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Immune thrombocytopenia

The value of the immature platelet count for managing immune thrombocytopenia (ITP) treatment and assessing the risk of bleeding

The immature platelet fraction (IPF) is a well-established haematological parameter and is defined as the percentage of newly released immature (or 'reticulated') platelets in relation to the total platelet count. Studies have shown that increased IPF values are likely to indicate hereditary, consumptive or recovering thrombocytopenic disorders whereas a normal-to-low IPF is seen in aplastic states.

As such, IPF can help physicians differentiate between thrombocytopenia caused by platelet destruction/consumption and thrombocytopenia caused by compromised platelet production.

The immature platelet count (IPF#) is a diagnostic parameter that specifically reflects the absolute number of newly produced immature platelets in peripheral blood. This means that the parameter is completely independent of the total platelet count and therefore not affected by platelet transfusions given to the patient (Fig. 1) [1, 2].

When monitoring chronic ITP or predicting response to treatment, the absolute platelet count and immature platelet fraction are not sufficiently informative as thrombocytopenia in patients with chronic ITP is due to impaired platelet production as well as accelerated platelet destruction. As will be explained later in this document, the IPF# value can provide valuable supportive information about the patient's response to treatment, notably about which mechanism proves effective, as well as the risk of bleeding.

The immature platelet count helps to assess which mechanism of treatment is proving effective in immune thrombocytopenia

Immune thrombocytopenia is an autoimmune disease, characterised by an isolated low platelet count. Most patients have autoantibodies against platelets that accelerate the removal of platelets from the circulation (retention and destruction by the spleen). During later stages of the disease (chronic ITP) megakaryocyte platelet production may also be impaired as antibodies may impair megakaryocyte development, induce megakaryocyte apoptosis or impede platelet release from bone marrow.

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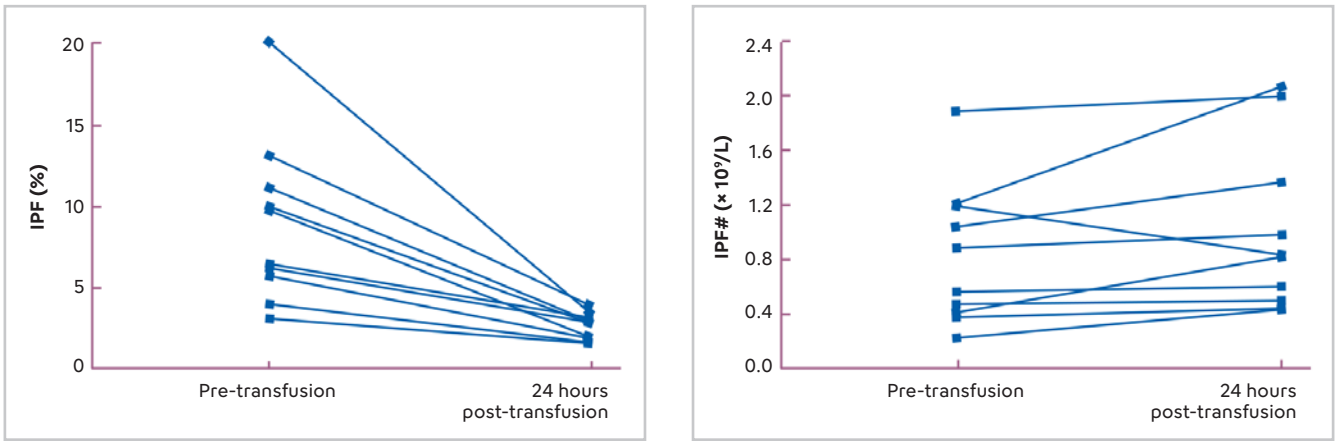

Fig. 1 IPF and IPF# values before and after platelet transfusion. Adapted from Have *et al.* [1].

