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Immature platelet fraction as a useful marker in the etiological determination of thrombocytopenia

Imtiaz Ali[a,b], Ciaren Graham[c], and Nina C. Dempsey-Hibbert[b]

[a]*Haematology Department, Airedale General Hospital, Steeton, UK;* [b]*Centre for Bioscience, Manchester Metropolitan University, Manchester, UK;* [c]*School of Biological Sciences, Queen's University Belfast, UK*

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The etiology of thrombocytopenia is important in treatment and management of the condition. Most platelet parameters that are routinely analyzed in the diagnostic laboratory have not proven useful in identifying the etiology, while specialized assays suffer from poor standardization and lack of agreement between laboratories. The immature platelet fraction (IPF), which indirectly provides a measure of bone marrow function, is showing promise as a valuable marker of thrombopoietic responses. This study set out determine whether the IPF could effectively identify specific underlying etiologies of thrombocytopenia in a large thrombocytopenic cohort, to allow for quicker, more effective management of the condition. The IPF was analyzed in a large cohort of 637 thrombocytopenic patients and 171 healthy control patients on the Sysmex XN 10 hematology analyzer using the specialized fluorescence optical analysis. The thrombocytopenic patients were divided into six cohorts based on etiology. The IPF% was significantly higher in cases of increased platelet consumption (median = 9.55, min = 1.1, max = 77.9) or pseudothrombocytopenia (median = 13.1, min = 0.4, max = 28.8) compared with control (median = 4.2, min = 1.3, max = 12.8). Furthermore, the IPF% was also able to identify idiopathic thrombocytopenic purpura (ITP) ($p < 0.05$) (median = 13.4, min = 2.8, max = 77.9) from other causes of increased platelet consumptive disorders (infection: median = 6.4, min = 1.1, max = 21.6; hemorrhage: median = 8.9, min = 1.2, max = 20.2). By use of this large thrombocytopenic cohort, the IPF% has been found to be of significant diagnostic value, providing a useful rapid test in the etiological investigation of platelet disorders.

Thrombocytopenia is a finding that is common to a number of underlying conditions [1–4]. Accurate identification of etiology is critical to appropriate management of these patients. Thrombocytopenia is defined as a platelet count (PLT) below the 2.5th percentile of a normal platelet distribution, with a concentration $<150 \times 10^9$/L in whole blood [5]. Yet clinically significant spontaneous bleeding does not usually occur until the PLT is $<10–20 \times 10^9$/L. Bleeding episodes can occur at higher PLTs in some patient groups, while in others, a lower PLT can be "tolerated" [5]. This heterogeneity in patient tolerability adds to the difficulty in managing thrombocytopenia in the absence of a definitive cause and means that the PLT is not always relevant when considering severity and need for platelet transfusion.

The cause of thrombocytopenia can be broadly divided into three main categories: (1) reduced thrombopoiesis (2)

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Offprint requests to: Nina Dempsey-Hibbert, Centre for Bioscience, Manchester Metropolitan University, Manchester, UK; E-mail: n.dempsey-hibbert@mmu.ac.uk

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increased platelet destruction or consumption, and (3) abnormal distribution (sequestration) of platelets [6]. However, this can be an oversimplification; there are multiple causes of increased platelet consumption, such as infection, hemorrhage, and immune destruction of platelets, each of which would be managed differently.

Full blood count (FBC) and blood films are used most frequently in the diagnosis of thrombocytopenia as they are cheap, easy to perform, and widely available. Specialized assays such as the thrombopoietin enzyme-linked immunosorbent assay (ELISA), direct platelet immunofluorescence test [7], and drug-dependent platelet antibody test [8] are used less often, suffering from poor standardization and lack of agreement between laboratories [9].

A number of platelet parameters measured as part of the FBC, such as mean platelet volume (MPV), platelet distribution width (PDW), and platelet–large cell ratio (P-LCR), have been reported to be useful in the investigation of thrombocytopenia. MPV was found to be significantly higher in "hyperdestruction" thrombocytopenia than "hypoproductive" thrombocytopenia [10], while both MPV and PDW have been reported be increased in immune thrombocytopenic purpura (ITP) [11,12]. However, these indices are vulnerable to changes in platelet size and volume, which can occur as an artefact between phlebotomy and sample analysis. Indeed, despite the potential for clinical utility evident from these studies, MPV, PDW, and P-LCR have had limited use in clinical practice for thrombocytopenia investigation [13].

