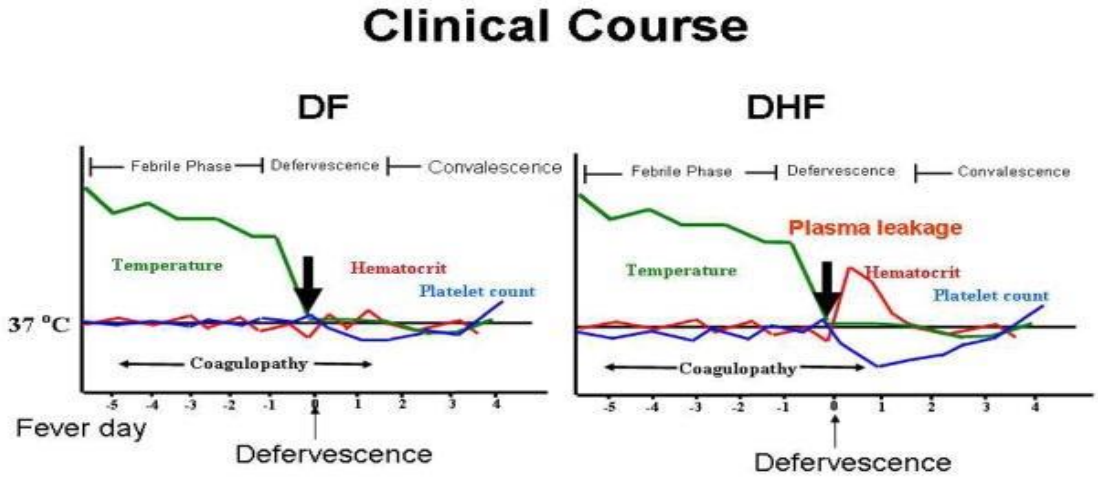


Figure 9: Clinical course of DF and DHF[60]

3. **Dengue NS1 Antigen and Dengue IgM/IgG Antibodies**

The NS1 (non-structural protein 1) antigen is a marker detectable in the early stages of dengue infection, typically within the first few days after symptom onset. Its presence can indicate active viral replication and is often associated with more severe disease outcomes, as high viral loads are linked to increased risk of complications like DHF and DSS.[62,63]

In addition to NS1, IgM and IgG antibodies against the dengue virus play a crucial role in predicting disease progression. IgM antibodies typically appear within a few days post-infection and are a sign of an acute or primary dengue infection, while IgG antibodies indicate a past infection or secondary infection. Elevated levels

of IgG antibodies, particularly in secondary infections, are associated with a higher risk of severe dengue due to antibody-dependent enhancement (ADE), a phenomenon that can lead to increased viral entry into host cells and more severe immune responses.[64–66]

4. **Cytokines and Inflammatory Markers**

Inflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ), have been studied as potential markers for severe dengue. Elevated levels of these markers are often associated with more severe forms of dengue, such as DHF and DSS, and can help predict disease progression. Similarly, markers like CRP and PCT are used to assess the degree of inflammation and potential bacterial co-infections.[67]

5. **Liver enzymes**

Elevation of liver enzymes, specifically aspartate aminotransferase (AST) and alanine aminotransferase (ALT), is commonly observed in acute dengue cases, affecting 65–97% of patients, with enzyme levels typically peaking during the convalescent phase (days 7–10).[68,69] Increased levels of AST and ALT have been linked to bleeding and the development of DHF.[68,70]

In 2009, the WHO updated its guidelines for dengue, introducing severe organ impairment, including liver involvement, as a criterion for severe dengue along with severe plasma leakage and significant bleeding. Severe liver involvement was defined as AST or ALT levels reaching or exceeding 1,000 units per liter (U/L).[28]

6. **Immature Platelet Fraction (IPF) in Thrombocytopenia**

Platelets are produced in the bone marrow by megakaryocytes through a process called thrombopoiesis. When platelets are newly released from the megakaryocytes, they are referred to as "immature" platelets, or *reticulated platelets*. These immature platelets have a higher RNA content and are less stable than mature platelets. Over time, they mature by losing their RNA content, becoming the typical anucleate, functional platelets that circulate in the bloodstream.[71]

Immature Platelet Fraction (IPF) is a laboratory parameter which refers to the proportion of immature platelets in the total platelet population. Since immature platelets are larger, they can be detected using flow cytometry or automated hematology analyzers, which can distinguish them from mature platelets based on their size and RNA content.[72]

2. Significance of IPF in Thrombocytopenia

Thrombocytopenia, which is defined as a platelet count below 150,000 platelets per microliter,[7] can result from a variety of causes, including:

- Decreased platelet production in the bone marrow (e.g., bone marrow failure, leukemia).
- Increased platelet destruction (e.g., immune thrombocytopenic purpura [ITP], drug-induced thrombocytopenia).
- Sequestration of platelets in the spleen (e.g., in conditions like cirrhosis or splenomegaly).
- Dilution due to large blood transfusions or other conditions.

In thrombocytopenia, the IPF can provide insight into the underlying cause of the platelet count decline and offer prognostic information.

3. Clinical Uses of IPF in Thrombocytopenia

The measurement of IPF is increasingly used in clinical practice to help differentiate between various causes of thrombocytopenia.

a) Assessment of Bone Marrow Response

IPF is a marker of bone marrow platelet production. A high IPF suggests that the bone marrow is actively producing platelets, likely in response to a decrease in the number of circulating platelets.[9] This may occur in Immune thrombocytopenic purpura (ITP) in which platelets are destroyed by the immune system, but the bone marrow responds by increasing platelet production, leading to a high IPF.[73] A low IPF may suggest impaired bone marrow production, where the bone marrow cannot produce sufficient new platelets despite a low platelet count.[10]

In dengue fever, where thrombocytopenia is a common complication, tracking IPF can provide early indications of platelet recovery. As the bone marrow resumes platelet production during the recovery phase of dengue, IPF levels may rise, suggesting that bone marrow function is stabilizing, which is a critical marker for patient prognosis.

b) Differentiation between Destruction and Production Issues

IPF can help differentiate between platelet destruction and decreased platelet production as causes of thrombocytopenia.

- High IPF with low platelet count indicates increased platelet destruction (e.g., ITP, disseminated intravascular coagulation [DIC], or thrombotic thrombocytopenic purpura [TTP]). In these cases, the bone marrow compensates by releasing immature platelets, which can be detected as an elevated IPF.[9] In dengue patients, a high IPF with low platelet count can indicate that thrombocytopenia results from platelet destruction and that bone marrow activity is still compensating, potentially minimizing the need for immediate transfusions.[11]
- Low IPF with low platelet count suggests bone marrow failure or hypoproduction. The bone marrow is not responding appropriately to the need for platelets, and there is a reduced release of immature platelets.[9]

c) Monitoring Treatment and Recovery

In patients with dengue, thrombocytopenia is a common complication due to increased platelet destruction and plasma leakage. Monitoring IPF in dengue can provide an early indication of platelet recovery, helping to differentiate between low platelet counts caused by transient infection-related suppression and ongoing bone marrow production issues. A rising IPF in dengue patients suggests that the bone marrow is beginning to replenish platelets, which is crucial for determining recovery and managing the need for platelet transfusions.[11]

Comparison of IPF and Other Prognostic Tools

Prognostic Tool	Advantages	Limitations	Clinical Utility
IPF	Reflects bone marrow activity and platelet production. High IPF indicates active production; low IPF suggests marrow suppression.	Requires specialized equipment for measurement. Interpretation must be combined with other clinical data.	Excellent for differentiating between platelet destruction and production issues. Can guide therapy, particularly in ITP and dengue.
Platelet Count	Simple, widely available, correlates with disease severity.	Doesn't distinguish between destruction and production; late marker.	Essential for monitoring disease progression. Can help guide platelet transfusion decisions.
Hematocrit	Indicates plasma leakage, hemoconcentration, and disease severity.	Not related to platelet production or destruction.	Key in managing fluid therapy and assessing the severity of dengue shock.
Liver Enzymes (ALT, AST)	Reflects liver involvement and disease severity.	Not related to platelet recovery or bone marrow function.	Useful in assessing liver damage and predicting the severity of dengue.
Serological Markers (NS1, IgM, IgG)	Useful for early diagnosis (NS1) and identifying past infections (IgM, IgG).	Not related to platelet recovery or progression.	Essential for confirming diagnosis but not predictive of disease severity or platelet dynamics.

Relevant studies

The study by Looi et al. investigated the role of IPF as an early indicator of platelet recovery in dengue patients. The study found that IPF levels were higher in patients with severe dengue compared to those with non-severe dengue between Days 3–5 of illness. As platelet counts decreased during the first week of illness, IPF% increased, reaching a peak before platelet recovery began. The study also observed a significant rise in reticulocyte count in severe dengue cases on Day 5.[11]

The study by Abeysuriya et al. was conducted among 240 patients diagnosed with dengue. The IPF% was measured using the Sysmex-XN-1000 automated hematology analyzer. Results showed that an IPF% greater than 7.15% on day 2 had a sensitivity of 80.0% and specificity of 70.4% for predicting platelet recovery by day 7. Similarly, an IPF% greater than 7.25% on day 3 had a sensitivity of 88.9% and specificity of 47.1% for predicting recovery by day 8. Patients with severe dengue had significantly lower IPF% values. After peak of IPF, platelets recovered within 48 hours.[74]

V.V. Kumar et al. conducted a study among 45 confirmed dengue cases with platelet counts below 100,000/cumm, either with or without a downward trend. The study found that within 24 hours, 86.4% of patients showed platelet recovery, and 13.6% of patients recovered within 48 hours after reaching peak IPF levels. IPF value above 10% was found to be a reliable indicator of platelet recovery within 24-48 hours. The study concluded that there is a positive correlation between IPF levels and platelet recovery in dengue.[75]

In a study conducted by Meenakshi Mohapatro et al., the mean total platelet counts and IPF values were monitored on Days 1, 3, 5, and 7. The results showed that

patients with an IPF >10% had a faster platelet recovery and showed a gradual decline in IPF as the platelet count improved. The study concluded that IPF is a consistent and reliable marker for predicting platelet recovery in dengue patients with thrombocytopenia, helping to guide decisions regarding platelet transfusions.[76]