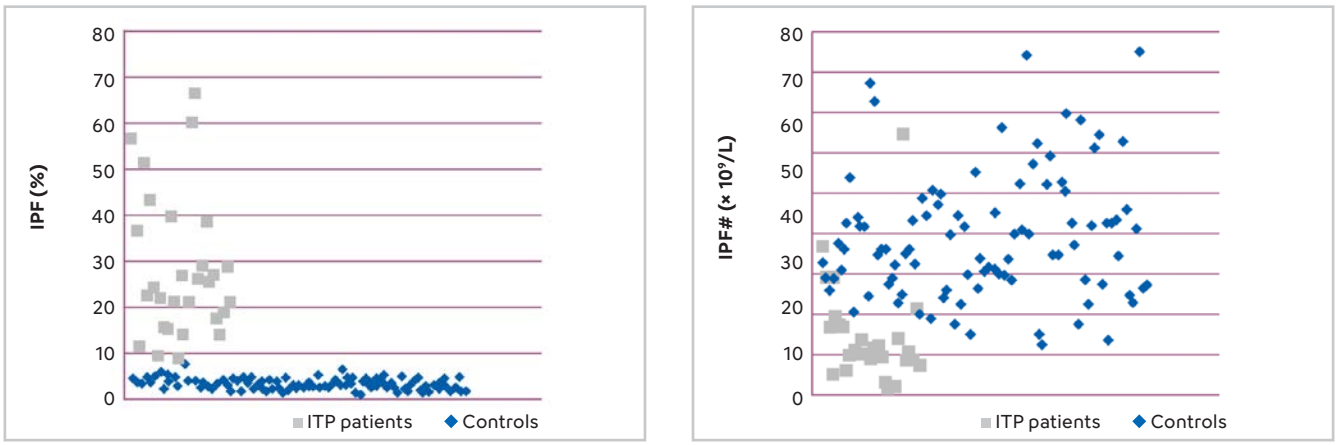

Fig. 2 The IPF value is higher in ITP patients compared to the control group. In contrast, the IPF# values suggest that platelet production is generally not increased in ITP patients, as the IPF# value is lower in ITP patients than in the control group. Adapted from Barsam *et al.* [3].

It was previously assumed that platelet production was enhanced in ITP to compensate for the accelerated platelet destruction. However, there is now substantial evidence that platelet production is often impaired or suboptimal given the rate of platelet destruction.

Given that ITP's pathophysiology is multifactorial, patients' response to treatment is also variable. ITP treatments often raise the platelet count acutely, but patients frequently relapse once treatment has been stopped and therefore require retreatment. The typical response time depends on the patient and the specific treatment used. As IPF# is independent of the total platelet count, it can support to assess the pathophysiological mechanisms and treatment response of ITP.

The immature platelet count (IPF#) can support the assessment of real-time platelet bone marrow response to ITP treatment and provides additional insight into the mechanisms of treatment.

Barsam *et al.* investigated the use of immature platelet indices (IPF, IPF#) for assessing treatment effects in ITP patients. Initially, IPF# was lower for the majority of ITP patients than for healthy controls (3.2 versus 7.8 × 10^9/L, respectively), but IPF was higher (29.2 % versus 3.2 %, respectively), as illustrated in Fig. 2 [3]. The IPF# value suggests that platelet production is generally not increased in ITP patients.

Further, the authors concluded that the IPF# is beneficial for assessing the mechanism of treatment taking effect in ITP. The IPF# could distinguish whether the observed increase in platelet count was due to increased platelet production or inhibition of antibody-mediated platelet destruction. Seven out of seven patients responding to RhoD immune globulin (IV anti-D) and six out of eight patients responding to intravenous immune globulin (IVIg) did not have corresponding increases in IPF#. Two out of eight patients with IVIg and the only patient treated with IV anti-D and IVIg had significant increases in IPF#.

This supports inhibition of platelet destruction as the primary mechanism of IV anti-D and IVIg, although IVIg may also enhance thrombopoiesis (Fig. 3) [3].

> The IPF# parameter can help in the identification of non-responders and poor responders to thrombopoietic agents early on.

The authors also found that non-responders to thrombopoietic agents had increased numbers of abnormal and apoptotic megakaryocytes in their bone marrow without an increased IPF#. This suggests that antibodies blocked the release of platelets into the blood circulation, and it shows that platelet production is not necessarily increased in ITP, as the absolute number of newly produced platelets is low. It can be concluded that the use of IPF# lets one support in the identification of non-responders and poor responders to thrombopoietic agents early on [4, 5].

Increased immature platelet counts are associated with a lower risk of bleeding due to the higher reactivity and haemostatic potential of immature platelets

Predicting which patients are at the highest risk of bleeding is important for identifying those who will benefit most from platelet concentrate treatment. Patients with similarly low platelet counts differ in their tendency to bleed. Some patients have bleeding manifestations at platelet counts of 20 × 10^9/L, whereas others rarely bleed. As shown in Fig. 4, the majority of patients with severely low platelet counts does not suffer from severe bleeding [6]. Consequently, one cannot rely on platelet counts alone to determine bleeding risk.

Greene *et al.* measured the IPF# in 112 ITP patients to investigate whether the immature platelet count correlates better with the acute bleeding score than the total platelet count or mean platelet volume (MPV). The IPF# demonstrated a stronger correlation with the acute bleeding score than total platelet counts among all subjects (Fig. 5) [7], while the MPV did not significantly correlate with the acute bleeding score in any analysed cohort.

