Review

Applications of Extended Platelet Profiles in Clinical Practice

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Applications of Extended Platelet Profiles in Clinical Practice

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Abstract

Thrombocytopenia is a frequent complication of patients presenting emergently across the world for a wide array of etiologies. From patients who develop thrombocytopenia due to invasive neoplastic disease affecting the bone marrow to patients who developed immune-complications secondary to formation of auto-antibody responses that drive patients' platelets counts lower or even infection, stress the clearest need of prompt tests to discern the more likely thrombocytopenic-inducing cause. It is in this setting that looking at other platelet variables easily obtainable from modern hematology analyzers have gained traction. One of these elements found in extended platelet profiles are immature platelets (youngest and newly released platelets) also known as reticulated platelets depending upon the platform performing the measurement. Among the advantages of obtaining these counts is that it represents the immediate responses by the bone marrow to the thrombocytopenia and depending on etiology inducing the thrombocytopenia it also provides information of the marrow response to therapeutic approaches. It is in this context that this review will present information of how these relatively novel platelet parameters can be used in clinical practice and how they can be a rapid gauge of the body's response to disease processes leading to thrombocytopenia. Thrombocytopenias resulting from infection (sepsis), autoantibody formation (immune thrombocytopenia and immune-mediated thrombotic thrombocytopenic purpura), immune dysregulation (systemic lupus erythematosus), and iatrogenic (drug-induced) will be discussed and be used to explain how these young platelet measurements can provide valuable clinical information.

Keywords: platelet profile; thrombocytopenia; immature platelet fraction; absolute immature platelet count; sepsis; ITP; TTP; SLE; inflammation

1. Introduction

Diseases that lead to thrombocytopenia not only cause changes to platelet counts in circulation, but also trigger a sequence of events resulting in either higher or decreased output of new platelets from the bone marrow. Some of these etiologies can be immunologic affecting platelets either directly or indirectly, iatrogenic, or secondary to mechanistic deficiencies in the bone marrow itself. Etiologies affecting new platelet production, and especially platelet counts, represent clinical challenges not only to diagnose but also to treat. These etiologies at times cannot be treated by just transfusing more platelets, since the disease can be made worse by transfusion. Thus, laboratory testing that determines the type of thrombocytopenia affecting the patient is of the utmost importance.

Nowadays there is a better understanding of diseases caused by immune dysregulation leading to autoantibody formation to either platelets, platelet mediators or to molecules needed for proper platelet function. Thrombocytopenia can be segregated into three "severity categories". A patient with a platelet count of 100 - 150 x 10^9/L is considered mild, moderate are patients with counts 50 – 100 x 10^9/L, and severe is reserved for patients with counts <50 x 10^9/L [1]. Diagnostically, however, there are still challenges differentiating etiologies since thrombocytopenic presentations can have overlapping

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clinical pictures that make discerning a particular entity difficult [2]. An example of this is malignant conditions with different degrees of thrombocytopenia that are confused with immune thrombocytopenia (ITP) [3]. For this reason, biomarkers that improve diagnostic capabilities in a time-efficient manner are needed. An ever-expanding literature has developed over the last two decades outlining the benefits of obtaining a more complete platelet profile to differentiate thrombocytopenic presentations. One of these approaches, is looking at the immature platelet fraction (IPF) also known as reticulated platelet percentage, which represent the youngest platelets found in circulation, recently released from the bone marrow, and reported by modern automated hematology analyzers with fluorescence capabilities [4-9]. From IPF, other variables can be derived such as the absolute immature platelet count (A-IPC). These counts have been used across thrombocytopenic states to discern a given etiology providing timely information in clinical settings [4-9].