Megha Agarwal et al. conducted a study among dengue patients with platelet count and IPF values recorded on Days 1, 3, 5, and 7 of admission. The study conducted sensitivity analysis to identify the IPF cut-off values predictive of an increase in platelet count by over 20,000 within the next 48 hours. The results revealed improvement in platelet values ($P<0.01$) when the IPF exceeded 6.1%.[77]

In an observational study on 124 dengue patients, Darshit Shah et al. 96% and 97% of patients had increased platelet count within 1 and 2 days, respectively, after reaching peak IPF levels. Additionally, in cases without bleeding, platelet transfusion was avoided in 64% of patients with an IPF level of 10% or higher, highlighting IPF's potential as a useful indicator for predicting platelet recovery in dengue patients and reducing unnecessary transfusions.[78]

The study by Puspita et al. among 30 adult DHF patients (18 males and 12 females, mean age 24.83 ± 9.18 years). The study measured IPF and platelet count changes in each patient. A Pearson correlation analysis showed a strong positive correlation (0.746) between IPF and platelet count changes ($p < 0.001$). The results suggest that IPF is closely associated with changes in platelet count in DHF patients.[79]

Monette S et al. conducted a prospective cross-sectional study among 77 dengue fever patients with thrombocytopenia. IPF increased as platelet count decreased, with the highest IPF values coinciding with the lowest platelet counts. Platelet recovery occurred in 87% of patients after the increasing trend in IPF, 87%

after the peak IPF value, and 95% after the decreasing trend in IPF. An IPF value greater than 6.6% was found to be predictive of platelet recovery within 24 hours, with a sensitivity of 45% and a specificity of 70%. There was an observed inverse relationship between IPF and platelet count, although the correlation was statistically weak. The decreasing trend of IPF may serve as a useful predictor for platelet recovery, suggesting that IPF could be an additional parameter for monitoring platelet recovery in pediatric dengue fever patients.[80]

MATERIALS AND METHODS

Study Design

This is an observational study conducted among dengue patients to assess the effectiveness of the IPF as a predictive marker for the time to platelet recovery.

Study Period

The study was conducted over a one-year period from January 2023 to December 2023.

Source of Data

The data for this study was collected from patients who met the inclusion criteria on admission to KLE, a tertiary care center in Belgaum, India, between January 1, 2023, and December 31, 2023.

Sample Size Calculation

The sample size was calculated using:

$N=p(100-p) \times Z^2E^2$

where:

N is the required sample size,

p represents the estimated proportion of patients showing a particular outcome (93.75% for platelet recovery within 24-48 hours when IPF > 10%),[12]

Z is the Z-score corresponding to a 95% confidence level (1.96),

E is the acceptable margin of error (5%).

Using these values:

$N=93.75\times (100-93.75) \times 1.96^2/5^2$

N= 90.0375

Thus, a minimum sample size of 90 is necessary to ensure sufficient power to detect significant associations and enhance the reliability of results.

Sampling Technique

All consecutive patients meeting the inclusion criteria during the study period were included.

Inclusion Criteria

- Adults aged >18 years.
- Confirmed dengue infection based on clinical signs, NS1 antigen positivity, or IgM antibody positivity.
- Clinical criteria for dengue based on WHO guidelines, which includes fever with at least two of the following: vomiting, rash, myalgia, retro-orbital pain, or any other warning signs indicative of severe disease progression.

Exclusion Criteria

Patients were excluded from the study if they present with any of the following conditions that may affect study outcomes or interfere with platelet count and IPF readings:

- Pregnancy
- Underlying congestive heart failure
- Liver failure
- HIV infection
- Malignancy or ongoing cancer treatments

Data Collection Procedure

This hospital-based observational study was conducted from January 2023 to December 2023 at KLE, Belgaum. It involved recruitment of patients who met the inclusion criteria on admission. Informed consent was obtained from all participants. On enrollment, baseline assessments and relevant clinical data, including fever history, warning signs, and laboratory-confirmed dengue status (NS1 or IgM positivity), were recorded.

Data Collection Tool

A structured clinical data collection sheet was used to document relevant patient information consistently. The tool includes:

1. Demographic Information – age, sex, comorbidities.
2. Clinical Presentation – symptoms, including fever, rash, myalgia, vomiting, and warning signs as per WHO case definition of Dengue fever.
3. Laboratory Investigations – Monitoring of daily platelet counts, IPF values on a daily basis.

Investigations The following investigations are essential to fulfill the study's objectives and were performed as part of routine patient care:

1. Complete Blood Count (CBC) to assess overall blood cell indices.
2. Platelet Count was monitored daily to track the fall and recovery.
3. Immature Platelet Fraction (IPF) measured at baseline thereafter on a daily basis to examine its potential in predicting platelet recovery time.

Anticipated Adverse Events

No serious adverse events (SAEs) were anticipated during this observational study. All procedures involve routine diagnostic tests that pose minimal risk to participants.

Outcome Measures

The primary outcome measure for this study was time to platelet recovery. Platelet recovery is defined as an increase in platelet count to at least 150,000, indicating resolution of thrombocytopenia.

Statistical Analysis

Data was analyzed using R version 4.2.1 and Microsoft Excel. Categorical variables were represented in frequency tables, while continuous variables were presented as mean ± standard deviation (SD) or median (min, max). Spearman's rank correlation was used to assess the relationship between platelet levels and IPF at each time point. Statistical significance was set at $p \leq 0.05$.

Ethical Considerations

The study followed ethical guidelines by the Declaration of Helsinki. Informed consent was taken from each participant, ensuring they are fully informed of the study's purpose, procedures, risks, and benefits. All data collected was kept confidential and anonymized to protect patient privacy. No additional tests or costs were incurred by participants, as all required investigations are part of routine dengue management. Ethical approval for the study was taken from the institutional ethics committee at KLE, Belgaum, before commencing data collection.

RESULTS

Table 1. Age distribution among the study participants (N=90)

Age (in years)	Frequency (n)	Proportion (%)
18-30	41	45.6
31-40	22	24.4
41-50	13	14.4
51-60	7	7.8
61-74	7	7.8
Total	**90**	**100**

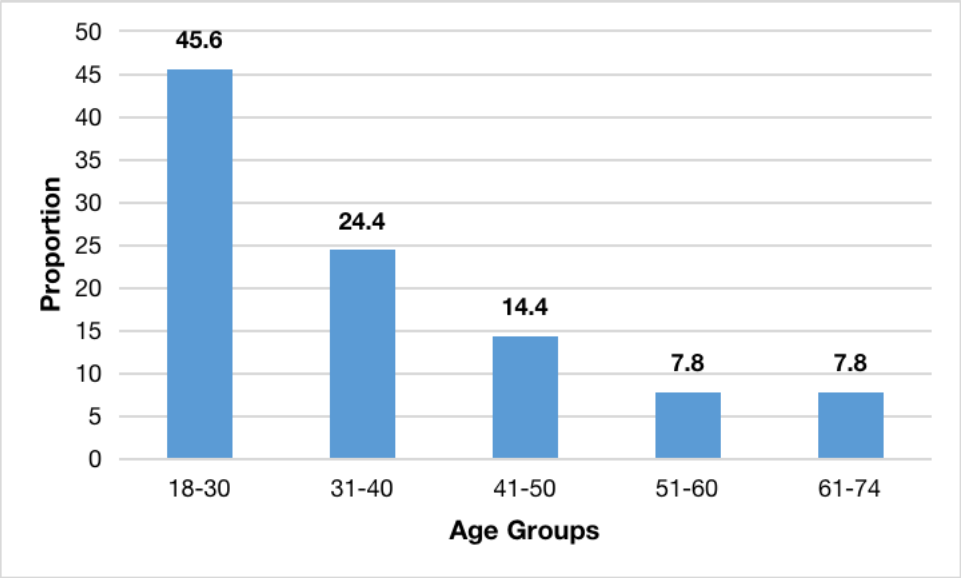


Figure 10. Age distribution among the study participants

The age distribution among the 90 study participants shows that, the majority of the participants are between 18-30 years of age (45.6%, n=41), followed by 24.4% (n=22) in the 31-40 age range. Participants aged 41-50 were 14.4% (n=13), while those aged 51-60 and 61-74 each accounted for 7.8% (n=7).

Table 2. Gender distribution among the study participants (N=90)

Gender	Frequency (n)	Proportion (%)
Male	61	67.8
Female	29	32.2
Total	**90**	**100**

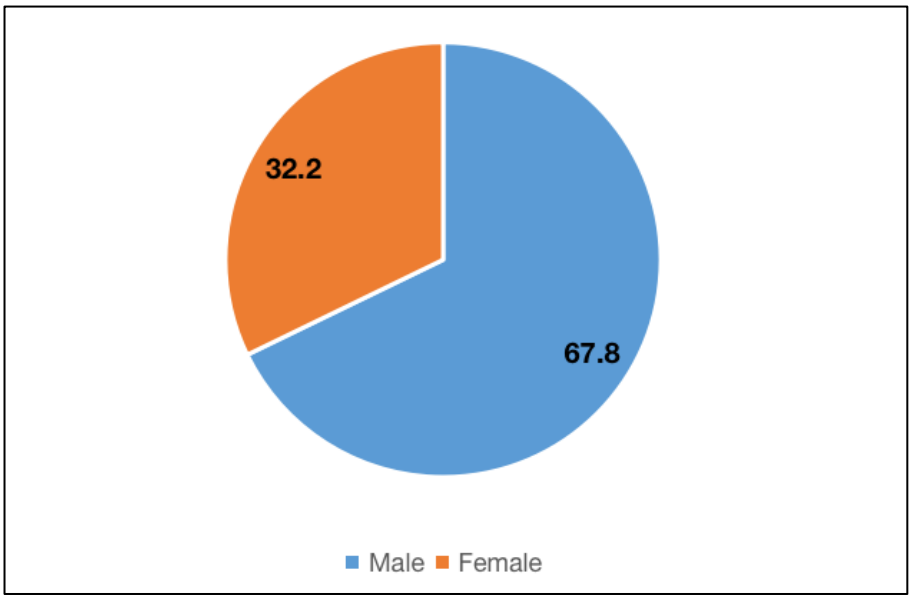


Figure 11. Gender distribution among the study participants

In the gender distribution of the 90 study participants, male were participants 67.8% (n=61) and female participants were 32.2% (n=29).