The immature platelet fraction (IPF) is analyzed as part of the FBC and may be useful as a rapid, cheap, reliable marker of thrombocytopenic etiology. Immature platelets are those recently released from the bone marrow. They contain small amounts of RNA within the cytoplasm and are more reactive than mature platelets [14]. The number of circulating immature platelets reflects the rate of thrombopoiesis and bone marrow function and, as such, may be useful in the determination of thrombocytopenic etiology [15].

Increased IPF has previously been found in some platelet destruction or consumption disorders and highlights the thrombopoietic response from the bone marrow [16]. IPF has also been reported to be reduced in bone marrow failure cases [16]. However, the majority of published work concentrates on IPF in a small selection of specific disorders (e.g., ITP or following stem cell transplantation). Research looking at larger thrombocytopenic cohorts with a wider range of underlying conditions is warranted. The present study, which included a large sample ($n = 637$) of thrombocytopenic patient samples with varying underlying causes, aimed to determine whether the IPF has potential to be used as a marker in the etiological determination of thrombocytopenia.

Methods

Study overview

The study was performed at the Airedale General Hospital (AGH) Haematology Department (Steeton, UK). Local ethics approval from the AGH Research Governance Department was granted. Ethics approval from National Research Ethics Service (NRES) was not required as all samples were being taken as part of the routine diagnostic workup. Blood samples for FBC were received from 34 hospital wards and 67 general practitioner practices from West and North Yorkshire as part of their investigations. A total of 637 patients were identified as thrombocytopenic (platelet count $<140 \times 10^9$/L, based on AGH reference range). Male and female patients were accepted into the study, and there were no exclusion criteria regarding age. Any patient that had received a platelet transfusion within the previous 30 days was excluded. A control group consisting of 171 patients was identified. These patients were pre-operative patients at AGH who had blood samples taken as part of the normal hospital surgical protocols and were tested for full blood count and IPF. All FBC parameters were within the reference ranges and there was no transfusion history within the previous 30 days.

Sample collection

Blood samples were collected into 4-mL (K2) EDTA vacutainers (Becton Dickinson). All samples were kept at room temperature (18°C–25°C) until testing, as at colder storage temperatures the IPF% rises, leading to false results [17]. All samples were processed within 6 hours from venipuncture, a time frame validated in previous studies [18]. As previously mentioned, although it has been demonstrated that MPV analysis is time-critical and should preferably be performed within 2 hours of venipuncture because of platelet swelling [19], IPF analysis is based on staining with oxazine, which specifically stains platelet RNA [20] and is therefore significantly less vulnerable to the effects of platelet size.

IPF analysis

Blood samples were processed for FBC on the Sysmex XN 10 hematology analyzers as part of the XN 9000 system, (Sysmex Corp., Kobe, Japan) in whole-blood mode. Both platelet impedance (PLT-I) and fluorescence platelet count (PLT-F) were analyzed. The PLT-F provides an accurate platelet count in thrombocytopenic patients using fluorescence flow cytometry. As part of the PLT-F count, an accurate measure of IPF is calculated. The hematology Sysmex XN 10 analyzer was calibrated and then quality controlled every 24 hours using XN CHECK L2 (Sysmex Corporation).

Data handling and statistical analysis

Statistical analyses were performed using GraphPad Prism software, version 5. The D'Agostino and Pearson omnibus test was used to test for normality. The PLT and IPF% for males and females in the control group were found to be normally distributed. For nonparametric data (all thrombocytopenic cohorts), Kruskal–Wallis analysis was employed with Dunn's post hoc testing, and p values < 0.05 were considered to indicate statistical significance.

Results

As expected, there was a significant difference ($p < 0.05$) in the PLT between males and females (data not shown). Males and females were therefore initially treated as two separate groups when considering the PLT for the thrombocytopenic cohorts. However, following further analysis, it was noted that the data trends and statistical differences between etiological groups within each sex group were identical so the PLT data were combined and discussed as one entity. The data for males and females were also treated as a single entity when considering the IPF%. The normal reference range established in the present study was 1.3%–12.8%, which was in keeping with that derived by Ali et al. [21]. However Ali et al. did report on small but significant differences in IPF% between healthy males and females and, therefore, derived two separate reference ranges. The reason for the different findings between studies may simply be sample size, with the present study deriving the reference range from 171 controls, and Ali et al. deriving it from a control population of 2,366 [21].