Immature platelets are significantly larger, with higher RNA content, and more biochemically active than mature platelets [10]. As a result, they have greater sensitivity to chemotherapy and irradiation, and can be found to be elevated above reference ranges in response to immune conditions targeting platelets [10,11]. Notably, they are stable in a specimen even 24 hours after phlebotomy and counts can still be obtained within this time frame [10,12]. In consumptive thrombocytopenic processes and those due to platelet hypoproduction, low A-IPCs are a frequent finding [13]. These low immature platelet counts often suggest that a given etiology has a direct effect over the bone marrow [6,14]. Importantly, A-IPCs have been reported not to be influenced by neither gender [15] nor age and their production is maintained as we age [16]. For example, among maternal thrombocytopenia predictors of a favorable response to intravenous immunoglobulin (IVIG) therapy is an IPF of 16% [17].

Immature platelets can be measured with a complete blood count (CBC), emphasizing that obtaining extended platelet profiles that include A-IPC does not delay timely results. As hematology analyzers become more advanced, analytical times have been further reduced. Improvements in dyes, gating adjustments to improve specificity, size correction, and wavelength detection have made obtaining counts fast and highly reproducible [18-20]. These improvements have also allowed for the development of protocols that sort and isolate immature platelets making it possible for research to be carried out on these platelets [21,22]. Importantly, preclinical variables such as time from collection, extent of platelet activation, anticoagulant used, and matrix elements such as degree of hemolysis do not necessarily impede immature platelet testing [18,23-26]. However, one factor that limits their application is that testing requires establishment of reference intervals for results interpretation [18,19].

It has been reported that A-IPC changes precede mature platelet count changes by 2-3 days [27-29]. One of these patient populations showing that immature platelets are a useful biomarker is hematopoietic stem cell transplant recipients, who show increases in A-IPC that foretell platelet count recovery and thus engraftment [27,30,31]. On the other hand, patients with bone marrow failure or invasive disease that involves the bone marrow would have low A-IPCs that does not compensate for existing thrombocytopenia [4]. Thus, we will present current literature describing how immature platelets are being used as earlier biomarkers to diagnose and treat thrombocytopenia-inducing etiologies.

2. Immature Platelets in Sepsis

Sepsis is characterized by dysregulated host response to infections resulting in organ dysfunction with potentially life-threatening consequences [32,33]. Sepsis is one of the most frequent causes of death worldwide, and it has been estimated that the global annual sepsis incidence is around 276-678/100,000 persons with case fatality ranging from 22.5 to 26.7% [34]. Multiple biomarkers exist for detection of sepsis that allow for earlier intervention to reduce morbidity and mortality. In this regard, lactate (LA), C-reactive protein (CRP), and procalcitonin (PCT) are some of the most commonly used biomarkers for sepsis; however, these are not specific to sepsis and research is ongoing to identify additional markers to improve early sepsis detection [35-37].

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Activation of coagulation has been implicated in the pathogenesis of severe sepsis and thrombocytopenia has been linked to poor prognosis in critical illness [38,39]. Since IPF is a measure of immature platelets that often increases prior to thrombocytopenia, this has motivated research into exploring its use as an easily accessible biomarker for sepsis [7]. Multiple studies, involving primarily intensive care unit (ICU) patients in both adult and pediatric settings, have reported significantly higher IPF values in patients with sepsis [40-42]. In an observational study of ICU patients over a period of 7 days, it was found that there was an increase in mean IPF for both patients with sepsis on admission (4.1%) and patients who developed sepsis within the observational period (5.3%) when compared to patients without sepsis (3.0%) [40]. Importantly, significantly higher IPF was also noted in patients 2-3 days before the diagnosis was made suggesting a potential use of IPF as an early maker for predicting the development of sepsis. These findings were corroborated by a separate study that looked at A-IPC and quantified the risk of developing sepsis in the ICU as a 13% increase in risk for every unit increase of A-IPC [41]. In the pediatric ICU (PICU) setting, it has been reported a higher IPF in patients with sepsis; however, in these cases, IPF showed only moderate performance in differentiating septic from non-septic patients with an AUC of 0.642 compared to the AUC of CRP (0.796) and PCT (0.828) [42]. It is important to note that at the optimal IPF cut off of >2.7%, its positive predictive value, negative predictive value, and accuracy were on par with PCT, the best performing biomarker, suggesting a possible influence of sepsis prevalence on diagnostic performance. While the IPF observed in many studies were statistically significant, there was considerable range and overlap of the values between patients with and without sepsis, which may partially explain differences in IPF diagnostic performance. On the whole despite reported differences, IPF appears to be useful in identifying ongoing sepsis and is comparable to established biomarkers such as CRP, PCT, LA, and immature granulocytes. A summary of the measured mean or median IPF is presented in Table 1.

