The Value-Driven Laboratory

The Role of the Immature Platelet Fraction (IPF) in the Differential Diagnosis of Thrombocytopenia

Sysmex America
White Paper
The Value-Driven Laboratory

**Immature Platelet Fraction (IPF): An insight into assessment and treatment of platelet disorders**

We have previously defined the value-driven laboratory as one that meets market demands by providing more and new types of diagnostic information to support the delivery of high quality and cost-effective patient care. This paper sets forth the value of an automated CBC parameter, the Immature Platelet Fraction (IPF), to help physicians understand the pathophysiological mechanisms leading to low platelet count. The IPF can help physicians determine in a timelier fashion if a thrombocytopenia is due to decreased platelet production by the bone marrow or increased peripheral consumption/destruction of platelets.

**Introduction**

The Immature Platelet Fraction (IPF) is a measure of thrombopoietic activity first described in 1992 by Ault et al., who coined the term “reticulated platelets” to describe large platelets with elevated ribonucleic acid (RNA) content. Reticulated platelets can be seen as an analog to the reticulocytes in red cell populations. Ault’s study and others have shown IPF to be a stable and reproducible parameter and superior to the measurement of reticulated platelets using flow cytometry for providing information to the physician on the rate of thrombopoiesis. The IPF rises as production of platelets increases in the bone marrow. Using a peripheral blood sample, its measurement provides an assessment of bone marrow platelet production in a similar way to how a reticulocyte count provides a measure of red cell production. The IPF result is useful in monitoring patients with thrombocytopenia and helps physicians differentiate thrombocytopenia caused by platelet destruction versus compromised platelet production. As a result, physicians can reach decisions on appropriate care pathways in a timelier manner.

**An Overview of Platelet Parameters**

**Platelet Count (PLT)**

A normal platelet count (PLT) (150,000 – 450,000/μL) is vital for the maintenance of hemostasis. Platelet counts of <150,000/μL are defined as thrombocytopenic and spontaneous bleeding not associated with injury has been associated with platelet counts of <20,000/μL. Current hematology instruments enable platelet counts of <50,000/μL to be accurately measured. However, such a measurement only reflects the circulating platelet count at a specific point in time.

**Mean Platelet Volume (MPV)**

A normal MPV is approximately 9 – 12 fl. Historically, some clinicians have used MPV as a surrogate marker for platelet production and to assist in the evaluation of thrombocytopenia. Platelets newly released from the bone marrow are generally larger and as platelets age, they become smaller. However, interfering substances such as schistocytes, microcytes or other particles that are similar in size to platelets and can be counted along with them can make MPV unreliable. Additionally, MPV results can show greater imprecision or be unmeasurable (suppressed by the analyzer) in samples with low platelet counts.

**Immature Platelet Fraction (IPF)**

An automated parameter, the Immature Platelet Fraction percent (IPF%) indicates the ratio of immature platelets to the total number of platelets in a patient’s peripheral blood. These immature platelets, newly released from the bone marrow, contain increased amounts of cytoplasmic RNA which allows them to be differentiated from mature platelets using a fluorescence staining method on an automated analyzer. The Sysmex® XN- and XE-Series Automated Hematology Analyzers are capable of reporting the IPF% result as a direct cellular measurement of thrombopoiesis, which can be used with other available clinical information to help physicians determine the pathophysiological mechanism of thrombocytopenia.

Clinicians have used the reticulated platelet information, or IPF%, as a measure of thrombopoietic activity of the bone marrow, which can be important in assessing the likelihood of bleeding.
Absolute Immature Platelet Fraction (IPF#)

The absolute-IPF (IPF#), calculated as IPF% x PLT count, reflects the number of immature platelets in circulation and is a measurement of real-time thrombopoiesis. IPF# has been used in clinical trials to assess the treatment effect of thrombopoietin receptor agonists, such as eltrombopag, and in platelet disorders of production and destruction, more specifically in Immune Thrombocytopenia (ITP). 6,7