The thrombocytopenic data were initially grouped into three general etiologies: (1) reduced thrombopoiesis, (2) increased platelet destruction or consumption, and (3) abnormal distribution (sequestration) of platelets. By definition, all etiological groups were shown to have a significantly lower PLT than the control group (Table 1). However, as expected, and shown in similar studies [22], the three thrombocytopenic cohorts could not be discriminated by the PLT (Figure 1A). The IPF was considered in these same three thrombocytopenic cohorts. The IPF% parameter was chosen for this study instead of the absolute IPF count (IPF#) because it has been reported to correlate better with megakaryopoiesis and thrombopoiesis than IPF# in various congenital and acquired disorders except for acute lymphoblastic leukemia (ALL) [23]. As expected, and in agreement with other studies [24,25], analysis of the IPF% in normal samples ($n = 171$) and all thrombocytopenic patients ($n = 637$) (Table 1) revealed a significantly higher IPF% in thrombocytopenia than in the control group, and this was also the case when comparing cohorts within a specific gender. This justified further investigation of the parameter to clarify its usefulness as a marker of specific underlying causes of thrombocytopenia.

Comparison of IPF% in the three etiological groups revealed significant differences between the reduced thrombopoiesis and increased consumption group ($p < 0.01$) and between the increased consumption group and the abnormal distribution group ($p < 0.01$). The high values observed in increased consumption allowed effective discrimination of this etiological group, thereby showing the usefulness of the IPF% in this setting.

Table 1. Patient clinical and laboratory data

Group	Sex	Sample size (n)	Mean age (SD)	Age range	Median PLT ($\times 10^9$/L) (range)	Median IPF% (range)
Reduced thrombopoiesis[a]	Male	55	72.89 (16.87)	15–95	100 (8–139)	5.75 (0.8–39.1)
	Female	21	78.00 (13.45)	46–92	104 (9–134)	5.25 (1.4–54.3)
Increased consumption[b]	Male	51	66.02 (25.87)	1–92	96 (1–138)	8.9 (1.1–36.4)
	Female	71	56.82 (25.26)	6–96	112 (1–139)	9.7 (2.1–77.9)
Drugs[c]	Male	31	72.32 (8.56)	51–89	101 (16–137)	6.4 (2.9–23.1)
	Female	34	66.12 (13.98)	27–87	98.5 (4–138)	5.25 (1.8–24.4)
Abnormal distribution (splenic sequestration)[d]	Male	39	54.54 (12.49)	31–83	99 (26–138)	6.9 (2–19.8)
	Female	25	56.28 (13.64)	35–82	97 (44–139)	5.3 (1.8–14.8)
Pseudothrombocytopenia[e]	Male	83	62.54 (19.78)	1–91	83 (10–138)	13.3 (0.2–28.8)
	Female	94	56.78 (21.86)	1–90	94.5 (1–137)	12.8 (1.9–28.0)
Unidentified etiology[f]	Male	83	67.83 (17.93)	1–95	117 (22–139)	8.8 (1.7–28.5)
	Female	50	61.48 (23.63)	1–100	117.5 (47–137)	6.6 (2.7–26.2)
Normal control	Male	72	62.44 (14.73)	21–84	239.5 (150–365)	4.5 (1.3–12.8)
	Female	99	56.54 (16.88)	25–85	286 (179–447)	4.2 (1.4–10.7)

SD=standard deviation; PLT=platelet count; IPF=immature platelet fraction.

[a]Includes any disorder that affects thrombopoiesis (e.g., chronic lymphocytic leukemia, acute myeloid leukemia, myelodysplastic syndrome, chronic myelomonocytic leukemia, lymphoma, or megaloblastic anemia).