Table 3. Hematological parameters distribution among the study participants (N=90)

Variables	Mean	SD	Median	IQR
Hemoglobin (g/dL)	13.6	2.1	13.8	12.1-14.9
Packed cell volume (%)	42.4	6.4	42.3	38.3-46.7
RBC count (million/mm^3)	4.5	0.8	4.6	4.0-5.1
Total count (million/mm^3)	5.2	3.5	4.2	2.6-7

Table 3 presents the distribution of hematological parameters among 90 study participants, showing a mean haemoglobin level of 13.6 g/dL with a standard deviation of 2.1, a median of 13.8, and an interquartile range of 12.1-14.9. The packed cell volume averaged 42.4% (SD=6.4), with a median of 42.3 and an IQR of 38.3-46.7. The mean red blood cell (RBC) count was 4.5 million/mm³ (SD=0.8), with a median of 4.6 and an IQR of 4.0-5.1. Lastly, the total white blood cell count had a mean of 5.2 million/mm³ (SD=3.5), a median of 4.2, and an IQR of 2.6-7.

Table 4. Platelets level (10^9/L) distribution among the study participants at different time points

Platelets (10^9/L)	N	Mean	SD	Median	IQR
Day 1	90	84.3	67.7	59	33-124
Day 2	89	82.9	57.4	68	40-122
Day 3	72	79.8	46.1	70	52-99
Day 4	57	95.6	48.6	90	75-109
Day 5	27	99.5	41.6	94	76-112
Day 6	10	99.6	14.5	102	92-106
Day 7	2	114	16.9	114	102-126

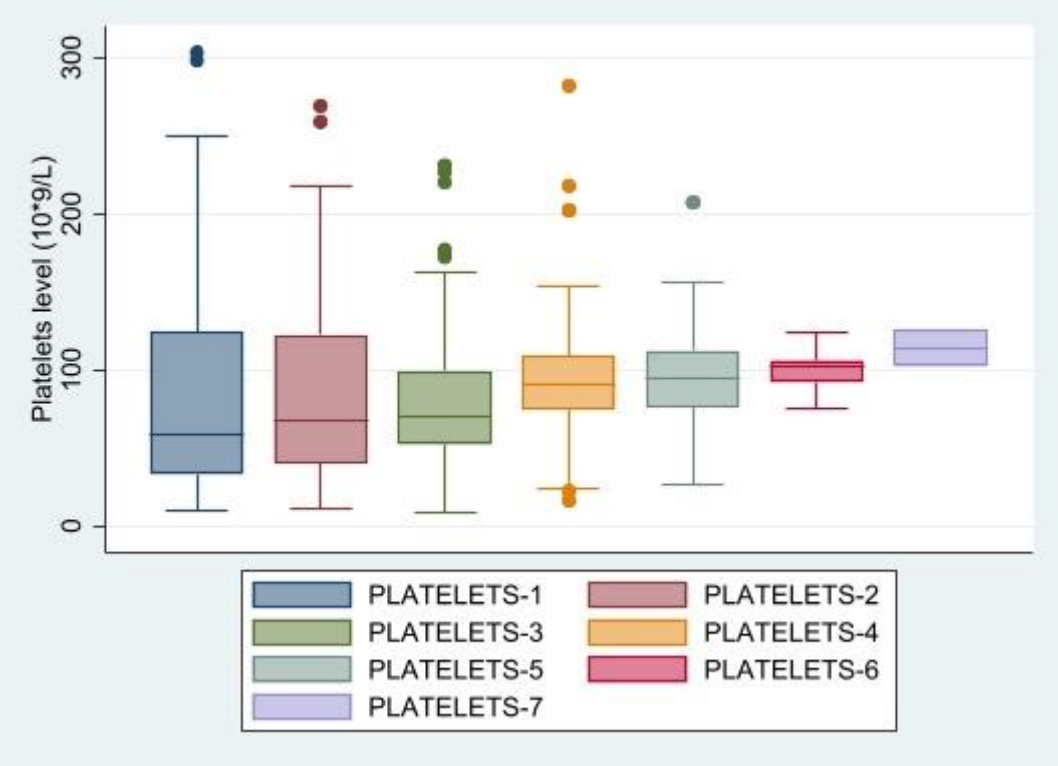


Figure 12. Box plot representing median platelet level (10^9/L) distribution among the study participants at different time points

The platelet counts (measured in 10^9/L) among the study participants showed a gradual increase over the seven days. On Day 1, the median platelet count was 59 (IQR: 33-124), rising to 68 (IQR: 40-122) on Day 2. By Day 3, the median reached 70 (IQR: 52-99), and on Day 4, it further increased to 90 (IQR: 75-109). This upward trend continued on Day 5 with a median of 94 (IQR: 76-112) and on day 6, the median reached 102 (IQR: 92-106). Finally, on Day 7, the median platelet count peaked at 114 (IQR: 102-126), indicating a significant overall increase in platelet levels.

Table 5. Immature Platelet Fraction distribution among the study participants at different time points

IPF (%)	N	Mean	SD	Median	IQR
Day 1	90	10.5	5.6	9.5	5.6-14
Day 2	89	10.3	4.9	9.7	6.2-13.3
Day 3	72	11.6	4.9	10.8	8.7-14.2
Day 4	57	11.2	6.4	10.4	8-13.1
Day 5	27	11.5	9.3	9.9	7.3-12.9
Day 6	10	11.4	1.8	11.1	10.6-12.4
Day 7	2	8.9	0.7	8.9	8.4-9.4

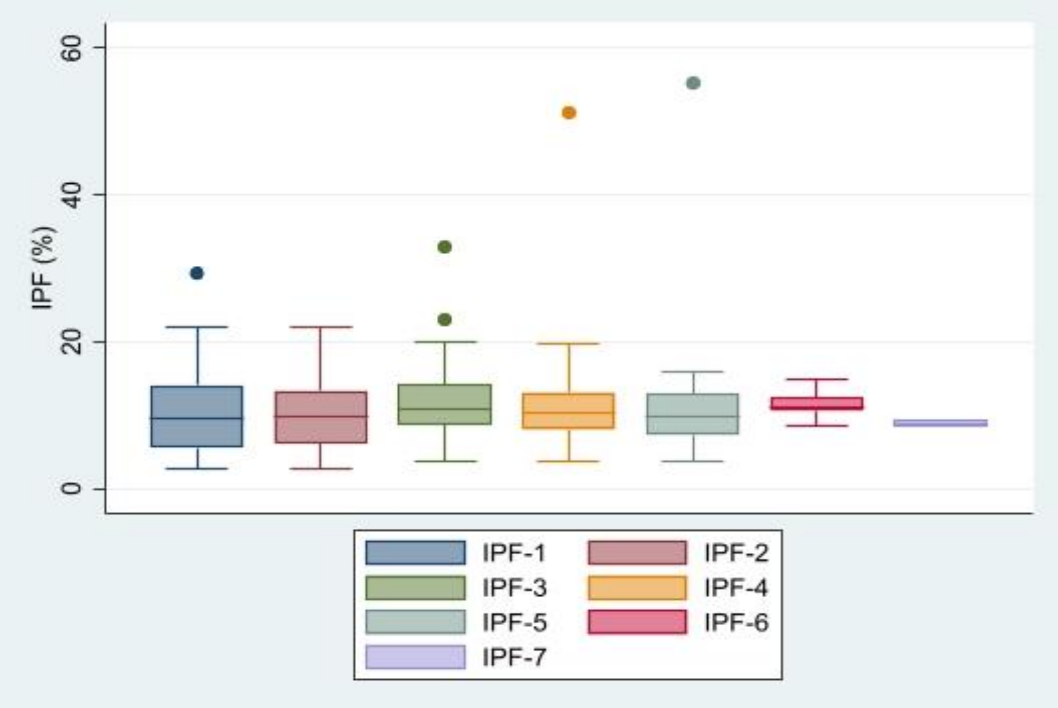


Figure 13. Box plot representing median Immature Platelet Fraction distribution among the study participants at different time points

The distribution of immature platelet fraction (IPF) percentages among the study participants exhibited fluctuations over the seven days. On Day 1, the median IPF was 9.5% (IQR: 5.6-14), with a slight increase to 9.7% (IQR: 6.2-13.3) on Day 2. Day 3 recorded the highest median at 10.8% (IQR: 8.7-14.2), followed by a decrease to 10.4% (IQR: 8-13.1) on Day 4. The median IPF continued to drop to 9.9% (IQR: 7.3-12.9) on Day 5, before rising again to 11.1% (IQR: 10.6-12.4) on Day 6. By Day 7, however, the median IPF decreased to 8.9% (IQR: 8.4-9.4), suggesting variability in IPF levels throughout the study period.

Table 6. Correlation between Platelets level and Immature Platelet Fraction among the study participants at different time points

	Immature Platelet Fraction			
	Time points	**Spearman Correlation**	**P value**	**N**
Platelets level	Day 1	-0.55	**<0.001**	90
	Day 2	-0.51	**<0.001**	89
	Day 3	-0.35	**<0.001**	72
	Day 4	-0.43	**<0.001**	57
	Day 5	-0.84	**<0.001**	27
	Day 6	-0.57	**0.01**	10
	Day 7	-1.00	0.80	2

Table 6 presents the correlation between platelet levels and the Immature Platelet Fraction (IPF) across various time points in the study. Significant negative correlations were observed on Days 1 to 6, with Spearman correlation coefficients ranging from -0.35 to -0.84 and P values all below 0.001, indicating a strong relationship as the platelet levels decreased. On Day 7, the correlation reached -1.00, but with a non-significant P value of 0.80. Overall, the findings suggest a consistent inverse relationship between platelet levels and IPF throughout the study period.