In studies assessing the effect of platelet transfusion on IPF% and IPF#, platelet transfusions were found to decrease the IPF% due to the increased circulating platelet count but did not affect the IPF# result, thus “validating the assay as a reflection of ongoing platelet production by the marrow...” 8

IPF in the Clinical Setting

Normal Ranges

There is remarkably good correlation of reference ranges for IPF% between laboratories (Figure 1). A 2006 study 9 reported a reference range of 0% to 6% (+/- 2SD) with the mean value of 3.1%. The reproducibility of the assay was good, with coefficients of variation (CV) ranging from 4.9% to 22.1%. As expected, the lower the IPF%, the higher the CV.

IPF Normal Ranges by Source

<table>
<thead>
<tr>
<th>Peer-reviewed Article</th>
<th>IPF Normal Range</th>
<th>Notation</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. Zucker 11</td>
<td>1.1% to 7.1%</td>
<td>N = 43 healthy adults</td>
</tr>
<tr>
<td>C. Briggs 3</td>
<td>1.1% to 6.1%</td>
<td>N = 50 healthy adults</td>
</tr>
<tr>
<td>I. Pons 4</td>
<td>1.0% to 7.5%</td>
<td>N = 336 healthy adults</td>
</tr>
<tr>
<td>T. Bat 8</td>
<td>0.9% to 7.2%</td>
<td>N = 107 healthy adults</td>
</tr>
<tr>
<td>T. Kickler 9</td>
<td>0.6% to 6.0 %</td>
<td>N = 80 healthy adults</td>
</tr>
</tbody>
</table>

Figure 1: Correlation of reference ranges for IPF% in different studies.

IPF in the Differentiation of Increased Platelet Destruction versus Decreased Platelet Production

To determine if they could differentiate peripheral thrombocytopenia due to bone marrow failure versus increased peripheral destruction, Briggs et al. 10 followed AITP (Autoimmune Thrombocytopenic Purpura) and TTP (Thrombotic Thrombocytopenic Purpura) patients with platelet counts of <50,000/μL. IPF values were elevated in both patient groups due to excessive platelet consumption. The IPF then decreased as the platelet count recovered.

A study by Kickler 9 at Johns Hopkins looked at IPF values as differentiators in cases of thrombocytopenia (Figure 2). High IPF% values were found in patients with increased production, particularly if associated with platelet destruction, while normal values were seen in decreased platelet production.
**IPF in Hepatitis C/Liver Disease**

Additional examples of clinical utility of IPF% is evaluation of the mechanism of thrombocytopenia in Chronic Hepatitis C patients as recently described by Zucker et al. The authors concluded that this mechanism is similar to thrombocytopenia associated with liver disease.

IPF% was monitored in all patients and found to be normal or increased, supporting the idea that peripheral destruction and sequestration are the major causes of the thrombocytopenia in Hepatitis C and liver disease in general.

**IPF in Bone Marrow Recovery**

Several groups have studied the clinical utility of the IPF in different patient populations: following hematopoietic progenitor cell (HPC) transplantation; myeloablative chemotherapy for hematologic malignancy; Disseminated Intravascular Coagulation (DIC); non-myeloablative therapy in cancer patients and aplastic anemia; and paroxysmal nocturnal hemoglobinuria (PNH).

Although it is customary to follow neutrophil recovery after hematologic transplantation procedures, IPF may be a more reliable parameter since it is not affected by graft-versus-host disease. Zucker and colleagues followed IPF% in 50 patients undergoing peripheral hematopoietic cell transplants and found that IPF recovered on average 3.1 days prior to platelet count recovery (Figure 3). Takami et al. also reported the use of IPF as a predictor of platelet engraftment following allogenic stem cell transplantation, finding that IPF preceded engraftment.

Other uses for IPF have been described. Briggs et al. have suggested that the IPF parameter may be able to alleviate the need for bone marrow examinations as well as to determine if platelet transfusions are necessary.

