

# Immature Platelet Fraction: A Promising Biomarker in Various Clinical Entities

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**Abstract:** Reticulated platelets are immature platelets circulating in blood; they reflect the activity of megakaryopoiesis in the bone marrow. Therefore, they can be used as a non-invasive test in patients with thrombocytopenia in various clinical conditions. Reticulated or immature platelet assays are useful for the differential diagnosis of thrombocytopenia and for monitoring bone marrow recovery after chemotherapy or stem cell transplantation and several other clinical entities. The concentration of retPLT in bone marrow is on the average 2–3 times higher than in peripheral blood, where they correlate with megakaryocyte numbers. The platelets persist in the circulation for 7–10 days, retPLT have a much shorter lifespan (<1 day). Therefore they can act as a marker of megakaryopoietic activity in the bone marrow which gives retPLT clinical and diagnostic utility. This review provides an overview of the clinical conditions in which reticulated platelets or immature platelets can be considered as a diagnostic tool or prognostic tool. This overview also indicates that more research is needed before reticulated or immature platelet assays can be applied in other clinical conditions than thrombocytopenia and after transplantation.

**Keywords:** Immature platelet Fraction, Thrombocytopenia, Covid, Dengue, sepsis, Coronary artery diseases, Liver diseases, preeclampsia

## 1. Introduction

Megakaryocytes in the bone marrow undergo cytoplasmic fragmentation, produce in platelets, which are nucleated cells. [1] They have 2-3 micrometer size and are discoid in shape. They normally live 9–10 days and have a count of 150,000–400,000/Lakh/ cumm [2]. They are well suited to quickly respond to vascular damage and draw leukocytes to injury sites since they are the second most abundant cell in the circulation. [3] It appears that platelets function as both gatekeepers of the vascular wall and building blocks of the hemostatic plug, maintaining vascular integrity while coordinating host defence. [4]

Haemostasis and thrombosis are "ruled" by platelets, but more recently, their participation in vasomotor activity, chemotaxis, inflammation, and atherosclerosis has received significant attention. [5] By expressing a variety of functional immunological receptors, platelets help innate immunity to influence adaptive immune responses. Example, pathogen-associated molecular pattern (PAMP) receptors, platelets are able to directly bind pathogens and promote anti-infective immunity. They can also kill bacteria by encapsulation and anti-microbial peptides. [6]

Newly produced platelets from the bone marrow are larger, more active, and contain more RNA than mature platelets. They are known as reticulated (RP) or immature platelets. RP appears to stay in the blood stream for 24-36 hours, during the time a progressive degradation of RNA and a decrease in volume take place. Under normal circumstances, "mature" platelets persist in the circulation for around 7–10

days. They can also serve as real-time markers of megakaryopoiesis because the number of RP is related to thrombopoiesis. [7]

They are thought to be more hyperactive and pro-thrombotic than mature platelets. They are known to have a higher tendency for thrombus development and to have a thrombotic predisposition. [8] These are easily discernible by modern haematology analyzers with fluorescence capabilities, which report the immature platelet fraction (IPF) as a percentage of the total platelet count. They correspond to the reticulated platelets that various analyzers had reported. [9].

## Clinical Utilities

Various potential clinical applications for this parameter in diagnosis and monitoring are summarized in table no.1

**Table 1**

Clinical Applications
Thrombocytopenia
Covid
Dengue Fever
Sepsis
Preeclampsia
Coronary Artery Disease
Liver Diseases

Reticulated platelets are immature platelets that are circulating in the circulation and represent the megakaryopoiesis activity that is occurring in the bone marrow. As a result, they can be utilised as a non-invasive

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test in a variety of clinical settings for patients with thrombocytopenia. Reticulated or immature platelet tests can be used to distinguish between different types of thrombocytopenia and to monitor the progress of the bone marrow after chemotherapy or stem cell transplantation. When recovery from thrombocytopenia is imminent, these assays may help clinicians make judgments about platelet transfusion.