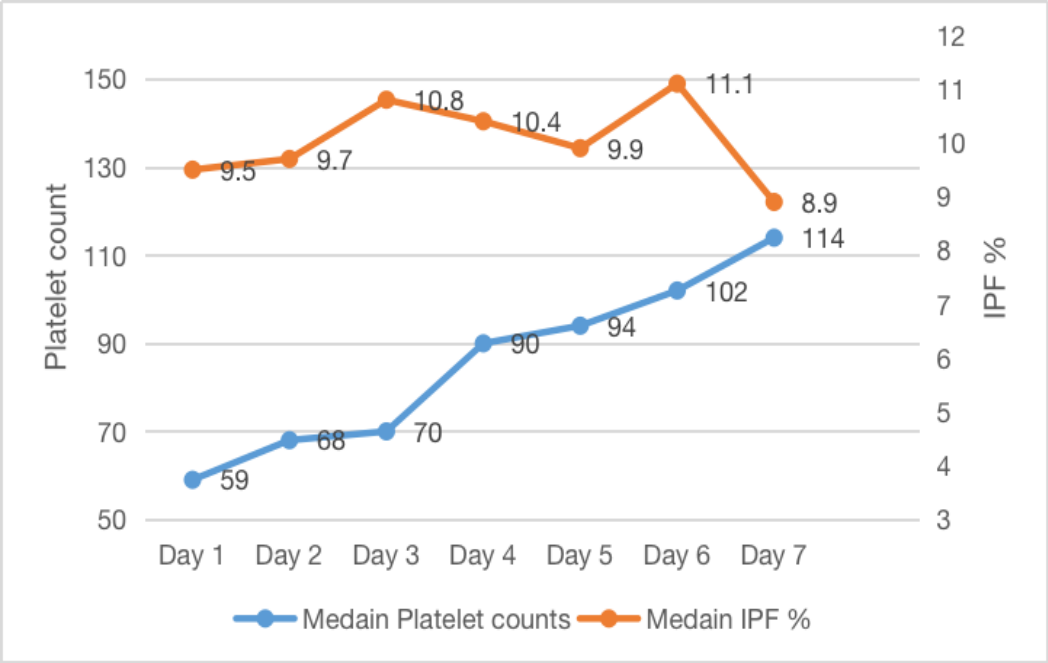
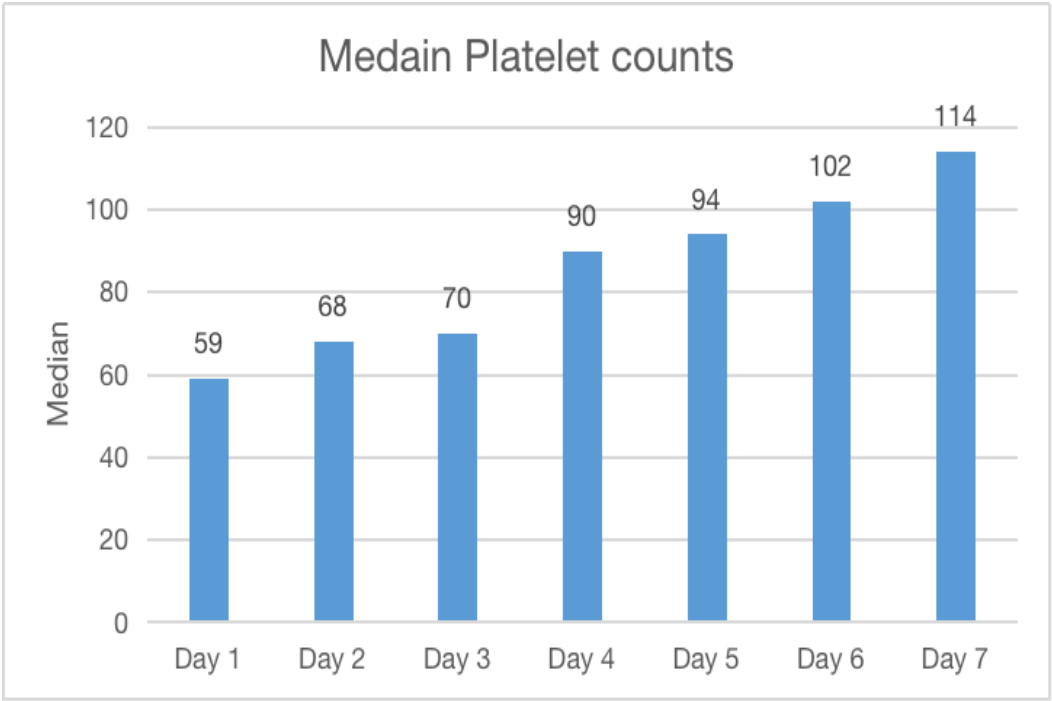


Figure 14. Pattern of IPF (%) and platelet count among the study participants at different time points

Overall platelet levels in dengue patients showed a consistent upward trend from Day 1 to Day 7,indicating gradual recovery.The IPF levels dropped from Day 1 to 7, reflecting a decline in the proportion of immature platelet. This was proportional to the gradual improvement in platelet count from Day 1 to Day 7. Patients with low platelet count consistently had higher IPF values,indicating an active platelet regeneration. As platelet levels increased over time,IPF values gradually decreased reflecting recovery.



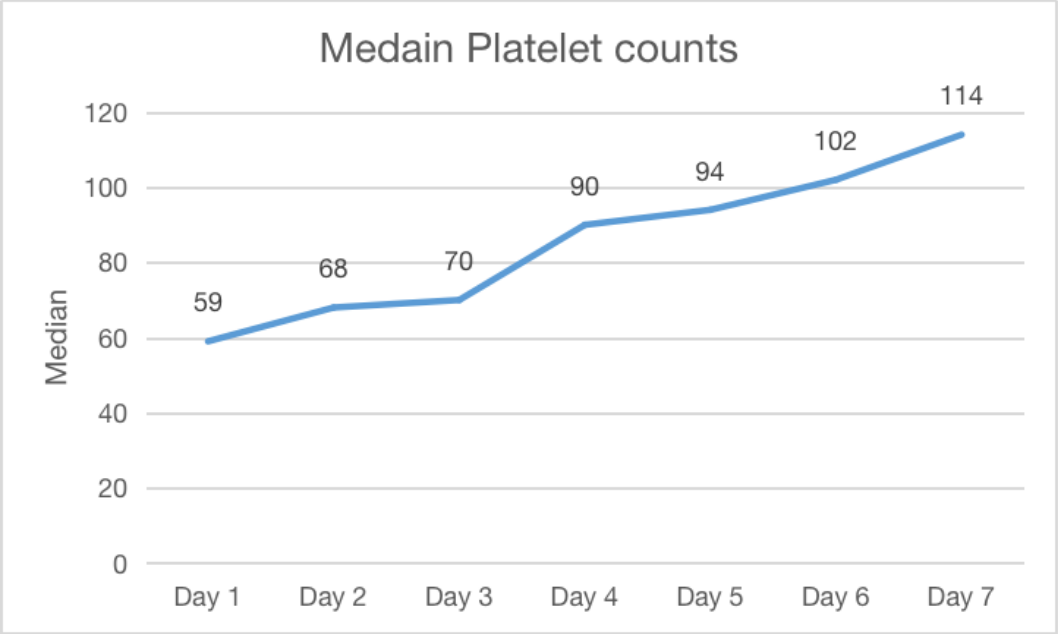
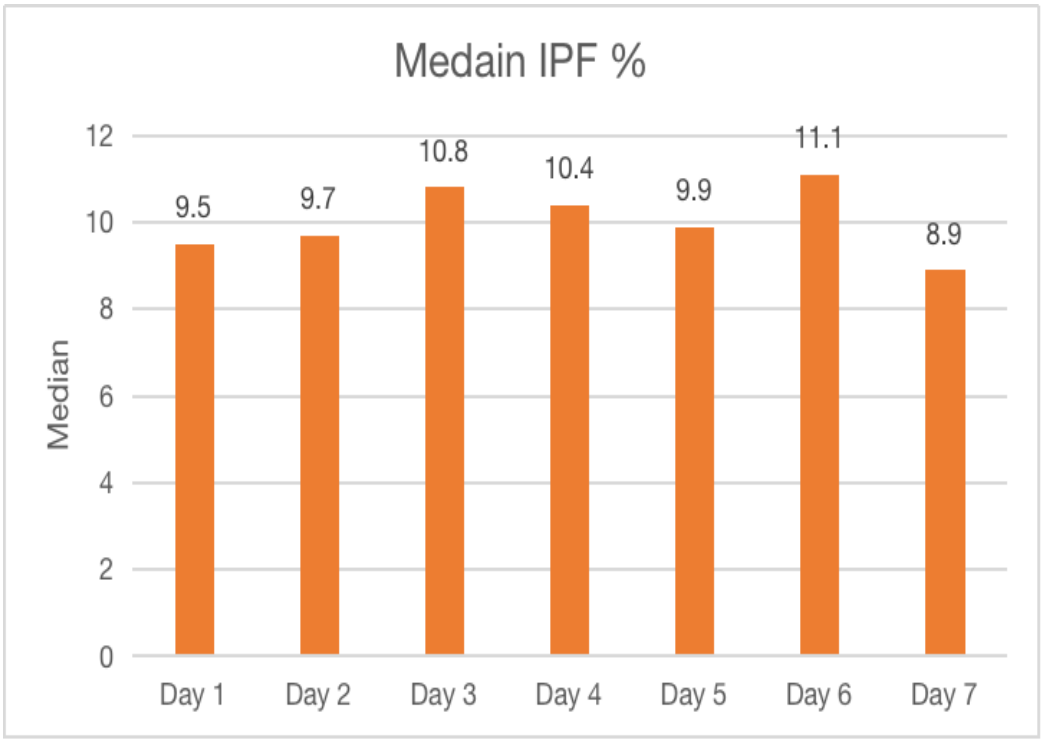


Figure 15: Pattern of platelet count among the study participants at different time points