A possible explanation for the correlation found by Greene *et al.* is that immature platelets have a higher haemostatic potential compared to mature platelets, as demonstrated by several studies [8, 9]. Young, newly formed platelets with residual amounts of RNA are more reactive and have higher haemostatic potential since they are able to produce and release more thrombogenic substances (e. g. thromboxane

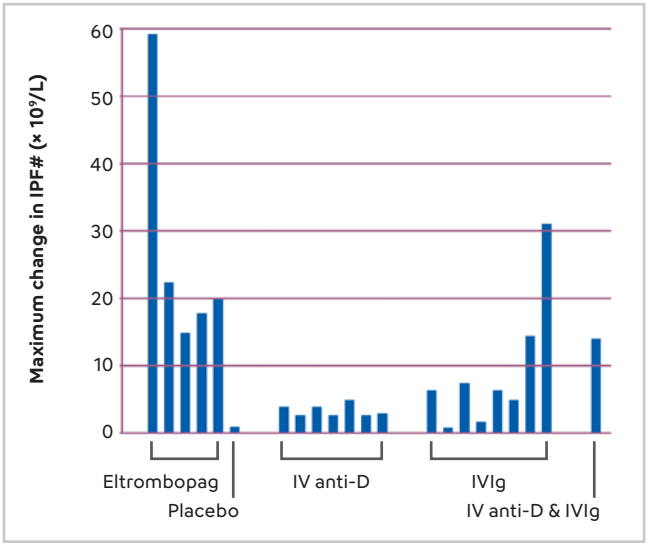

Fig. 3 Maximum observed change in IPF# value within 10 days after various treatments in patients with ITP. Adapted from Barsam *et al.* [3].

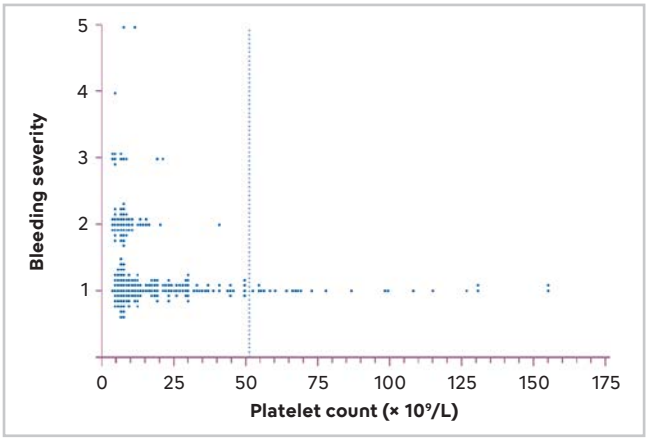

Fig. 4 Distribution of adverse bleeding events by severity and platelet count in patients with chronic ITP. Each point represents one adverse bleeding event. Adapted from Gernsheimer *et al.* [6].

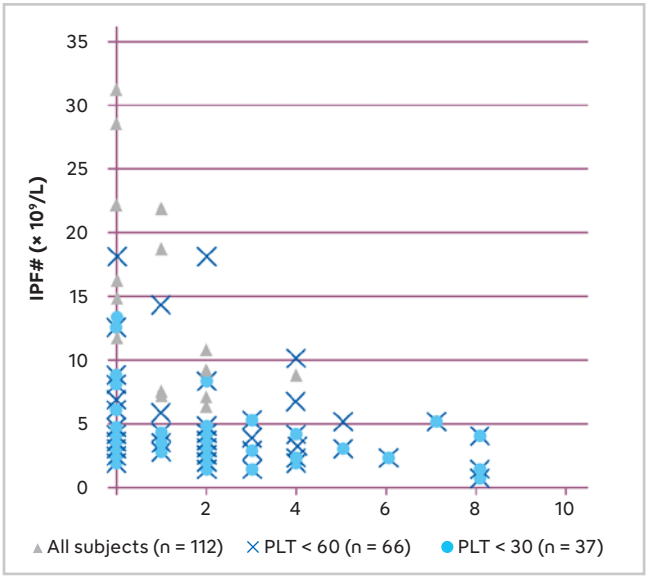

Fig. 5 Correlation of the immature platelet count (IPF#) with acute bleeding score (ABS). Adapted from Greene *et al.* [7].

TX) and to express more specific surface receptors (e. g. glycoproteins GPIIb/IIIa, P-selectin (CD62P)), which are important platelet activation markers.