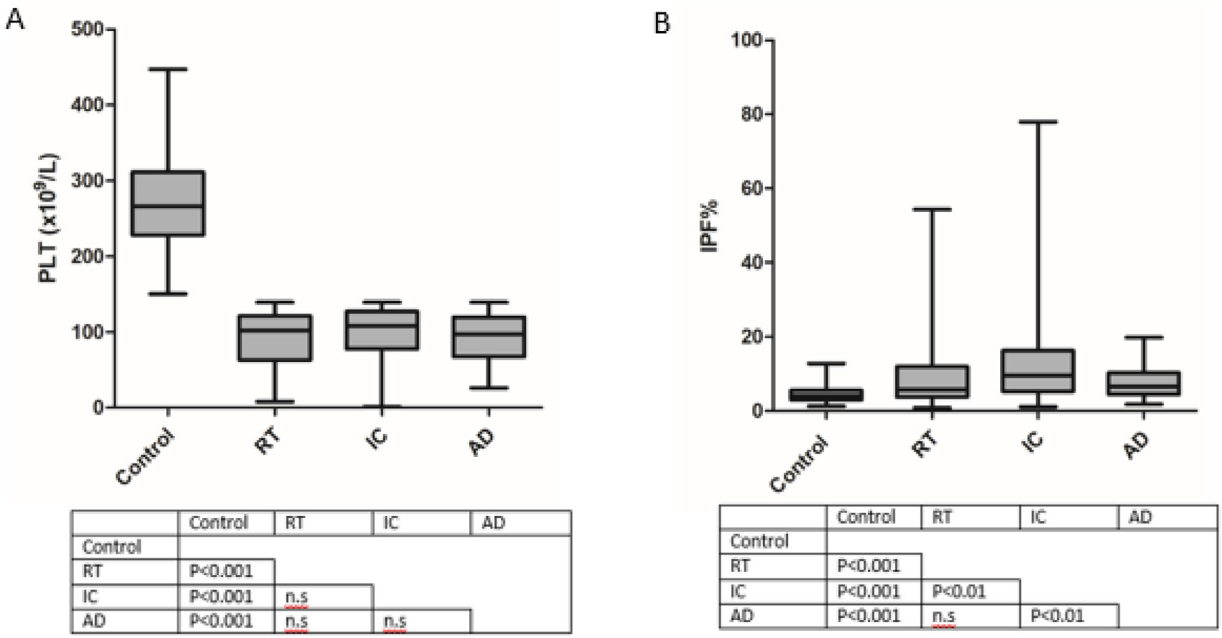
[b]Includes any disorder that resulted in consumption or destruction of platelets (e.g., infections, immune thrombocytopenic purpura, or hemorrhage).

[c]Includes any thrombocytopenia directly caused by administration of a medication (e.g., chemotherapy, methotrexate, sulfasalazine, or antibiotic).

[d]Splenic sequestration group had disorders that resulted in platelet pooling as part of the mechanism of thrombocytopenia (e.g., alcohol-related liver disease, hepatitis, or portal hypertension).

[e]Includes any disorder that showed a low numerical platelet count but was identified as normal from a blood smear (e.g., platelet clumps, platelet clots, or satellitism).

[f]Includes thrombocytopenic cases where no cause can be identified.