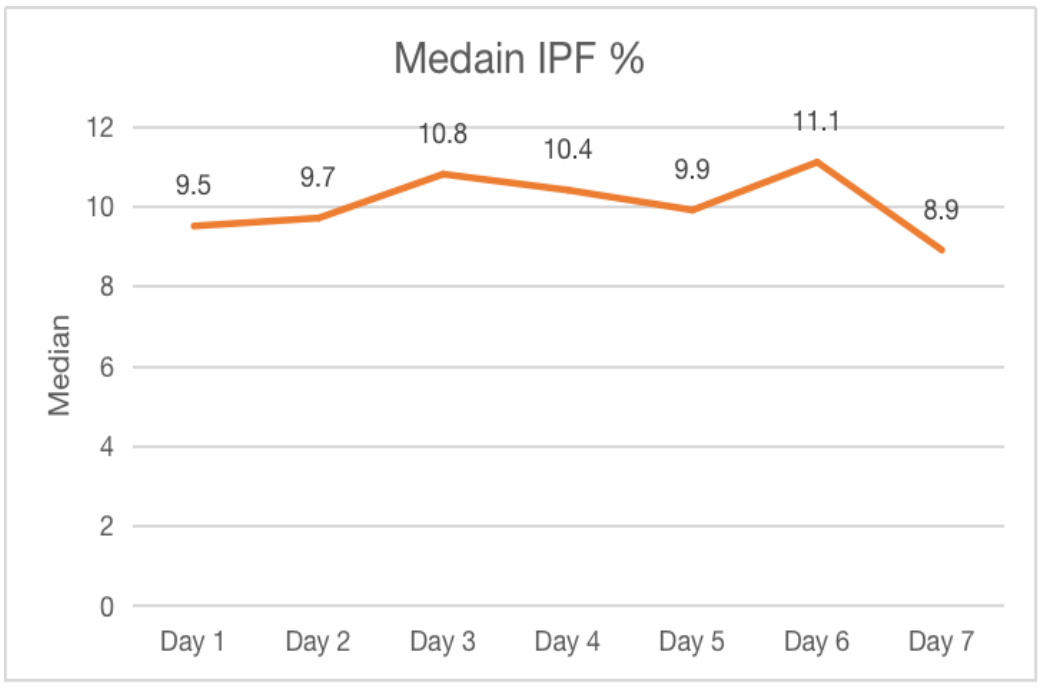


Figure 16. Pattern of IPF (%) among the study participants at different time points

Table 7. Comparison of Platelets level and Immature Platelet Fraction among the study participants at different time points

Platelets level at Day 1 (10^9/L)	**IPF (%)**	
	Median	**IQR**
< 90	11.8	8.9-15.8
≥ 90	5.3	4.2-8.9

Platelets level at Day 2 (10^9/L)	**IPF (%)**	
	Median	**IQR**
< 90	11.3	9.3-15.1
≥ 90	5.6	4-8.7

Platelets level at Day 3 (10^9/L)	**IPF (%)**	
	Median	**IQR**
< 90	11.6	9.2-15.2
≥ 90	9.3	5.2-10.8

Platelets level at Day 4 (10^9/L)	**IPF (%)**	
	Median	**IQR**
< 90	11.3	10-13.6
≥ 90	8.6	7.2-11.7

Platelets level at Day5 (10^9/L)	**IPF (%)**	
	Median	**IQR**
< 90	13.2	11.4-19.7
≥ 90	8.6	7.2-11.7

Platelets level at Day 6 (10^9/L)	**IPF (%)**	
	Median	**IQR**
< 90	11.4	11.4-12.1
≥ 90	10.7	10.1-13.0

Platelets level at Day 7 (10^9/L)	**IPF (%)**	
	Median	**IQR**
< 90	-	-
≥ 90	8.9	8.4-9.4

Table 7 compares platelet levels and Immature Platelet Fraction among study participants over seven days. For participants with platelet levels < 90 x 10^9/L, median IPF values ranged from 11.3% to 13.2% .This was consistently higher than those with platelet levels ≥ 90 x 10^9/L, whose median IPF values ranged from 5.3% to 10.7%. Notably, on Day 5, the median IPF for the <90 x 10^9/L group, peaked at 13.2%(lower platelets were associated with higher IPF). By Day 7, for the ≥ 90 x 10^9/L group median IPF was 8.9%(as platelets starts increasing,IPF was comparitively low). Overall, lower platelet levels were associated with significantly higher IPF values across the time points measured.

Table 8. Transfusion distribution among the study participants (N=90)

Transfusion	Frequency (n)	Proportion (%)
Random Donor Platelets	23	25.5
Single Donor Platelets	5	5.6
Both	5	5.6
None	57	63.3
Total	**90**	**100**

Transfusion distribution among the study participants (N=90)

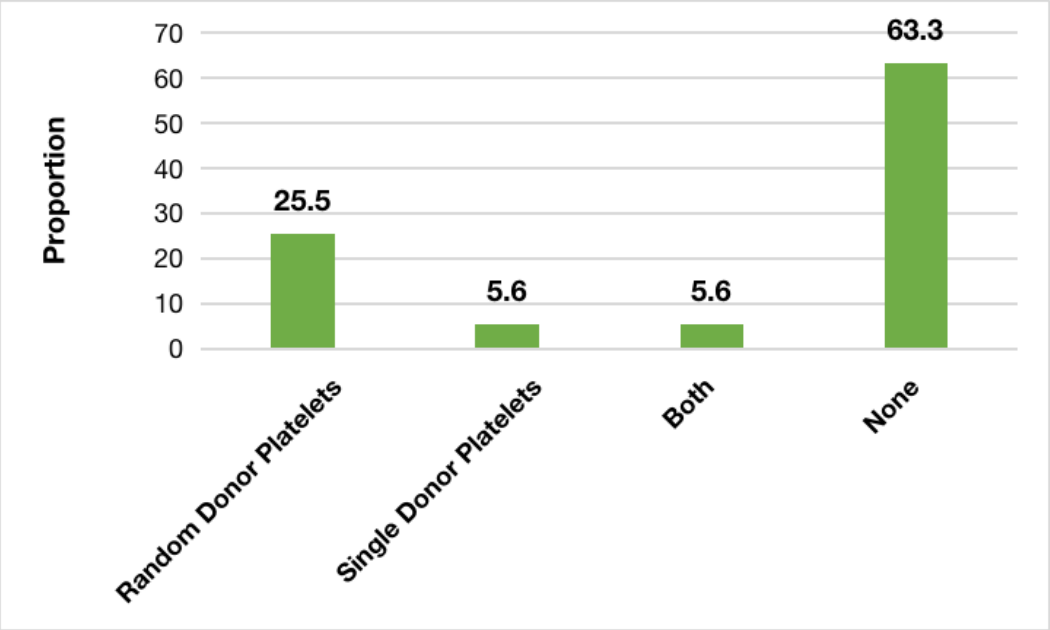


Figure17:-Transfusion distribution among the study participants

The transfusion distribution among the 90 study participants reveals that a majority of participants did not receive any transfusions 63.3%(n=57).In this study, 33 participants received transfusion. Amongst them, 25.5% (n=23) received random donor platelets and 5.6% (n=5) received single donor platelets and an equal percentage of 5.6% (n=5) received both types of platelet transfusion .In those 33 participants,17 participants had low platelet count and low IPF, these particiapants were correctly identified and transfusion was done. However,16 participants had low platelets with a high IPF,in these participants transfusion could have been avoided ,if the improving IPF trend was followed.

DISCUSSION

This observational study was conducted among dengue patients to evaluate the effectiveness of IPF in predicting the time to platelet recovery. The study was conducted among 90 patients at KLE's Dr prabhakar kore hospital ,Belagavi India, over a one-year period from January to December 2023. In the study, 45.6% of participants were in the 18-30 age group. The 31-40 age group followed with 24.4%, while 14.4% were in the 41-50 age range. Both 51-60 and 61-74 age groups, accounted for 7.8% each. The higher representation of younger adults in this study may be due to factors such as, increased outdoor activity in these age groups during the daytime when Aedes mosquitoes are most active, occupational risks in sectors like agriculture or construction. Additionally, urbanization may lead to increased exposure for younger adults, who are more likely to live in areas with abundant mosquito breeding sites.

Similar distribution was observed by Purti C. Tripathi et al., at a tertiary care center in Chhindwara, Madhya Pradesh. The 21–30 age group represented 14.8% of the total suspected cases, highlighting a significant prevalence of dengue in young adults. The 31–40 age group accounted for 5.8%, while the 41–50 age group represented 7%. 51–60 age group accounted for 6.1% , followed by the 61–70 age group accounted for 3.8%. Finally, the 71–80 age group had a minimal proportion of 0.3%.[81] A study by Zohra et al., found that highest number of cases was recorded in the 21-30 age group (32.2%), followed by the 11-20 (21.6%) and 31-40 (20.8%) age groups, suggesting a higher vulnerability among adolescents and young adults. Fewer cases were observed among older age groups, particularly those over 50, with only 2.8% of cases recorded in individuals aged over 70.[82] In another hospital-based observational study by Haroon et al., 2000 suspected dengue cases were evaluated.

Among these, age distribution showed that the 21–40 age group had the highest prevalence, accounting for 38% (160 patients) of dengue cases, followed by the 1–20 age group with 21% (89 patients).[83]

In our study, the majority of participants were male (67.8%), while females made up 32.2%. Similar distribution was seen in a study by Haroon et al., 2000 suspected dengue cases were evaluated amongst these, 415 cases (21%) were confirmed positive for dengue infection, 74% of the cases were male and 25% female.[83] Purti C. Tripathi et al., also reported findings in line with this, a total of 196 male and 158 female suspected dengue cases were recorded over the study period. In a study conducted by Manoj Kumar et al., 978 out of 4252 blood samples were found to be seropositive. The study found a male-to-female ratio of 1.54:1 ($P < 0.0001$).[84]

Several studies conducted in India, including those by Agarwal et al., Ray et al., and Wali et al., have consistently found a higher number of male patients infected with dengue compared to females, with sex ratios of 1.9:1, 1:0.57, and 2.5:1, respectively.[85–87] A large seroanalysis study also reported that males were more affected in the past three years of epidemic data.[88] This trend is consistent with findings from other Asian countries, suggesting that males are more commonly affected by dengue.[89] The higher prevalence in males may be attributed to sociocultural factors, as males are more likely to engage in outdoor activities with less body coverage, increasing their exposure to mosquito bites compared to females.[90]

In this study, the hematological parameters of the study participants (N=90) showed a mean hemoglobin level of 13.6 g/dL (SD = 2.1), a mean packed cell volume (PCV) of 42.4% (SD = 6.4), and a mean RBC count of 4.5 million/mm^3 (SD = 0.8). In a study by Babuji et al. among 175 cases. The results showed that the majority of

patients (40%) had Hb levels between 12 and 15 g/dL, followed by 21.14% of patients had Hb levels above 15 g/dL.[91] In a study by Wisanuvej et al. the median hemoglobin level at the time of dengue presentation was found to be 13.8 g/dL, while the median hematocrit was 41.6%.[92] In the study by Sharma et al., various hematological parameters were assessed in dengue patients. The mean RBC count was found to be 4.1 million cells/mcL with a standard deviation of 1.1. The mean packed cell volume (PCV) was 43.8%. Additionally, the mean hemoglobin level was recorded at 10.25 g/dL.[93] These studies highlight that while dengue can lead to mild reductions in hematological parameters, significant anemia or extreme changes in RBC count, hemoglobin, and PCV are not commonly seen unless there is a more severe or complicated form of the disease.