Reticulated or immature platelets have a role in the risk assessment of acute coronary syndromes and the monitoring of the therapeutic response to antiplatelet drugs in patients with coronary artery disease. The goal of this research is to give an overview of the current state of RP's clinical use and, this overview shows that additional studies are required before reticulated or immature platelet tests can be used in therapeutic settings other than thrombocytopenia.

## 2. Literature Survey

### 1) Thrombocytopenia

1. The condition known as thrombocytopenia is one that has a number of underlying causes. To handle these individuals

effectively, it is essential to accurately identify the aetiology. Reduced thrombopoiesis, 2.increased platelet consumption, and 3.incorrect platelet distribution (sequestration) can be grouped together as the three main causes of thrombocytopenia.

In patients having thrombocytopenia, retPLT research focused on a potential differential diagnostic tool. IPF have been shown to be useful in determining the source of thrombocytopenia in numerous investigations. In most cases, a rise in retPLT occurs 2–3 days before a platelet count recovery. This offers the chance to postpone needless platelet transfusions. [10] Spontaneous bleeding that is clinically significant typically doesn't start until the PLT is 1020 109 /L. In some patient groups, bleeding episodes might happen at higher PLTs, but in others, a lower PLT can be "tolerated". The difficulty in treating thrombocytopenia in the absence of a definitive cause is exacerbated by the heterogeneity in patient tolerance, and as a result, the PLT is not always applicable when determining the severity and necessity for platelet transfusion. [11]

**Table 2:** Clinical utility of IPF in Thrombocytopenia: Quick review of articles used to write this article

Authors Name	Topic	Outcome
Garima Goel et al.[12]	Immature Platelet Fraction: Its Clinical Utility in Thrombocytopenia Patients	IPF is a cutting-edge diagnostic technique that can be utilised to distinguish between patients with thrombocytopenic anaemia caused by various aetiology. IPF may also be able to predict platelet recovery in people with thrombocytopenia
Arshi Naz et al.[13]	Importance of immature platelet fraction as predictor of immune thrombocytopenic purpura	The IPF% is a useful diagnostic technique for firmly determining in individuals the diagnosis of idiopathic (or immune) thrombocytopenic purpura. The IPF should therefore be made a normal routine parameter for the diagnosis and serial monitoring of the thrombocytopenic patient
Kibum Jeon et al.[14]	Immature platelet fraction: A useful marker for identifying the cause of thrombocytopenia and predicting platelet recovery	To distinguish between hyper destructive/ consumptive and hypoproduative thrombocytopenia, the IPF is a helpful marker. Future therapeutic suggestions may benefit from this, and unnecessary transfusions may be reduced.
Min Ji Jeon et al.[15]	Immature platelet fraction based diagnostic predictive scoring model for immune thrombocytopenia	Though IPF (%) alone is hardly a gold standard for the diagnosis of ITP, it could be more useful in combination with other laboratory variables.
Sobia Ashraf1 , Sindhu Rehman et al.[16]	Comparison of Immature Platelet Fraction (IPF) in Patients with Central Thrombocytopenia and Peripheral Thrombocytopenia	It is possible to reliably identify patients with thrombocytopenia brought on by peripheral destruction or usage by using the helpful measure known as immature platelet fraction.

### 2) COVID

Coronavirus illness (Covid-19) is a pandemic that has an impact on mortality and morbidity all over the world. Several case series have described the clinical characteristics of the illness, which can range from a minor respiratory infection to a multi-organ dysfunction syndrome and catastrophic respiratory failure. Recent research revealed SARS-CoV-2 affects platelet gene expression and activity,

causing hyperreactive platelets. This raises the question of how thrombopoiesis functions in COVID. The immature platelet fraction (IPF%, calculated as a percentage of the total platelet count) is an example of thrombopoiesis biomarkers that may have significant predictive value [17]

There is a substantial frequency of venous thromboembolic events in severe Covid-19 (VTE).