	Control	RT	IC	AD
Control				
RT	P<0.001			
IC	P<0.001	n.s		
AD	P<0.001	n.s	n.s	

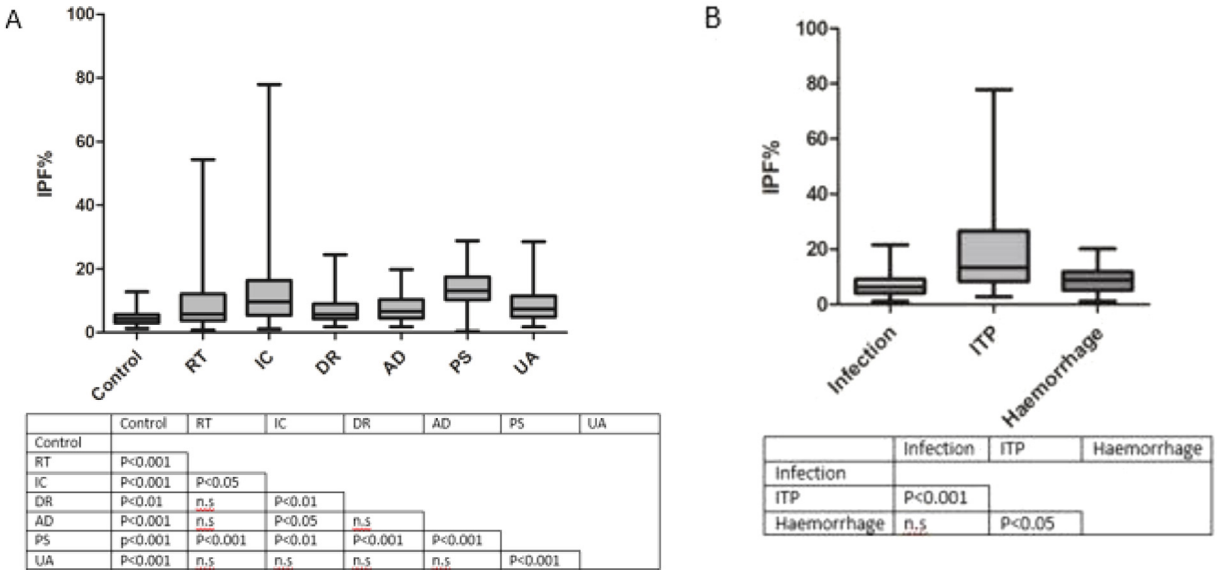
	Control	RT	IC	AD
Control				
RT	P<0.001			
IC	P<0.001	P<0.01		
AD	P<0.001	n.s	P<0.01	

Figure 1. Ability of **(A)** platelet count (PLT) and **(B)** immature platelet fraction (IPF%) to differentiate between three thrombocytopenic cohorts (*RT*=reduced thrombopoiesis, *IC*=increased consumption, *AD*=abnormal distribution). Statistical analysis was performed using the Kruskal–Wallis test with Dunn's post hoc analyzes. Data are presented as the median ± range. Statistical significance between the groups is outlined in the tables in the lower part of the figure.

The data were further subdivided into the six thrombocytopenic cohorts stated in Table 1. The median IPF% values were compared to determine significant differences between the groups (Figure 2A). Surprisingly, the most notable group to be differentiated was the pseudothrombocytopenia group, which had significantly higher IPF% values than all other groups, highlighting the usefulness of this marker in identifying possible etiology. The high IPF% in pseudothrombocytopenia is an interesting finding. In this case, the elevated value is not reflective of an increased thrombopoietic response but rather is an artefactual effect of platelet size or platelet aggregation [26]. As mentioned earlier, IPF% should be less vulnerable to sample artifacts, from use of EDTA and also delays in sample analysis, than MPV or PDW analysis. However there will still be some degree of interference. Yet, when considering the utility of a new parameter, one must consider the feasibility of analysis in a high-workload environment in standard sample types. The results presented here demonstrate the usefulness of IPF% analysis in standard EDTA samples measured in a time frame that is achievable in a diagnostic hematology laboratory.

The increased consumption group was also easy to differentiate from other cohorts, exhibiting a significantly higher median than four out of the five etiological groups. Indeed, patients with increased platelet consumption were found to have a significantly higher IPF% values than patients with reduced thrombopoiesis, drug-related thrombocytopenia, platelet sequestration (abnormal distribution), and pseudothrombocytopenia. The value of IPF% was not as useful when differentiating other groups. The reduced thrombopoiesis group could be separated from two groups (increased consumption and pseudothrombocytopenia); however, it could not be differentiated from drug-related thrombocytopenia, platelet sequestration, or thrombocytopenia of unidentified etiology. Furthermore, the drug and splenic sequestration groups could not be differentiated from each other by IPF% (Figure 2A).

The thrombocytopenic cohorts were further split into the underlying conditions causing the platelet pathology in these patients (see Table 1 footnotes). The increased consumption group was subdivided into infection, ITP, and hemorrhage. It is expected that patients with infection would show an increased IPF%, since the resulting platelet activation from bacterial invasion results in adhesion of platelets to other immune cells or to thrombus formation, which in turn leads to a consumptive state. More than 50% of sepsis patients develop a low platelet count, ranging from a mild decrease to severe thrombocytopenia, and the degree of thrombocytopenia can be used to predict mortality in sepsis [27]. Increased IPF% would also be expected in cases of hemorrhage, as a result of increased thrombopoiesis in response to platelet consumption to limit blood loss. However, elevated IPF% values are not always seen in hemorrhage patients and are dependent on the time of testing in relation to active bleeding. Naturally, there will be a delay between active bleeding and the thrombopoietic response [28], and this period will be dependent on