In this study, the platelet levels in dengue patients showed a general improvement over the course of the week. On Day 1, the mean platelet count was 84.3 × 10^9/L, with significant variability (SD = 67.7). By Day 4, the mean platelet count had risen to 95.6 × 10^9/L, indicating recovery. By Day 6, the platelet levels further increased to 99.6 × 10^9/L, and by Day 7, the mean platelet count reached 114 × 10^9/L, reflecting a stabilization and recovery in most patients as the disease progressed. Overall, platelet levels in dengue patients showed a consistent upward trend from Day 1 to Day 7, indicating gradual recovery as the disease progressed. The decrease in platelet counts initially observed may reflect the severity of thrombocytopenia during the acute phase, with subsequent recovery aligning with the typical progression of dengue fever. The IPF levels demonstrated variability over the course of the week. On Day 1, the mean IPF was 10.5% (SD = 5.6), indicating moderate variability. By Day 2, the mean IPF slightly decreased to 10.3% (SD = 4.9), followed by an increase to 11.6% (SD = 4.9) on Day 3, suggesting a transient rise in

immature platelet production. On Day 4, the IPF decreased marginally to 11.2% (SD = 6.4), and remained stable at 11.5% (SD = 9.3) on Day 5. By Day 6, the mean IPF stabilized at 11.4% (SD = 1.8), with a reduced range of variability. On Day 7, the IPF dropped to 8.9% (SD = 0.7), reflecting a decline in the proportion of immature platelets as the patients' conditions improved. In a comparison of platelet counts and IPF over seven days in dengue patients. Patients with platelet counts below 90 x 10^9/L consistently had higher IPF values, indicating active platelet regeneration. On day 1, patients with <90 x 10^9/L platelets had a median IPF of 11.8%, while those with ≥90 x 10^9/L had 5.3%. As platelet levels increased over time, IPF values gradually decreased, reflecting recovery. By day 6, the difference in IPF between the two groups was minimal, suggesting stable platelet counts. This trend confirms IPF as a useful indicator of platelet recovery in dengue patients.

In the study conducted by J. Asha et al., platelet counts in dengue fever patients showed an increasing trend from Day 1 to Day 9. On Day 1, the mean platelet count was 78,700/µl and on Day 2 it was 80,900/µl, reflecting gradual improvement. The normal range for Immature Platelet Fraction (IPF) values is between 1.1% and 6.1%. At baseline, the majority of patients had high IPF values while 30% had normal IPF value and less than 1% had low IPF values. On Day 5 , there was a decrease in the percentage of patients with IPF values exceeding 6.1%.[94] In study done by Looi et al.,demonstrated that, platelet counts initially decreased from Day 2and further on reaching a lowest point of 28,000/mL on Day 4. However, by Day 7, the platelet count improved to 96,000/mL. The IPF continued to increase until Day 7, after which it began to decline from Day 8 onwards.[11] Ojha et al, observed that ,platelet counts were low (mean < 50,000/µL) on Day 4 of the fever, but gradually recovered to normal levels (greater than 170,000/µL) by Day 10.[59] The relationship between

platelet count and IPF in dengue patients appears to be indicative of the body's compensatory mechanisms. Low platelet counts trigger the production of immature platelets in acute phase, as reflected by the elevated IPF values. As recovery occurs, both the platelet count and the IPF level stabilize, suggesting that the body is gradually returning to normal platelet production and regulation. The decreasing IPF in the later stages of the disease may indicate a shift from the initial compensatory production of immature platelets,to a more regulated steady state of platelet production,as platelet counts normalize. This relationship highlights the dynamic nature of platelet production and destruction during dengue fever, as well as the body's capacity to restore normal platelet levels over time.[9]

In this study, platelet levels and IPF at different time points showed a significant negative relationship throughout the study period. On Day 1, the Spearman correlation coefficient was -0.55 ($p < 0.001$), and on Day 2, it was -0.51 ($p < 0.001$), on Day 3, the correlation was -0.35 ($p < 0.001$), which was still statistically significant but weaker. On Day 4, the correlation remained negative at -0.43 ($p < 0.001$). A stronger negative correlation of -0.84 ($p < 0.001$) was observed on Day 5, and on Day 6, the correlation was -0.57 ($p = 0.01$), still significant but less strong. On Day 7, the correlation reached -1.00 ($p = 0.80$), indicating a negative correlation, although the p-value was not significant.

In a study by Mohapatro et al., the mean platelet count was 22,400 cumm, and the mean IPF was 17.79 % on day 1. The platelet count increased on day 3 to 33,842 cumm, with an IPF of 16.93 %, platelet count further increased to 72,760 on day 7, with the IPF decreasing to 11.79%.[76]

In a study by Looi et al., all participants showed a decrease in platelet count in the first week with a rise in IPF% for three days followed by an increase in platelet levels. Patients with severe dengue had higher IPF. Additionally, the reticulocyte count was markedly elevated in severe dengue cases by day 5.[11] In an observational study by Shah et al. IPF values above 10% were associated with an increase in platelet counts in 90.9% of patients within 24 hours and in 93.5% of patients within 48 hours. This increase in platelet counts was found to be strongly correlated with peak IPF levels ($p < 0.001$).[78] Another study had similar findings, Monette S et al. found that 87% of patients had platelet recovery after the increase in IPF, 87% after the peak IPF value, and 95% after the decreasing trend in IPF, although the correlation was statistically weak.[80]

In our study, among the 90 participants,33 received transfusion,amongst them 25.5% received RDP, while 5.6% received SDP. An additional 5.6% received both types of platelet transfusions. The distribution of RDP transfusions was as follows: 8 participants received 2 RDP (8.9%), 7 received 4 RDP (7.8%), 2 received 6 RDP (2.2%), 4 received 8 RDP (4.4%), 1 received 9 RDP (1.1%), and 1 received 11 RDP (1.1%). A smaller number of participants received SDP, with 4 participants receiving 1 SDP (4.4%) and 1 receiving 3 SDP (1.1%). Some participants received combinations of RDP and SDP, including 1 participant who received 4 RDP + 2 SDP, another with 4 RDP + 3 SDP, and others with different combinations, all accounting for 1.1% each. In a study by Sonam Kansay et al., a total of 185 patients received RDP only, accounting for 65.4% of the total, while 48 patients (15.6%) received both random donor platelets and single-donor apheresis platelets (RDP + SDP), and 25 patients (13.5%) received only SDP.[95] In a review of platelet transfusion practices (2013) by Chaurasia, a total of 1,750 RDP and 114 SDP were administered to 531

patients.[96] The varied transfusion patterns suggest that platelet needs are individualized and dependent on the severity of the patients' conditions, with some requiring a higher volume of RDP (ranging from 2 to 11 units) and others needing a combination of RDP and SDP. The fact that only a small proportion of patients (5.6%) received SDP indicates that single donor apheresis platelets, while effective for severe cases, were used sparingly due to their higher concentration and cost, potentially reflecting a more targeted approach to managing thrombocytopenia.

In our study, the majority of participants (63.3%) did not require any platelet transfusions. Similarly, Nagarekha Kulkarni et al. found that 79% of 195 DF patients required platelet transfusion, with 71% of 35 DHF patients and all DSS patients in the study needing transfusions.[97] In a study by R.N. Makroo et al., 39.69% required platelet transfusion. Among the 21 patients with DHF, 71.42% required platelet transfusion, while 40% of patients with DSS needed platelet transfusion.[51] Additionally, Asha J et al. reported that 16% of dengue fever patients had a platelet count below 20,000/µl, of whom 41% required transfusions.[94] In the study by Alex Chairulfatah et al., 12% of all DHF and DSS cases received platelet transfusions.[98] The variation in platelet transfusion rates across different studies can be attributed to several factors. The threshold for administering platelet transfusions may be varying between studies, influenced by local clinical protocols and guidelines. Some studies may have a lower platelet count threshold for transfusions, leading to higher rates of transfusion. The differences in platelet transfusion rates reflect variations in the severity of dengue, study design, clinical practices, and regional factors.

In our study, patients with low platelets and low IPF, all 17 were correctly identified as transfusion candidates. However, 16 patients with low platelets but high IPF, despite not being candidates, still received transfusions. Since high IPF indicates

active platelet production, these transfusions may have been unnecessary. But in patients with high IPF, transfusion is justified in cases of severe or suspected bleeding when a patient remains unstable, which may explain these cases.

STRENGTH

1. The observational design and the inclusion of daily monitoring of platelet counts and IPF values provide a comprehensive and real-time assessment of platelet recovery in dengue patients, enhancing the reliability of the findings.

2. All data collection tools, including platelet counts and IPF values, are part of routine clinical care, which minimizes additional cost burden on patients and enhances the feasibility of implementing the study in real-world settings.

3. This study highlights that un-necessary transfusions can be avoided.Thus ,lowering the risk of transfusion related infections and allo immunization.

4. Structured data collection, including baseline assessments, regular monitoring of platelet counts, and IPF, ensures consistency and accuracy in capturing patient information and outcomes.

LIMITATION

1. Excluding patients with co-morbidities such as heart failure, liver dysfunction, or malignancy may limit the generalizability of the study to the patient population with comorbid conditions.

2. All possible confounding factors were not accounted for (e.g., variations in treatment regimens or the use of adjunctive therapies), which could impact platelet recovery and IPF values.