The study from Guthikonda *et al.* found that the proportion of circulating immature platelets (determined by immune flow cytometry) correlates strongly with platelet activation and aggregation. Ninety patients were stratified into tertiles according to platelet size and the proportion of immature platelets. Of all immature platelets, 61% were present in the pool with the largest platelets, compared to 7% of all immature platelets present in the pool with the smallest platelets (Fig. 6). A higher expression of both GPIIb/IIIa and P-selectin was found in the pool with the largest platelets compared to the pool containing the smallest platelets. Platelet aggregation was significantly higher in the upper tertile of platelets compared to both the middle and lower tertiles (Fig. 7) [8].

The value of determining immature platelet counts has been recognised and implemented by some clinicians. For example, Cremer *et al.* proposed a novel clinical score for bleeding risk in thrombocytopenic neonates, which, besides clinical factors, contains the immature platelet count [10]. Furthermore, Parco *et al.* investigated whether transfusion solutions with high immature platelet counts (during autologous peripheral blood stem cell transplantation) reduce the occurrence of bleeding and haemorrhagic complications. The 20 patients who received solutions with a high IPF (3–9%) required 83 transfusions while the 20 patients who received transfusions with a low IPF (0–1%) required 129 transfusions. Consequently, prophylactic transfusions decreased from three to two per week [11].

Conclusion

The total platelet count is not sufficiently informative when monitoring ITP, predicting response to its treatment or assessing the bleeding risk. Thrombocytopenia in ITP is due to impaired platelet production as well as accelerated platelet destruction and the immature platelet count can provide valuable supportive information about the patient's response to treatment.

IPF# is a haematological diagnostic parameter available directly from a routine blood test that can be performed together with the complete blood count.

The IPF# value is a measure of real-time bone marrow response and reflects the absolute number of newly produced immature platelets released into peripheral blood.

The immature platelet count can be used in ITP as a supportive information to assess whether the treatment mechanism is having an effect: To have a supportive parameter to answer the clinical question as to whether the observed increase in the platelet count is due to increased platelet production or inhibition of antibody-mediated platelet destruction.

Due to the higher reactivity and haemostatic potential of immature platelets, an increased immature platelet count was also found to be associated with a lower risk of bleeding with severely thrombocytopenic patients.

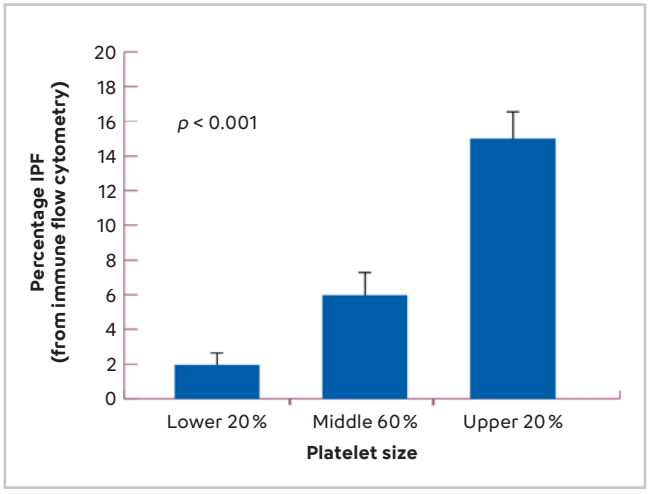

Fig. 6 Percentage of immature platelets in the lower 20%, middle 60% and upper 20% platelet size pools. Adapted from Guthikonda *et al.* [8].

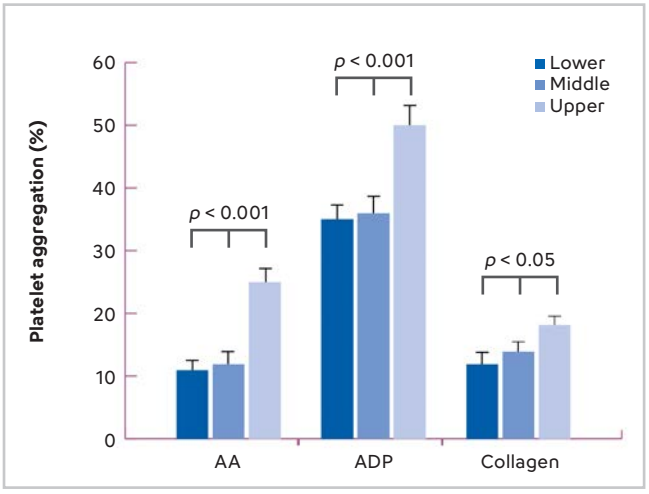

Fig. 7 Platelet aggregation in response to 1.5 mmol/L arachidonic acid (AA), 5 µmol/L adenosine diphosphate (ADP) or 1 µg/mL collagen (tertiles according to platelet size). As described above, the upper tertile contains a high proportion of immature platelets. Adapted from Guthikonda *et al.* [8].

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