**Table 3:** Clinical utility of IPF in Covid 19: Quick review of articles used to write this article

Authors Name	Topic	Outcome
Tessa J. Barrett et al[18]	Platelets contribute to disease severity in COVID-19	IPF serve as indicator of platelet activation and increased risk of thrombosis
Said Incir et al.[19]	Immature platelet fraction: is a novel early predictive marker for disease severity in patients with Covid-19 pneumonia	IPF% would be a solitary predictor of COVID-19 pneumonia severity.
Robert W. Maitta et al.[20]	Immature platelets in COVID-19 infection	IPF may increase in individuals with more coagulopathy and thrombocytopenia due to higher platelet consumption, which may

		increase the risk that covid affected patients will present with a more severe condition.
Daniel Welder et al.[21]	Immature platelets as a biomarker for disease severity and mortality in COVID-19 patients	IPF%, IPC, and platelet counts may be used as readily available prognostic indicators that indicate the likelihood of severe outcomes in COVID-19 patients, according to the findings of our study.
Sobia Ashraf1 et al.[22]	Comparison of Immature Platelet Fraction (IPF) in Patients with Central Thrombocytopenia and Peripheral Thrombocytopenia	It is possible to reliably identify patients with thrombocytopenia brought on by peripheral destruction or usage by using the helpful measure known as immature platelet fraction.

**3) Dengue Fever**

Dengue is the fastest spreading arboviral infection of major concern to public health in the tropical regions where dengue sickness is most prevalent, neither safe, effective, and economical .

Vaccines or specific medicines are readily accessible. Understanding and choosing relevant early illness progression markers is so crucial for the diagnosis [23]. Several processes, such as peripheral platelet destruction and bone marrow suppression, have been connected to DENV-associated thrombocytopenia. Research have indicated that

DENV-infected bone marrow stromal cells or haematopoietic progenitors cause the suppression of hemopoiesis, and anti-platelet antibodies are one of the clinical indicators that platelets are being prematurely destroyed in the peripheral circulation

One of the frequent dengue consequences is that it often requires for platelet transfusion in thrombocytopenia. IPF, which measures immature platelets that indirectly represent thrombopoiesis and is useful in predicting platelet recovery, measures immature platelets [24]

**Table 4:** Clinical utility of IPF in Dengue Fever:Quick review of articles used to write this article

Authors Name	Topic	Outcome
T. Dadu, K. Sehgal,et al. [25]	Evaluation of the immature platelet fraction as an indicator of platelet recovery in dengue patients	That IPF can be utilised to assess the platelet recovery in dengue patients. It shows a lot of promise as a future resource for making sound decisions about platelet transfusion
Kah Wai Looi et al [26]	Evaluation of immature platelet fraction as a marker of dengue fever progression	Patients with severe dengue have a higher IPF levels than patients with non-severe dengue or other non-dengue illnesses.
Maria Monette S. Ong-Misa et al.[27]	Relationship between immature platelet fraction and platelet count among paediatric patients with dengue fever: A prospective study	IPF and platelet count did not correlate well statistically, however there was an inverse association between the two. decreasing trend of IPF may be a reliable indicator of a rising trend in platelet count.
Visula Abeysuriya et al. [28]	The immature platelet fraction, a predictive tool for early recovery from dengue-related thrombocytopenia: a prospective study	IPF% levels on days two and three of the illness are suggested to be a good prediction indicator for swift recovery from thrombocytopenia caused by dengue
Jefri Ahmad et al [29]	Estimation of a cut-off value for immature platelet fraction (IPF) in predicting platelet recovery in dengue patients with thrombocytopenia	IPF can predict platelet recovery more accurately than platelet count growth, which is helpful in the management of dengue, especially when the requirement for platelet transfusion is present.