CONCLUSION

This study aimed to evaluate the Immature Platelet Fraction (IPF) as a predictor of platelet recovery time in dengue patients. The majority of participants (45.6%) were young adults (18-30 years), with a male predominance (67.8%). Platelet counts and IPF values showed gradual recovery, stabilizing by Days 4-7. A negative correlation between platelet counts and IPF values was observed, strongest on Days 1, 2, and 5. Higher IPF levels at admission predicted faster platelet recovery, suggesting IPF's potential as a prognostic marker in clinical practice. IPF can help predict platelet recovery time, improving dengue patient management. The observed age and gender patterns emphasize the need for targeted interventions in high-risk populations. Further research with larger, diverse samples is needed to validate these findings.

SUMMARY

The study participants were predominantly in the 18-30 years age group, comprising 45.6% of the total sample.

The majority of participants were male (67.8%), while female participants made up 32.2% of the study population.

The average hemoglobin level among participants was 13.6 g/dL, with a packed cell volume of 42.4%. The RBC count averaged 4.5 million/mm^3, and the total leukocyte count was 5.2 million/mm^3.

On Day 1, the mean platelet count was 84.3 x 10^9/L, and by Day 7, it had increased to 114 x 10^9/L, reflecting a gradual increase in platelet levels over the course of the study.

The Immature Platelet Fraction (IPF) showed a slight decrease from 10.5% on Day 1 to 8.9% on Day 7. The trend indicated a steady decline in IPF throughout the study.

A negative correlation between platelet levels and Immature Platelet Fraction (IPF) was observed across all time points. The correlation was strongest on Day 7, where the Spearman correlation coefficient reached -1.00.

At Day 1, participants with platelet levels less than 90 x 10^9/L had a significantly higher IPF (median 11.8%) compared to those with platelet levels greater than or equal to 90 x 10^9/L (median 5.3%). This trend of higher IPF values for lower platelet levels persisted on subsequent days, with the pattern continuing through Day

6. On Day 7, the data was only available for participants with platelet levels above 90 x 10^9/L, with a median IPF of 8.9%.

Most participants (63.3%) did not receive any transfusion. Among those who did, 25.5% received Random Donor Platelets (RDP), and 5.6% received Single Donor Platelets (SDP). A small percentage of participants received both types of transfusions.

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ANNEXURES

ANNEXURES – I INFORMED CONSENT FORM

Consent form format
KAHERs JNMC BELAGAVI
INFORMED CONSENT FORM
"USE OF IMMATURE PLATELET FRACTION TO PREDICT TIME TO PLATELET RECOVERY IN PATIENTS WITH DENGUE INFECTION AND OPTIMAL MANAGEMENT"

Name of Student/Principal Investigator:

Name of Guide/Co Investigators:

Introduction: Immature platelet fraction (ipf) is a new parameter which is automated measure of reticulated platelets in peripheral blood.

1. The number of reticulated platelets reflects the rate of thrombopoiesis.
2. It is an indicator to predict the recovery of platelets in dengue infection.
3. IPF levels rise as bone marrow production o f platelets increase and therefore, its measurement provides an assessment of bone marrow platelet production from peripheral blood sample.

Explanation of procedure: Patients who are enrolled in the study, peripheral blood samples were collected in EDTA tubes and sent for CBC,IPF. All samples were analyzed within 4hrs after collection.Automated hematology analyser was used to calculate IPF.

Withdrawal from participation in the study: (In simple language, which can be understood by a layman as applicable to your study) Participation in this study is voluntary. You will be free to decide whether to participate in this study or continue participation once enrolled. In case you decide to withdraw your participation, you are free to do so. However, please convey the decision to the principal investigator.

Possible benefits from participating in the study: You will/will not get any benefits by participating in this study. **(In simple language, which can be understood by a layman as applicable to your study)** The data gathered will help the population at large.

Possible risks from participating in the study: There are no risks involved in participating in this study.
(In simple language, which can be understood by a layman as applicable to your study)
Privacy and confidentiality: The information collected from you will be coded, to prevent any person from identifying you. Your identity will never be revealed. The data collected from you will be kept confidential and only processed or aggregated data will be used for publication.

Financial incentives: You will not receive any payment for participating in this study.

Cost of investigations done during the course of study will be paid by the **principal investigator / Participant.** (Strike out which is not applicable)

Authorization for publication of aggregated data: Results obtained after processing of the aggregated data will be published for scientific purposes and or presented to scientific groups. However, your identity will never be revealed.

Questions:
mobile number, email ID" If you have any question or complaints with regard to your right as study participant you may contact Dr Harsha Hegde, Chairperson, Ethical committee of JNMC, 0831-2473777 Extension 4052.
Legal rights: By signing this consent form, we are not waving any of your legal rights.

CONSENT STATEMENT

I am making a voluntary decision to participate in the study "**USE OF IMMATURE PLATELET FRACTION TO PREDICT TIME TO PLATELET RECOVERY IN PATIENTS WITH DENGUE INFECTION AND OPTIMAL MANAGEMENT**".

My signature below indicates that I have decided to participate and I have read the information provided above or the information provided above has been read to me in the language that I understand best. I was given the opportunity to ask questions and that they have been answered to my satisfaction.

Name of the participant:

Signature or left thumb impression of the participant:

Name of the witness:

Signature or left thumb impression of the witness:

Name of the investigator:

Signature of the investigator:

ANNEXURES – II PROFORMA

CASE NO	
NAME	
IP NO	
AGE	**YEARS**
SEX	
ADDRESS	
OCCUPATION	

Complaints at presentation	
Past history	
Family history	

VITALS

Temperature	
Pulse	
Respiratory Rate	
Blood pressure	

PHYSICAL EXAMINATION

	Yes	No
Pallor		
Icterus		
Lymphadenopathy		
Cyanosis		
Clubbing		
Edema		

SYSTEMIC EXAMINATION

C.V.S	
R.S	
C.N.S	
PER ABDOMEN	

INVESTIGATIONS

Hemoglobin		Monocytes		RBC	
Total count		Basophils		MCV	
Neutrophils		Immature platelet fraction		MCH	
Lymphocytes		Platelets		MCHC	
Eosinophils		Reticulocyte Count			

ANNEXURES – III MASTER CHART

SL NO	IP NUMBER	AGE	GENDER	DENGUE NS1/IgM	PLATELETS-1	IPF-1	PLATELETS-2	IPF-2	PLATELETS-3	IPF-3	PLATELETS-4	IPF-4	PLATELETS-5	IPF-5	PLATELETS-6	IPF-6	PLATELETS-7	IPF-7	PLATELETS-8	IPF-8	HEMOGLOBIN(%)	RBC COUNT	TOTAL COUNT	TRANSFUSION-Cat	TRANSFUSION	PCV
1	10075550	18	M	POSITIVE	104	3.3	102	3.2													13.8	3.93	1.7	NO	NO	41.5
2	10082369	18	M	POSITIVE	103	5.3	72	4.3	106	8.2											12	5.16	2.1	NO	NO	40.3
3	10077212	19	M	POSITIVE	15	20.4	26	18.3	62	16.7	93	14									15.8	6.37	7	SDP	1SDP	51.4
4	10082538	19	F	POSITIVE	151	5.4	171	3.8	231	3.8	282	4.2									12.5	4.22	3.5	NO	NO	39.8
5	10080632	19	F	POSITIVE	44	5.2	30	8.6	28	6.4	85	7.6	135	5.7							15.2	5.29	1.8	RDP	8RDP	47.4
6	10081919	20	M	POSITIVE	49	4.4	54	5.5	43	8.2	94	4.6									14.1	4.41	1.9	NO	NO	45.3
7	10080081	20	M	POSITIVE	12	16.2	27	11.4	53	10.8	83	10.2									14.7	4.68	5.2	RDP	4RDP	41.7
8	10076478	20	M	POSITIVE	54	8.6	68	9.2	96	3.8											15.2	5.1	1.7	NO	NO	45.6
9	10081855	20	M	POSITIVE	23	3	48	3.4	32	14.2	77	11.1	118	8.4							13.5	4.35	1.2	RDP	2RDP	39.6
10	10075974	21	M	POSITIVE	24	13.4	40	11.2	67	10.2	92	8.6									15.3	5.04	3.2	RDP	2RDP	47.9
11	10077049	22	F	POSITIVE	23	13.4	40	11.6	42	13	80	10.4	104	7.2							10.7	3.26	2.8	SDP	1SDP	33.8
12	10074960	23	M	POSITIVE	195	5.6	168	6.2													15.4	4.68	1.6	NO	NO	47.2
13	10082047	23	M	POSITIVE	29	18.1	50	18.6	114	16.8	137	14.1									15.4	5.15	2.6	RDP	2RDP	47.5
14	10076119	23	M	POSITIVE	50	10.5	62	10.1	84	9.8	112	9									14.9	4.66	5.0	NO	NO	44.4
15	10075784	23	F	POSITIVE	220	3.3	218	3.2													10.1	3.84	1.8	NO	NO	31.4
16	10082014	23	M	POSITIVE	10	11.4	19	9.5	37	10.6	85	9.8	126	8.2							20.7	5.73	7.1	RDP	2RDP	59.4
17	10083547	23	F	POSITIVE	150	5.6	138	7.1	105	9.2	111	5.9	207	3.6							12.6	4.21	2.3	NO	NO	37.3
18	10075783	23	F	POSITIVE	83	6.3	42	11.4	68	9.2	101	7.4									9.5	3.26	8.1	NO	NO	28.8
19	10082577	24	M	POSITIVE	14	9.7	24	15.1	34	12.8	48	12.7	96	8.6							15.7	4.94	2.6	RDP	4RDP	46.7
20	10074994	24	M	POSITIVE	29	15.8	33	13.6	58	10.6	90	8.1									12.8	3.99	9.0	RDP	4RDP	39.4
21	10077966	25	M	POSITIVE	249	4.2	259	4.1	227	4.7											14.9	5.11	4.1	NO	NO	47.2
22	10075879	25	F	POSITIVE	102	9.4	100	9.2													12.7	4.49	3.6	NO	NO	41.5
23	10081229	25	M	POSITIVE	39	10.8	48	10.5	74	9.6	202	8.6									10.4	2.6	2.8	NO	NO	34.2
24	10077273	25	F	POSITIVE	55	20.4	68	21.9	103	14.3											10.6	2.4	2.8	SDP	1SDP	32.7
25	10069578	26	M	POSITIVE	89	6.9	73	8.9	96	9.2											14.6	5.14	10.4	NO	NO	44.3
26	10074537	26	M	POSITIVE	61	9.4	84	8.7	54	12.6	34	15.6	23	23.1	56	14.7	78	13.5	96	12.4	14.3	4.37	7.6	SDP	3SDP	42.4
27	10076978	26	F	POSITIVE	80	14.1	72	13.3	38	16.4	27	13.6	54	12.9	78	13.6	102	9.5			13.2	4.36	5.8	RDP	6RDP	41.4