Table 1. Summary of studies and their reported IPF in control groups and sepsis/sepsis related conditions. IPF values are expressed as either mean ± standard deviation or median (interquartile range (IQR)) or median (range) as indicated.

Study	Study Population	No Sepsis/Sepsis Related Condition IPF	Sepsis/Sepsis Related Condition IPF	Optimal Cutoff Value for IPF for Diagnosing Sepsis
[41]	ICU 21 developed sepsis during study 41 without sepsis	Median 4.7 (3.2-7.1) IQR	Median 6.3 (4.8-9.5) IQR	n/a
[40]	Adult ICU 31 with sepsis 33 developed sepsis during observation period 31 without sepsis	Mean 3.0±1.6	Mean 5.2±2.6 in those who developed sepsis during observation period Mean 4.1±2.5 in those with sepsis	>4.7%
[43]	Adult patients 153 blood samples for culture	Mean 1.79±0.63	Mean 4.86±2.67	n/a
[44]	Adult ICU 11 with sepsis	N/A	Mean 3.6±2.6 for patients with sepsis Mena 6.2±3.0 for patients with severe sepsis/septic shock	n/a

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[45]	12 with severe sepsis/septic shock NICU 16 with transient tachypnea of newborn 14 with congenital pneumonia	Mean 2.93±0.75	Mean 4.62±2.53	>2.9%
[46]	NICU 50 early onset sepsis 56 late onset sepsis 44 control patients	Median 3.7 (0.9-6.5) range	Median 9.2 (4.4-39.2) in early onset sepsis Median 14.6 (6.1-32.3) in late onset sepsis	>5.5% in early onset sepsis >6% in late onset sepsis
[47]	Adult 45 patients with lower respiratory tract infection 39 healthy patients	Mean 1.72±0.77	Mean 2.76±2.27	n/a
[48]	Adult 215 septic patients with 64 complicated sepsis and 151 complicated sepsis 97 non-septic patients separated into non-septic and non-septic with local infection	Median 2.9 (1.1-5.8) range for non-septic patients Median 3.2 (1.1-11.3) range for non-septic patients with local infections	Median 4.1 (0.8-25.6) range for uncomplicated sepsis Median 5.3 (0.8-37.4) range for complicated sepsis	>4.1
[49]	Adult admissions 75 with bacteremia 75 without bacteremia	ΔIPF of 0.7 (8-39) IQR	ΔIPF of 1 (0.4-3.6) IQR	>3.4
[42]	PICU 125 critical patients with 78 being septic and 47 non-septic 65 healthy controls	Median 0.85 (0.56-1.3) IQR	Median 2.2 (1.2-3.5) IQR	>2.7

Detection of bacteremia is one of the key criteria of sepsis, but traditional culture can take 2-4 days, delaying targeted intervention [50]. In an early study involving 153 adults showed that blood culture positive samples had a higher mean IPF of 4.86% compared to a mean of 1.79% in those who were culture negative [43]. This finding is supported by a clinical study in late preterm neonatal patients with respiratory distress that demonstrated higher IPF in patients with infectious causes vs. those without [45]. Using an IPF cutoff of >2.9% measured 12-24 hours after birth, the authors concluded that IPF can moderately predict pneumonia with a sensitivity of 65% and specificity of 71.4%. This correlation between infection and higher IPF levels was also noted in adult populations [47]. Furthermore, the observation that IPF dropped within 48-72 hours after initiating antimicrobial therapy, further strengthens the linkage between IPF and bacteremia, while lending support to its potential use as an early predictor of culture positivity and antimicrobial response [45].