**4) Sepsis**

Sepsis is a fatal organ failure syndrome with a very complex inflammatory host response brought on by a severe systemic infection. One of the biggest challenges in treating sepsis is making an early diagnosis because waiting too long to identify the condition increases mortality rates [30]

The most frequent process is traditionally "platelet consumption" via thrombin-mediated platelet activation. Disseminated intravascular coagulation (DIC), which can happen in severe cases of sepsis, is characterised by broad activation of coagulation, intravascular fibrin production, and finally thrombotic blockage of small and medium-sized

arteries. It is an acquired disorder that is more common in septicemia than in any other clinical situation [31]

Procalcitonin and C-reactive protein (CRP) are two of the best researched biomarkers available today for the detection and monitoring of sepsis [32]

According to the recent studies, the immature platelet fraction may be a useful as prognostic indicator for determining the severity of the condition and death in sepsis patients. Being a potentially fatal condition, sepsis calls for prompt diagnosis.

**Table 5:** Clinical utility of IPF in Sepsis: Quick review of articles used to write this article.

Authors Name	Topic	Outcome
Djuang MH et al.[33]	Immature Platelet Fraction in Bacterial Sepsis Severity Assessment	IPF might reflect the activity of platelet production in bone marrow but had no relation with PCT in this study. On the other hand, platelet count as one of the parameters for evaluating sepsis severity showed a significant result when compared to the PCT level
Liu QH, et al.[34]	Clinical significance of measuring reticulated platelets in infectious diseases.	IPF showed no significance among the three groups (p-value>0.05) while platelet count was significant (p-value<0.05). Mean Platelet Volume (MPV) and Platelet Distribution Width (PDW) showed a strong positive correlation with IPF

Muronoi T, et al.[35]	Immature platelet fraction predicts coagulopathy-related platelet consumption and mortality in patients with sepsis.	The admission IPF in septic patients predicts a subsequent decrease in platelet count, indicating platelet consumption with ongoing coagulopathy and risk of poor prognosis.
Wu Q, et al.[36]	An elevated percentage of reticulated platelet is associated with increased mortality in septic shock patients.	Increased RP% identifies septic shock patients who have a high risk of death. RP% has the potential to act as a marker for patient stratification in future clinical trials.
Okasha D.et al.[37]	Immature Platelet Fraction Predicts Outcome and Sepsis Development in Critically Ill Patients Admitted to a General Intensive Care Unit, Washington	This study suggests that the validity of IPF% as a predictor of outcome depends on the bone marrow capacity. In patients with normal bone marrow admitted to ICU, IPF% correlates with the significance of stress and severity of the disease.

**5) Coronary Artery Disease**

Clinical professionals are required to accurately diagnose CAD patients within 10 minutes, according to current clinical recommendations.

In order to treat patients as fast as possible after diagnosis, clinicians should further categorise patients based on their ECG and blood levels of cardiac biomarkers. The current biomarkers for the diagnosis of ACS are cardiac troponin I (cTnI) and cardiac troponin T (cTnT). Hence, numerous researchers are looking at a potential novel biomarker for

ACS diagnosis in order to diagnose better and treat individuals with acute chest pain. [38]

High platelet turnover and arterial thrombotic events including acute coronary syndrome and acute stroke have both been linked to elevated levels of RPs. Moreover, among CAD patients, IPF and IPF-related indicators are powerful independent predictors of response to antiplatelet therapy. IPF should be examined even after treatment because it is linked to the disease prognosis [39]

**Table 6:** Clinical utility of IPF in Coronary Artery Disease :Quick review of articles used to write this article

Authors Name	Topic	Outcome
Monica Verdoia et al. [40]	Immature platelet fraction and the extent of coronary artery disease: A single centre study	the immature platelet fraction (IPF) is not associated with the prevalence and extent of coronary artery disease, and, therefore, should not be overlooked as a marker of coronary atherosclerosis.
Daro Bongiovanni et al. [41]	Role of Reticulated Platelets in Cardiovascular Disease	RPs are a new biomarker helpful to highlight patients at high risk for adverse ischemic events. The biological prothrombotic features of RPs could explain their implications on platelet reactivity and provide an explanation for RP’s correlation with cardiovascular events in patients with different diseases.
Erik Lerkevang Grove et al. [42]	Immature platelets in patients with acute coronary syndromes	The fraction of immature platelets is increased in acute coronary syndromes, especially in the acute phase
Francesca Cesari et al [43]	Reticulated platelets predict cardiovascular death in acute coronary syndrome patients	RP are independent predictors of cardiovascular death and may be useful in improving risk stratification for ACS patients.