28	10077498	26	M	POSITIVE	37	12.1	38	10.2	52	9	75	10.4	91	9.8							13.6	3.68	2.8	NO	NO	42.2
29	10081394	27	F	POSITIVE	124	4.8	100	6.9	66	20	22	10.9	76	15.9	73	18.2	81	18.4	126	15.6	13.1	4.52	1.4	Both	4RDP+3SDP	35
30	10074958	27	M	POSITIVE	20	11.2	32	12.6	46	13.4	73	8.9									12.1	3.69	8.3	Both	4RDP+2SDP	38.9
31	10082099	27	M	POSITIVE	37	15.6	38	15.4	59	19.7	89	12.8	112	10.7							15.4	4.43	5.8	NO	NO	46.2
32	10082360	27	M	POSITIVE	81	4	61	5.5	62	7.2	108	6.2	207	3.8							14	4.77	2.8	NO	NO	44.7
33	10074855	28	M	POSITIVE	75	13.8	85	11.6	125	10.8											13.9	3.55	4.2	NO	NO	41.3
34	10074855	28	M	POSITIVE	75	13.8	85	11.6	125	10.8											13.9	3.55	4.2	NO	NO	43.6
35	10075966	28	M	POSITIVE	33	16.7	37	16.3	59	14.7	80	11.3	112	9.6							17.6	5.23	6.6	NO	NO	54.2
36	10080951	28	M	POSITIVE	60	8.7	68	10.3	121	10.7	202	10.4									14.2	5.36	4.6	NO	NO	44.4
37	10076983	29	M	POSITIVE	35	21.4	86	19.8	162	12.6											14.6	4.62	2.8	RDP	2RDP	51.9
38	10082254	29	M	POSITIVE	30	6.4	11	5.1	9	23	16	51.2	50	55.2	92	14.8					16.2	5.26	4.4	Both	13RDP+1SDP	49.9
39	10074172	29	M	POSITIVE	120	6.4	112	6													13.8	2.79	2.6	NO	NO	44.8
40	10080692	30	F	POSITIVE	33	18.2	52	15.5	76	17.7	105	14.2									13	4.72	8.9	RDP	6RDP	41.4
41	10068783	30	F	POSITIVE	106	9.4	86	10	100	9.8											14.4	4.95	6.2	NO	NO	45.1
42	10077502	31	M	POSITIVE	32	29.3	37	21.4	78	16.4	109	13									13.6	3.76	8.4	NO	NO	42.7
43	10082366	33	F	POSITIVE	25	16.9	37	20.8	35	18.9	62	13.6	102	9.8							12.1	4.22	2.6	RDP	2RDP	38.8
44	10074901	34	M	POSITIVE	133	9.6	128	8.4													11.6	3.8	3.4	NO	NO	41.1
45	10076021	34	M	POSITIVE	56	8.9	42	9.8	30	10.2	64	13.1	86	11.4	124	8.6					12.8	4.59	18.6	RDP	4RDP	47
46	10074899	34	F	POSITIVE	44	15.8	86	13.7	102	11.6											9.6	3.71	2.6	NO	NO	29.4
47	10074585	35	M	POSITIVE	210	3.3	189	2.9													15.2	4.36	5.2	NO	NO	49.4
48	10080680	36	F	POSITIVE	303	5															11.8	4.85	18.3	NO	NO	39.4
49	10074484	36	F	POSITIVE	298	3.6	269	3													14.2	4.86	3.9	NO	NO	46.5
50	10075973	37	M	POSITIVE	51	8.9	55	8.7	80	6.8	92	7									16.6	5.35	7.2	NO	NO	49.6
51	10082581	38	M	POSITIVE	56	15.2	131	9	114	9.4	218	5.9									14.2	5.13	5.7	NO	NO	43.2
52	10076001	38	F	POSITIVE	15	6.6	12	7.2	34	5.8	65	6.1	86	7.3							12.8	4.67	2.6	RDP	8RDP	41.3
53	10075553	38	M	POSITIVE	84	19.3	56	19	28	16.6	48	16.9	76	13.2	102	12.5					13.5	4.48	12.5	RDP	9RDP	42.1
54	10069976	38	M	POSITIVE	26	9.4	46	10	72	9.8	97	8.3									9.2	3.22	9.8	RDP	8RDP	29.8
55	10082521	38	M	POSITIVE	156	4	169	3.9	172	4											12.7	5.07	3.1	NO	NO	41.2
56	10079458	39	F	POSITIVE	150	6.1	132	5.5	177	5.2											12.4	4.31	3	NO	NO	38.3
57	10076481	39	M	POSITIVE	80	11.8	46	9.7	73	7.9	103	8									14.5	4.76	5.0	NO	NO	42.2
58	10082738	39	F	POSITIVE	83	13.7	77	18.1	86	18.8	115	9.6									11.2	4.05	2.4	NO	NO	35.5
59	10082737	40	M	POSITIVE	38	8.4	44	11.4	75	12.8	137	11.2									17.3	4.6	3.4	NO	NO	55.6
60	10074320	40	M	POSITIVE	161	8.9	158	7.6													13.6	5.14	11.2	NO	NO	42.6
61	10077697	40	M	POSITIVE	230	4.8	205	4.3	220	5.1											13.8	4.94	6.7	NO	NO	43.9
62	10082314	40	M	POSITIVE	98	13.2	92	14.6	101	14.2	138	12.3									13.8	4.6	2.6	NO	NO	43.9
63	10074944	40	M	POSITIVE	99	11.8	128	9.8													12.1	5.14	3.5	NO	NO	37.1
64	10046340	41	M	POSITIVE	128	5.6	165	5.2													14.8	4.65	3.8	NO	NO	46.7
65	10075978	41	M	POSITIVE	47	15.8	48	15.2	76	13	89	12.1									13.7	4.07	2.4	NO	NO	41.3
66	10069558	42	M	POSITIVE	79	9.9	101	8.9													19	5.64	3.0	NO	NO	59
67	10076482	43	M	POSITIVE	42	9.5	39	9.7	63	8.2	92	7.6									12.0	3.1	11.1	NO	NO	35.4
68	10074846	43	M	POSITIVE	13	9.4	38	16.2	48	12.4	76	13	92	10.4							16.7	3.1	3.8	RDP	4RDP	44.3
69	10083506	44	M	POSITIVE	96	3.3	37	5.4	20	13.3	25	14.1	30	19.7	78	15.4	104	13.6			15.8	5.83	2.6	NO	NO	49.3
70	10082765	45	M	POSITIVE	196	2.8	201	2.6													13.5	4.92	4.3	NO	NO	41.7
71	10077666	45	M	POSITIVE	176	4.3	140	4.3	88	4.6	109	3.8									11.2	4.6	2.8	NO	NO	34.6
72	10080354	46	M	POSITIVE	135	4.3	122	4.8	52	32.9	24	14.6	26	11.6	75	12.1	102	9.4			14.6	4.64	2.8	RDP	2RDP	50.2

73	10081783	48	M	POSITIVE	77	5.4	71	10.1	133	9.1	154	8.7									14.9	5.33	2.6	NO	NO	45.9
74	10080917	49	M	POSITIVE	28	22.1	34	17.6	61	14.1	84	10.8	109	9.9							16.6	5.63	5.6	RDP	11RDP	48.6
75	10077091	49	F	POSITIVE	199	4.7	157	5.6	80	8.4	46	10	74	11.2	106	10.9					12.2	4.65	4.5	NO	NO	43.5
76	10076334	50	M	POSITIVE	31	11.2	43	12.6	61	9.6	94	8.8									16.1	5.03	1.7	Both	8RDP+1SDP	50.5
77	10080392	52	M	POSITIVE	196	4.8	165	4													14.6	5.64	7.4	NO	NO	47.1
78	10083103	52	M	POSITIVE	11	21.1	18	20.4	63	19.8	109	19.6									15.9	5.65	4.2	RDP	4RDP	49.5
79	10080087	54	F	POSITIVE	34	14	46	11.2	68	11	90	7.4									13.9	4.66	6.9	NO	NO	42.1
80	10082328	56	F	POSITIVE	32	12.7	76	9.4	94	9.2	126	16.6									15.4	5.57	5.1	NO	NO	47.1
81	10074705	57	F	POSITIVE	58	10.4	84	9.2													10.2	4.84	15.6	NO	NO	32.7
82	10081543	58	F	POSITIVE	150	6.4	123	8.7	98	9.9	134	7.8									10.8	3.88	3.8	NO	NO	35.5
83	10072937	60	M	POSITIVE	68	15.8	34	13.6	16	15.2	47	15.8	61	13.6	114	10.6					9.6	3.18	10.7	Both	12RDP+6SDP	30.7
84	10074516	62	F	POSITIVE	135	19.4	146	14.6													12.3	2.6	9.6	NO	NO	38.3
85	10074568	63	M	POSITIVE	12	6.9	28	8.4	56	11.4	79	13.4	94	10.6							11.2	5.87	4.6	SDP	1SDP	35.3
86	10069308	65	F	POSITIVE	49	13.3	47	12.8	87	11											12.1	4.82	7.2	RDP	8RDP	37.6
87	10069308	65	F	POSITIVE	49	16.3	47	13.2	80	11.7											12.1	4.82	7.2	NO	NO	37.1
88	10074860	68	F	POSITIVE	138	19.4	137	18													11.1	3.92	5.5	NO	NO	33.4
89	10077709	72	F	POSITIVE	22	10.1	41	9.3	52	7.6	131	8.6	156	6.8							9.8	2.6	7.6	RDP	4RDP	30.2
90	10076496	74	M	POSITIVE	34	6.4	32	7.6	58	7.2	90	6.2	102	4.2							14.6	4.94	2.4	RDP	2RDP	43.5