In addition, for earlier detection of sepsis, there has been interest in determining if there is a relationship of IPF to sepsis severity. In one small study comparing IPF in 11 patients with sepsis and 12 patients with severe sepsis or septic shock as defined by sepsis severity scores, the mean IPF was

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significantly higher in patients with severe sepsis or septic shock (6.2%) compared to less severe form of sepsis (3.6%) [44]. This trend was corroborated in a later larger study where a significantly higher median IPF was found in patients with complicated sepsis (5.3%) compared to uncomplicated sepsis (4.1%), both of which were in turn higher than the IPF of patients without sepsis (2.9%) [48]. By contrast, while the authors concluded that IPF can discriminate between septic and non-septic patients, it performed less well at differentiating between uncomplicated and complicated sepsis, having only a moderate sensitivity of 64.9% and specificity of 53.1% when using the optimal cutoff IPF of >4.1%. Concurrently, in an ICU study of septic patients, higher IPF (4.3% median compared to 2.1% in controls) was identified 1-5 days prior to fall in platelets, signaling severe sepsis [51]. Multivariate cox regression additionally revealed that IPF was an independent predictor marker for 28-day mortality with an accuracy rate on par with the sepsis severity score, acute physiology and chronic health evaluation II (APACHE II) (AUC 0.886 for IPF vs 0.857 for APACHE II). Furthermore, the authors noted that a combination of IPF and APACHE II score increased AUC of 28-day mortality to 0.912. By contrast other variables such as CRP, PCT, and coagulation markers showed either low AUC or did not reach statistical significance.

Thus far, the discrepancies in predictive performance of IPF for sepsis may be attributed to different measurements, distinct hematology analyzers, and individual variations in values. As a consequence, other studies moved away from singular measurements of IPF towards a measurement of change in IPF (ΔIPF) in order to minimize individual variations [49,52]. While these studies confirmed ΔIPF to be significantly higher in patients with sepsis or bacteremia, there were persistent differences in the performance of ΔIPF prediction of sepsis. One of these studies indicated that the change in IPF (ΔIPF) from day 1 to day 2 of ICU stay provided a strong predictor for sepsis with an AUC of 0.9113, vastly higher than that of CRP or PCT whose AUC were 0.6233 and 0.6579 respectively [52]. At the optimum cutoff ΔIPF of 1.95% the authors noted a relatively strong sensitivity of 75.00% and an excellent specificity of 95.95%. Importantly, they reported that a combination of ΔIPF and day 2 PCT, provided a positive predictive value and negative predictive value of 100% and 96.10%, respectively. In the second study, they defined ΔIPF as the difference in IPF between the day the blood culture sample was collected and the IPF from the day before [49]. A ΔIPF cutoff of >3.4% conferred higher specificity of 97.3% in predicting bacteremia but with low sensitivity of 25.3%. Similar to the prior study, combination of both ΔIPF and PCT led to improved diagnosis resulting in excellent sensitivity of 90.5% and a moderate specificity of 56.6%. When they looked at the 30-day mortality in relation to ΔIPF within the bacteremia group, they found a significantly higher value in those who did not survive (2.7% in non-survivors compared to 0.8% in survivors); the 30-day mortality prognosis of ΔIPF at a cut off of >1.5% showed similar prognostic performance to PCT.