**6) Liver Diseases**

Chronic liver disorders are frequently accompanied by thrombocytopenia. Reduced ability of megakaryocytes to produce blood platelets, an increase in peripheral oxidation, or splenic sequestration are a few possible causes. Reticulated platelets as a marker of megakaryopoiesis in liver cirrhosis; relation to thrombopoietin and hepatocyte growth factor serum concentration [44]

Thrombocytopenia is a frequently occurring consequence of severe liver disease, and patients with liver cirrhosis are more likely to experience it. Patients with chronic liver disease who have thrombocytopenia have a higher risk of

bleeding, which can result in more frequent ambulatory visits and inpatient hospital stay, in contrast to patients who do not have thrombocytopenia. [45]

The poor prognosis of patients with chronic liver disease or liver cirrhosis is attributed to a wide range of additional variables. Both doctors and patients are reluctant to do bone marrow examinations since they are invasive and painful for the patient. The use of other noninvasive methods, such as immature platelet fraction (IPF%), is then suggested as a substitute for bone marrow testing in order to make a differential diagnosis [46]

**Table 7:** Clinical utility of IPF in Liver Diseases :Quick review of articles used to write this article

Authors Name	Topic	Outcome
Panasiuk A et al.[47]	Reticulated platelets as a marker of megakaryopoiesis in liver cirrhosis; relation to thrombopoietin and hepatocyte growth factor serum concentration.	Reticulated platelets as a marker of megakaryopoiesis in liver cirrhosis; relation to thrombopoietin and hepatocyte growth factor serum concentration.
Muhammad Javid Iqbal et al.[48]	Immature Platelet Fraction in Patients with Chronic Liver Disease, :A Marker for Evaluating Cirrhotic Changes	The use of other noninvasive methods, such as immature platelet fraction (IPF%), is then suggested as a substitute for bone marrow testing in order to make a differential diagnosis
T,Nomura , et al.[49]	Immature platelet fraction measurement in patients with chronic liver disease: a convenient marker for evaluating cirrhotic change	proposed IPF% measurement for diagnosing liver cirrhosis.

### 7) Preeclampsia

Pregnancy can cause an imbalance in hemostatic processes, which can raise the risk of thrombosis and hypercoagulability. Platelet indices like immature platelet fraction, change in pregnant women with hypertension, especially those who have preeclampsia [50]

Hypertensive disorders are a relatively common pregnancy. It is one of the major causes of maternal and foetal morbidity and mortality. After the 20th week of pregnancy, preeclampsia (PE) is characterised by high blood pressure and pathological proteinuria. Pregnancy haemorrhage and

improper syncytiotrophoblast implantation both enhance thrombin synthesis, which in turn increases platelet activation and releases antiangiogenic substances into the maternal circulation. Moreover, the complement system and membrane attack complex are both activated by platelet activation. [51]

Platelet indices in hypertensive pregnancies showed a distinctive profile. It implies that these indicators could be utilised as an additional tool in daily life to manage pregnant women. [52]

**Table 8:** Clinical utility of IPF in Preeclampsia: Quick review of articles used to write this article.

Authors Name	Topic	Outcome
Terezinha Paz Munhoz et al.[53]	Immature platelet fraction in hypertensive pregnancy	Platelet indices like immature platelet fraction, help in the management of pregnant women with hypertension, especially those who have preeclampsia
Daniela Moraes et al.[54]	Immature Platelet Fraction and Thrombin Generation: Preeclampsia Biomarkers	Platelet indices in hypertensive pregnancies showed a distinctive profile. It implies that these indicators could be utilised as an additional tool in daily life to manage pregnant women
Ulrike Bernstein et al.[55]	The immature platelet fraction in hypertensive disease during pregnancy	IPF levels are higher in pregnant women with hypertension than in controls who had normal blood pressure. They might be utilised to identify hypertension disorders in pregnant women.