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**Figure 2:** IPF% in Different Populations of Thrombocytopenic Patients.

**Figure 3:** Mean days to recovery for IPF, Immature Reticulocyte Fraction (IRF), platelet count (PLT) and Absolute Neutrophil Count (ANC) following stem cell transplantation.
IPF in Acute Myeloid Leukemia and Myelodysplasia (AML/MDS) Versus Immune Thrombocytopenia (ITP)

It has been difficult to measure platelet function in the presence of severe thrombocytopenia, a finding in both AML/MDS and ITP patients. Psaila et al. have noted that “Platelet count alone does not always predict bleeding in severely thrombocytopenic patients”, i.e., it is necessary but not sufficient. The study found that the difference in bleeding tendencies between these two groups of patients may be accounted for by the production of younger, larger platelets in ITP patients versus AML/MDS patients who had lower IPF values and smaller platelets (Figure 4).

IPF in the Assessment of Thrombopoietin Agonists

Another key role of IPF is in determining the efficacy of various treatment protocols for ITP, such as thrombopoietin receptor agonists (TPO-A). A study by Barsam et al. showed that patients receiving TPO-A have a higher IPF.

What’s Out?

1. Inaccurate PLT measurements at the very low levels, as can be seen in severe thrombocytopenia.
3. Waiting for Absolute Neutrophil Count recovery to determine bone marrow recovery.

What’s In?

1. A comprehensive platelet evaluation beginning with a fluorescent platelet count and simultaneous measurement of the IPF to evaluate the maturity of circulating platelets as an indicator of rate of PLT production (thrombopoiesis), i.e., using IPF to assist the physician in defining the best clinical pathway based on destruction/consumption vs. production issues.
2. Use of IPF to predict bone marrow recovery and rate of thrombopoiesis.
3. Evaluating TPO medication’s effects on thrombopoiesis.
4. Evaluating the use of the IPF% parameter as a reflex test in the presence of thrombocytopenia for reporting to hematologists/oncologists.

**Figure 4:** Platelet parameters in ITP and AML/MDS. (A) Platelet count, (B) Platelet size, (C) Immature platelet count (IPC) and (D) Immature platelet fraction (IPF).
**Conclusion**

Immature Platelet Fraction is a parameter that, although new to the clinical setting, has been studied for over a decade. IPF can function as a routine value reported with every platelet count in certain patient populations or as a reflex test based on your laboratory's platelet count cut-off. It provides guidance to the physician on the etiology of various thrombocytopenic states, and may help anticipate bone marrow and platelet recovery. Regardless of how it is applied, you will be supporting the delivery of high quality, cost effective patient care for a positive impact on patient outcomes.

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**Clarify the current strategy for thrombocytopenia management**

1. How often are you unable to report a low platelet count because of linearity or result vote-out issues with your hematology analyzer?

2. What percentage of your pre-admission CBCs are identified as thrombocytopenic patients?

**Identify the clinical lab tests that currently trigger follow-up testing by physicians**

3. What existing laboratory tests or clinical conditions trigger additional platelet studies in your institution?

4. What are the clinical conditions associated with thrombocytopenia at your organization?

5. What hospital service lines would need to know that a patient is thrombocytopenic?

6. What classes of pharmacologic agents have thrombocytopenia as an adverse event?

**Identify potential improvements that the clinical laboratory can support**

7. Given that the IPF recovers prior to the recovery of the peripheral blood platelet count, are we offering enough information with just a platelet count?

8. How can the laboratory educate physicians and nurses, pharmacists, coding and other ancillary departments about the value of the IPF parameter in the differential diagnosis of thrombocytopenia?
Bibliography


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The uses or clinical applications described in these publications have not been approved or cleared by the FDA. It is the clinician’s responsibility to validate any off-label applications for use in routine clinical practice.

Notice of Intended Use
“The Immature Platelet Fraction (IPF) parameter on the XN- and XE-Series Automated Hematology Analyzers is intended for in vitro diagnostic use to enumerate the immature platelet fraction”.