Infections lead to decreases in mature platelets as the body fends off infectious agent(s). Notably, even though thrombocytopenia occurs during infections, A-IPCs are mostly maintained so that platelet production attempts to keep up with the higher consumption [53]. These A-IPC increases seemed to correlate with a higher mortality risk and disease severity in septic patients [54]. These observed increases in immature platelets occur earlier in patients prior to sepsis onset [41], and are predictive of subsequent decreases in mature platelet counts once infection sets in [51]. This may be due to the significant immune hyperreactivity under states of severe infection resulting in disseminated platelet consumption requiring a higher immature platelet output. However, these increases are not seen in neonates where suppressed A-IPC characterizes those patients who did not survive disseminated infections [55]. Along these lines, older children who recovered from dengue fever had increased immature platelet outputs up to 3 days prior to recovering their platelet count [56]. Therefore, in infections, the negative feedback between immature platelets and mature platelets appears preserved in older children and adults contrary to neonates.

In summary, studies indicate a significant correlation between increased IPF and A-IPC in patients with sepsis or who are at risk of developing sepsis. Unlike, other markers, immature platelets help predict sepsis severity. Likewise, compared to other markers such as CRP or PCT, immature platelets can be performed off of a CBC, making it an attractive sepsis biomarker. Despite these

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advantages, there is currently no consensus in the optimal cutoff value of IPF or when and how often IPF should be measured, which explains the differences in IPF performance in predicting sepsis. Furthermore, while significant differences were noted in mean IPF in sepsis compared to non-sepsis, IPF values had a wide range with overlap between the two groups that further complicated test performance. Nevertheless, even though it remains unclear if immature platelets are sufficient as a standalone biomarker, integration of IPF in the laboratory workup of sepsis along with traditional biomarkers contribute towards earlier sepsis detection.

3. Immature Platelet Count Changes in ITP

ITP is a clinical syndrome involving extensive platelet destruction secondary to autoantibody production, oxidative stress and limited megakaryopoiesis [57]. The latter becomes important when considering IPF as a diagnostic biomarker. It has been two decades since an early report indicated that increases in IPF from its baseline was evident in patients with ITP during acute presentations or disease exacerbations, which was indicative of bone marrow response to the thrombocytopenia [58]. This results in a higher platelet distribution width due to the higher proportion of large young immature platelets found in circulation [59]. In this disease, the degree of platelet destruction and resulting thrombocytopenia appear to determine the higher risk of associated bleeding [60]. In ITP, IPF tends to be significantly higher compared to controls and patients with bone marrow failure, specifically $\geq$25% of platelets in circulation are immature and this increase can be an independent predictor of ITP diagnosis [61]. This however, becomes of greater significance when A-IPC changes are analyzed. An A-IPC of 2.1 x 10^9/L or better has been suggested as diagnostic to differentiate ITP from aplastic anemia [62]. As a result, it has been proposed to use an algorithm that takes isolated thrombocytopenia without evidence of dysplasia in peripheral blood, normal to high thrombopoietin, and IPF at the upper limit of normal to suspect an ITP diagnosis [63]. Furthermore, lower platelet counts uniformly leads to a much higher IPF (27%) in new ITP patients compared to patients with higher platelet counts at presentation [64].

It has been reported that changes in A-IPC characterize ITP patients responding to treatment [9,65]. Pre-treatment A-IPC appears specific and indicative of treatment response to dexamethasone in ITP when compared to other variables measured to establish disease response [66]. On the contrary, additional variables such as platelet sialylation have failed to prove utility in disease diagnosis and management since it does not differ between patients with ITP and those with inherited forms of thrombocytopenia (IT), even though platelets are in a higher activated state in ITP compared to IT [67]. Recently, a study suggested that pseudothrombocytopenia is closely associated to ITP, so it is necessary to differentiate them which can be done based on presence of larger platelets (immature) and higher IPF compared to healthy controls [68].

Cumulative evidence indicates that during ITP presentations the bone marrow attempts to compensate for platelet destruction by increasing IPF to cope with the consumptive/destructive pathology [3,9,25,58,69-71]. However, there are measurable differences in the degree of compensation between patients with chronic ITP vs. those with new onset disease. Immature platelet output increases are higher in chronic ITP patients [72]; specially among those patients with a higher bleeding risk [69,73,74]. These bone marrow compensatory increases in ITP patients are even more significant when taking A-IPC changes into account [75]. Along these lines, a greater specificity in predicting bleeding risk is indicated by a significantly low A-IPC [73]. Nevertheless, an isolated study which raised concerns that immature platelet measurement was of limited use in differentiating ITP from other etiologies, acknowledged that this was likely due to the type of hematology analyzer used to derive counts but made such claims without providing A-IPC data analysis [76].