	Control	RT	IC	DR	AD	PS	UA
Control							
RT	P<0.001						
IC	P<0.001	P<0.05					
DR	P<0.01	n.s	P<0.01				
AD	P<0.001	n.s	P<0.05	n.s			
PS	p<0.001	P<0.001	P<0.01	P<0.001	P<0.001		
UA	P<0.001	n.s	n.s	n.s	n.s	P<0.001	

	Infection	ITP	Haemorrhage
Infection			
ITP	P<0.001		
Haemorrhage	n.s	P<0.05	

Figure 2. **(A)** Differentiation of six thrombocytopenic cohorts, and **(B)** further differentiation of the underlying mechanism responsible for the increased platelet consumption, by analysis of immature platelet fraction (IPF%). *RT*=reduced thrombopoiesis; *IC*=increased consumption; *AD*=abnormal distribution (including alcohol-related liver disease, hepatitis infections, portal hypertension); *DR*=drug-related; *PS*=pseudothrombocytopenia; *UA*=unidentified etiology; *ITP*=idiopathic thrombocytopenic purpura. Statistical analysis was performed using the Kruskal–Wallis test with Dunn's post hoc analyzes. Data are presented as the median ± range. Statistical significance between the groups is outlined in the tables in the lower part of the figure.

the reserve pool of platelets which will be released to cover the depletion. Yet, it was the ITP subgroup that had the highest IPF%, and this allowed differentiation of ITP from the other two etiologies (infection, p <0.001, and hemorrhage, p <0.05). Indeed, the highest IPF% recorded in this study was in a sample from a patient with ITP (77.9%). However, the IPF% is not universally elevated in ITP. If the ITP autoantibodies affect the bone marrow in ITP, it follows that the IPF will not be as high when compared with cases in which the autoantibodies have not reached the bone marrow [29]. The results, however, do demonstrate the power of IPF% as a differential indicator of ITP when infection and hemorrhage have not been ruled out during the investigative process. In similar studies, higher IPF% values were observed in ITPcompared with reduced thrombopoietic disorders [22,25], and these studies also focused on EDTA-anticoagulated samples. Ferreira et al. [22] were also able to demonstrate that the IPF% was significantly higher still in patients with hereditary macrothrombocytopenia, again demonstrating the usefulness of this parameter in differential diagnosis.

When reduced thrombopoiesis, drug-related thrombocytopenia, abnormal distribution, and pseudothrombocytopenia groups were further subdivided, there were no significant differences in IPF% among the underlying pathologies within these groups (data not shown). The IPF% in the drug-related group was relatively low in comparison with the other groups. Further subdividing the data based on drug type (chemotherapy, methotrexate sulfasalazine, and antibiotics) did not reveal any significant findings. Chemotherapy drugs can destroy the megakaryocytic progenitors at the beginning of differentiation, preventing immature platelet production, which explains the lower IPF values [30,31]. Although some antibiotics have also been reported to cause thrombocytopenia, this response is not seen in all patients on the same drug [32], and the underlying infection plays a bigger role in the thrombocytopenia in most patients than the antibiotic itself. As the mechanisms involved in drug-induced thrombocytopenias are varied, with some affecting the bone marrow and others not, the IPF% cannot be used to separate or diagnose the etiology of drug-related thrombocytopenia. The abnormal distribution group had only 7 results out of a total of 64 that were above normal ranges. The multiple disorders that involve splenic sequestration of platelets as a secondary consequence may also affect the bone marrow in a large majority of patients, resulting in normal IPF% values, in a setting that should promote thrombopoiesis [33].

Discussion

The data obtained in this study significantly expand on those of similar studies reporting on smaller thrombocytopenic sample sizes with fewer underlying etiologies [34,35]. The present study provides solid evidence that the IPF% can allow the separation of increased consumption disorders, especially ITP. The etiology of thrombocytopenia is important in the treatment and management of the condition. Therefore, increasing inclusion of this marker in the hospital diagnostic

testing panel and standardization of defined ranges, will have significant impact on the time taken to identify the underlying cause of thrombocytopenia and allow for effective treatment and management of thrombocytopenic patients.

Conflict of interest disclosure

The authors declare that they have no competing financial interest

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