### 8) Detection Methods

Two key features -enormous size of the platelets and their high fluorescence intensity determine it's immaturity. The reticulocyte/ platelet channel in the first generation of fully automated analyzers uses flow cytometry to determine the proportion of immature platelets to platelets [56].

In analyzers, the fluorescently labelled cells are exposed to a semiconductor diode laser beam, and the forward scatter (cell volume) and fluorescence intensity (mostly caused by RNA content) that results are quantified. Based on the intensity of forward light and fluorescence, a computer programme can distinguish between mature and immature Platelets. The immature/RP, like that of the reticulocyte, can be expressed as a percentage or an absolute quantity (109/L), which is obtained by multiplying the platelet count by the value %. [57]

The reference range for the IPF% in healthy persons was found to be 1–6%, with a mean of 3.4 using the Sysmex XE-2100 series.

The reference intervals for IPF% in all participants were 0.5-3.3% (0.5-3.1% in males; 0.5-3.4% in women) according to the study by KO, Y.J, H Kim et al. [58] The reference interval of IPF was 1.3–9.0% according to mikala klok et al [59]. According to another study by Johannes J et al. Normal IPF range was 1.1-18.7% [60]

### 3. Discussion

According to the research by carol briggs et al in 2004, study of various thrombocytopenic groups were done, and the results generated some evidence that suggests the IPF may be helpful in the diagnosis and follow-up of thrombocytopenic patients. Patients with autoimmune thrombocytopenic purpura had the highest IPF% values out of all the patient populations analysed indicating an active production of platelet. Active TTP patients similarly had very high IPF% readings. Although the IPF% results for the

patients receiving cytotoxic chemotherapy were at the lower end of the normal reference range, their association with thrombocytopenia suggested that the bone marrow was not producing enough platelets. [61]

According to the current studies ,other clinical entities in which IPF can be utilized as a predeictive marker is antiplatelet therapy, bone marrow activity, sepsis and other inflammatory conditions, preeclampsia etc.

### 4. Conclusion

- One of the earliest and most extensively researched applications is the importance of RP/IPF in differentiating between thrombocytopenia caused by peripheral destruction or acute blood loss, where the percentage of RP is increased, and forms of bone marrow failure (BMF), where the proportion is within the reference range, although the data reported on this issue appear to be contradictory.
- To forecast the severity of SARS-COV-2, a number of biomarkers have been put forth, however none of them have proven reliable. IPF% is a biomarker that can be used to assess thrombopoiesis and has high prognostic significance.
- In patients having PBSC (peripheral stem cell)or getting chemotherapy, prophylactic platelet transfusion can be delayed because it is possible to forecast platelet regeneration a few days following an increase in IP.
- In patients with preeclampsia, changes in IPF may be a good indicator of the development of thrombocytopenia because there is an association between increased IPF and a lower platelet count, even in the absence of thrombocytopenia.
- IPF could be an early recovery indicator of thrombocytopenia in dengue.
- A low percentage of reticulated platelets appears to be consistent with impaired bone marrow function in chronic liver disease. The IPF value also offers a

differential diagnosis between cirrhosis and chronic hepatitis in patients with liver disease.

- The clinical usefulness of IP for risk assessment in acute coronary syndrome and the possible relationship with outcome in patients with cardiovascular disease appear to be supported by recent investigations in patients with cardiovascular disease. Cardiovascular issues are also associated with a rise in RP.
- Although the outcomes of the various researches gained are somewhat conflicting, several studies have focused on the potential utility of IPF in the early diagnosis and in the control of infectious conditions. IPF is a trustworthy sepsis predictive marker.

## 5. Future Scope

As concluded above IPF can be exploited in so many other clinical entities also, further studies may provide the supporting information

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