In regard to being used as a biomarker to develop a diagnostic prediction scoring model, an IPF of at least 7% characterizes patients with the disease that is more predictive of disease compared to mature platelet counts [3]. When combined with red blood cell counts, hemoglobin concentration and lymphocyte count, IPF significantly improved the specificity and sensitivity of scoring models [77]. In children scoring models and development of markers are similarly needed to aid in triaging and

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increasing suspicion of the disease. Reports describing that pediatric ITP patients can be readily identified by an IPF of 9.4% from other patient populations, and that this may be used as a threshold to predict prognosis and remission once immature platelets return to baseline are encouraging [72]. A-IPC changes have shown a high positive predictive value [78], with the added benefit that the higher immature platelet counts seen as ITP patients recover from the disease precede by >2 days changes in mature platelet counts [29], similar to data from other thrombocytopenic presentations. Thus, a disease model emerges based on immature platelet counts in which mature platelet counts and immature platelets exist in a negative feedback-type of mechanism. In ITP, as platelets get consumed or destroyed in the periphery due to the immune process, the bone marrow concomitantly responds by increasing immature platelet production to compensate for platelet losses [11], and when platelet counts improve in response to disease therapy, and remission is achieved immature platelet output downtrends and returns to baseline [11,79].

4. Immature Platelet Count Changes in Thrombotic Thrombocytopenic Purpura (TTP)

TTP is a severe type of microangiopathic hemolytic anemia (MAHA) that historically led to significant morbidly and mortality due to formation of diffuse microthrombi affecting organ systems throughout the body [80]. Deficiency of the ADAMTS13 enzyme defines the disease and this can be either innate (congenital) or immune-mediated (i) secondary to presence of antibody to the enzyme [81,82]. To differentiate the two forms, anti-ADAMTS13 antibody would be absent in congenital TTP but detectable in iTTP [83,84]. The antibody formed can be either neutralizing or not depending if the antibody is specific to the spacer domain of the ADAMTS13 molecule [85]. The gold standard test is measurement of ADAMTS13 activity using the fluorescence resonance energy transfer test (FRET) which measures cleavage products of a fluorescently-labeled synthetic vWF peptide, with an activity of <10% considered as diagnostic of TTP [86]. This test, however, is labor-intensive and not available at most institutions, which have to send it out to large reference laboratories. This explains why daily therapeutic plasma exchange (TPE) using plasma as replacement fluid is first line therapy for the disease, and is often initiated empirically as soon as the disease is suspected despite ADAMTS13 results not being available. This is not without potential risks, since TPE using plasma is associated with adverse events such as transfusion reactions and apheresis-associated complications making a timely accurate diagnosis essential [87-89]

Accordingly, alternative test approaches that increase the suspicion for TTP without delaying therapy initiation can be clinically useful. Twenty years ago it was described that the IPF of immune-mediated (i)TTP patients was significantly lower than ITP patients [58]. Reports from our group have shown that patients who were later found to have ADAMTS13 activity consistent with iTTP had A-IPCs at presentation that were significantly lower, below the reference range, than healthy controls and other thrombocytopenic patients without enzyme deficiency [28,90,91]. In patients with refractory disease, A-IPC obtained early in the disease course was useful in establishing therapy needing adjustment [92,93]. In iTTP patients, improvement in A-IPC uniformly preceded by 2 days corresponding changes in mature platelet counts following initiation of daily TPE [28,90,94]; and A-IPC returned to baseline once mature platelet counts normalized [94]. Regardless, the most significant finding was that A-IPC suppression at presentation was seen in all patients who were found to have iTTP, that these counts had strong correlation with ADAMTS13 activity <10%, and that this could be used to rule out most patient who had other MAHA etiologies [95]. Notably, A-IPC suppression or decrease in counts appeared to be not as severe in patients with relapsing disease, and the magnitude of A-IPC decrease appeared to be dependent upon the mature platelet count [95,96]. A-IPC also predicted response to TPE in patients with high ADAMTS13 inhibitors who for the most part required a greater number of procedures to restore platelet counts [94,97]. A-IPC measurement had the added benefit that it identified iTTP or ruled it out even in cases where the PLASMIC score, which has been proposed to increase suspicion of a TTP diagnosis, underestimated or overestimated presence of the disease [97]. Furthermore, unlike the PLASMIC score which has been shown not to

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be useful in pediatric settings, A-IPC specifically identified children with iTTP even among those whom the score suggested disease was not present [97,98].

Etiologies such as pseudo-thrombotic microangiopathy represent one of those MAHA-like presentations that can be confused with iTTP. It is a rare complication of B12 deficiency that can be readily identified by testing for the presence of intrinsic factor antibodies in the setting of normal B12 levels [99]. Even though it is unclear what the immature platelet counts are in such setting due to its rarity, it is worth mentioning that testing for this entity may reveal if similarities or differences exist with A-IPC seen in iTTP. Case in point, in pregnant patients, IPF testing in combination with schistocyte counts readily discerns TTP from HELLP syndrome [100].

Suppressed A-IPC of iTTP patients at presentation suggest either disruption or suppression of the platelet production's negative feedback which is rapidly reversed by initiation of daily TPE [28,90,94]. This finding favors the presence of additional pathological insults needed for an acute iTTP presentation to occur [84]. For example, using the zebrafish ADAMTS13 knockout model, it has been shown that just as in humans there is a higher number of vWF multimers characterized by a marked decrease in the number of immature and mature thrombocytes in a background of erythrocyte fragmentation and inflammation [101]. Based on these observations, a model in which impaired immature platelet/ mature platelet negative feedback is part of the pathophysiology of new onset iTTP [84]. In this disease model, the bone marrow does not respond uniformly to the existing thrombocytopenia with a corresponding increase in immature platelets unless TPE is initiated. Once apheresis is started, A-IPC steadily increases prior to the equivalent change in mature platelet count, and this results in restoration of the platelet production negative feedback. Finally, when mature platelet counts reach a normal nadir, A-IPC returns back to baseline. Future research addressing the mechanism(s) underlying A-IPC suppression and disruption of the negative feedback in iTTP patients is needed.

5. Immature Platelets in Inflammatory Settings

Inflammation-inducing disease processes that result in impaired thrombopoiesis can be triaged looking at immature platelets as shown in patients with impaired liver function/cirrhosis [102]. Similarly, states in which inflammation leads to platelet count changes can be discerned looking at immature platelets. Case in point, high immature platelets in circulation predict those patients at risk of developing subsequent inflammation post cardiac surgery [103]. Even a week after surgery, a correlation between pro-inflammatory interleukin (IL)-6 in patients and immature platelet counts has been reported [104]. In theory, increases in immature platelets may be directly stimulated by IL-6 since this cytokine leads to thrombocytosis and platelet activation in intestinal inflammatory presentations [105]. However, this higher risk may be related to cardiovascular disease itself since human immunodeficiency virus (HIV) patients on antiretroviral therapy with cardiovascular disease have a significantly higher number of immature platelets compared to HIV patients on similar therapy without cardiovascular disease [106].

Thrombocytopenia can be seen in patients with systemic lupus erythematosus (SLE), but this tends to be a rare complication of the disease accounting for only 3-10% of cases. For example, in a patient with SLE who received steroids for over a decade to treat SLE-induced autoimmune hemolytic anemia, thrombocytopenia manifested as nasal bleeding, petechiae, and purpura with findings suggestive of ITP [107]. Laboratory examination revealed that thrombocytopenia presented with hypocomplementemia, and positive anti-cardiolipin and anti-β_2-glycoprotein I IgG antibodies. Steroid pulse therapy, followed by high dose prednisolone and hydroxychloroquine on alternate days resulted in increase in platelet count with concomitant decreases in IPF from 14.9% to 6.3%. Anti-cardiolipin and anti-β_2-GPI antibodies, considered to be associated with thrombocytopenia and higher risk of thrombotic events, led to aspirin use after platelet count normalization to prevent thrombosis [107]. Likewise, immature platelets appear to correlate with SLE disease activity. In a large cohort of 282 SLE patients, it was shown that 12.4% of patients had thrombocytopenia [108]. Importantly, even though IPF correlated with platelet count, A-IPC was significantly better as a

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marker in relation to disease activity index. Both, disease severity index and thrombocytopenia were independent parameters that accounted for immature platelet increases. Notably, the probability of clinical remission in AIPC-high patients was higher than in AIPC-low patients, indicating that as a biomarker it is better at predicting response to steroids in thrombocytopenic patients with SLE [108].

Inflammation is also associated with hypertension and this leads to cardiovascular disease and other complications [109]. This can be seen in patients with malignant hypertension who developed thrombocytopenia with significantly higher immature platelet counts that differentiates them from patients with other microangiopathic hemolytic anemia processes such as TTP [91,110]. Possibly, sheer forces in hypertension lead to vascular damage and platelet consumption which drive higher immature platelet output from the bone marrow. Notably, just as seen in other inflammatory presentations it appears that changes in A-IPC allows for a better distinction between preeclampsia and those patients with hemolysis, elevated liver enzymes, and low platelet count syndrome [110]. Smoking represents an inflammatory insult that causes vascular stenosis resulting in hypertensive changes and higher concentration of immature platelets [111]. Interestingly, low grade inflammation may not provide enough of a stimulus to drive immature platelet production [112]. Without question additional research is required to further understand the role that immature platelet changes plays in inflammatory presentations.

6. Immature Platelets and Drug-Induced Presentations

Immature platelets have been used to establish when drugs affect thrombopoiesis [113]. In heparin-induced thrombocytopenia (HIT), antibody-mediated reactions to complexes that include platelet factor 4 are driven by heparin use. Since platelets are removed from circulation by the presence of antibodies to PF4-heparin complexes, changes in immature platelet output occurs. Increases in IPF have been reported in samples tested during HIT investigations [114]. Of interest, patients who tested positive (HIT^+) for the presence of anti-PF4-heparin antibodies have A-IPC similar to the reference range unlike patients who tested negative and had immature platelets well below this range [115]. This appears to indicate that HIT^+ patients have immature platelet responses that attempt to maintain the platelet count not necessarily in sufficient amounts. These results indicate that further research to indicate the mechanisms by which the body, and specifically the bone marrow, compensates in setting of drugs leading to thrombocytopenia are needed.

7. Conclusions

This review has presented a growing body of evidence indicating use of immature platelet measurements in a variety of thrombocytopenic settings [27,53,75,115,116]. Studies in the presented clinical areas are not all inclusive since new reports are published showcasing the use of these counts. Yet, these reports support the development of clinical trials looking at how immature platelet counts change during a disease presentation and can promptly provide clinical information to affect therapy timing [117]. This greater understanding of immature platelets will depend on deriving adequate reference ranges to minimize discordant results as those seen in some literature due to the use of different hematology analyzers. Importantly, since newer analyzers will have higher specificity and sensitivity ranges, such reference ranges will need to be revised as needed. In summary, immature platelets are equivalent to reticulocyte counts in the setting of anemia and thus provide information to clinicians when treating thrombocytopenic patients. The added benefit is that immature platelet counts provide real-time information of bone marrow responses to the etiology-driven thrombocytopenia; and once therapy is initiated, it can indicate how therapy results in changes in the production of these young platelets.

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