Platelet distribution width for differential diagnosis of thrombocytosis

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Differential diagnosis of thrombocytosis is not always obvious. The routine clinical chemistry laboratory classically provides only limited help in distinguishing between reactive thrombocytosis (RT) and autonomous thrombocytosis, where platelet production escapes normal regulatory processes, and which is seen in myeloproliferative diseases (MPD) such as essential thrombocythemia and polycythemia vera. We explored the clinical use of platelet distribution width (PDW) in the differential diagnosis of thrombocytosis. During a 3-month period, 250 patients presenting with a platelet count >500 × 10^9/L were studied; 174 were classified as having RT, 42 had a diagnosis of MPD, and 34 patients were excluded because they had a hemopathy different from MPD, and either did or did not present a known etiologic factor for RT. First, we determined that in the RT group the value of PDW was closely linked to both mean platelet volume (MPV) and platelet count (PLT) (PDW = 79.5 – 0.005 PLT – 3.5 MPV; r = 0.848, R^2 = 0.720). Therefore a new parameter, PDW_{residual}, was defined (PDW_{residual} = PDW_{observed} – PDW_{expected}). Second, the discrimination between reactive and autonomous thrombocytosis obtained with PDW_{residual} was compared with that obtained with either PDW, MPV, or PLT. PDW_{residual} proved much more powerful than each of the other parameters used separately: 76% of MPD patients had a PDW_{residual} above the 95th percentile value of the RT population and none of the MPD patients had a PDW_{residual} below the 50th percentile. Thus, the combined interpretation of PLT, MPV, and PDW through the use of a PDW_{residual} appears highly useful in the differential diagnosis of thrombocytosis. Also, through simple modeling, more information can be drawn from parameters such as PDW that hitherto were mostly discarded as being without clinical interest.

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Differential diagnosis of thrombocytosis is not always obvious, since multiple causes may be involved. Reactive or secondary thrombocytosis (RT),4 which may occur during rapid blood regeneration, and “rebound” thrombocytosis accompanying various situations such as infections and inflammatory diseases, neoplasms, asplenic states, or iron-deficiency anemia, should be distinguished from autonomous thrombocytosis, in which platelet production apparently escapes normal regulatory processes [1], and which is seen in myeloproliferative diseases (MPD) such as essential thrombocythemia (ET) and polycythemia vera (PV) [2]. The main interest of the distinction between reactive and autonomous thrombocytosis resides in the increased incidence of thrombohemorrhagic complications in the latter group [3, 4].

Factors contributing to a differential diagnosis are few in the absence of an obvious cause for RT. The spleen size should be evaluated, the presence of splenomegaly supporting the diagnosis of MPD. The bone marrow also can contribute to differential diagnosis. Almost 30 years ago, Harker and Finch [1] showed an inverse relation between platelet count (PLT) and megakaryocyte volume. This relation is observed in chronic myeloid leukemia (CML) but not in ET, where the megakaryocyte volume is increased because of the autonomous endoproliferation. A previous study [5] examining megakaryocytes with respect to nuclear DNA content in marrow smears and nuclear morphometry in marrow sections showed that both the mean DNA content and the mean megakaryocyte area were significantly larger in a group of patients with PV and ET compared with a group of patients with RT.

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4 Nonstandard abbreviations: RT, reactive thrombocytosis; MPD, myeloproliferative diseases; ET, essential thrombocythemia; PV, polycythemia vera; CML, chronic myeloid leukemia; PLT, platelet count; MPV, mean platelet volume; PDW, platelet distribution width; and MF, myelofibrosis.
Such procedures, however, are not routinely available. In peripheral blood, increased concentrations of lactate dehydrogenase are much more often observed in patients with ET than in patients with RT [6]. Similarly, the PLT tends to be higher in the former group than in the latter one [7]. Furthermore, platelets in MPD are known to present functional abnormalities such as defective aggregation in response to ADP, epinephrine, and collagen [8, 9]. Platelets of patients with ET are also abnormal in plasma membrane and adenine nucleotide content [10].

Although platelet parameters, including the mean platelet volume (MPV) and the platelet distribution width (PDW), have been routinely available to clinicians for some time, their role in the diagnosis and management of patients remains unclear. Several studies [9, 11, 12] tried to use MPV and (or) PDW to distinguish between RT and thrombocytosis associated with MPD. Although they constantly observed significant differences between the two groups with respect to MPV and PDW, the sensitivity was not sufficient to allow differential diagnosis in an individual patient. All these studies, however, interpreted PDW independently from both MPV and PLT.

The aim of this study was twofold. In a first step we tried to verify whether in a population of patients with high PLTs the PDW was dependent on both MPV and PLT. In a second step, we examined if the combined interpretation of these three parameters could allow an improved discrimination between patients with reactive and autonomous thrombocytosis.

**Materials and Methods**

**Patients**

During a 3-month period, 250 patients who presented with a platelet count >500 × 10^9/L were studied. Recruitment occurred in accordance with the ethical standards of the Ethical Committee of St-Luc University Hospital. According to the information available from the patients' records, these individuals were divided into three groups: (a) 174 patients without obvious hemopathy, and presenting with a disease condition known as an etiology for RT (35 were recovering from recent major surgery, 53 were infected, 33 had a combination of infection and surgery, and 23 presented with nonhematologic malignancy); (b) 42 patients with well-documented MPD [CML: 6; ET: 12; PV: 22; myelofibrosis (MF): 2]; (c) 34 patients with a hemopathy, different from MPD. Most, but not all, of these patients had a known etiologic factor for RT. To avoid any confusion between reactive and autonomous thrombocytosis, they were excluded from further study.

**Blood Analysis**

Whole-blood cell counting was routinely performed on one of two different analyzers (Technicon H1 and H2; Bayer, Tarrytown, NY) on which the red blood cell/platelet channel produces the following parameters: PLT (10^9/L), MPV (fL), and PDW [calculated as (or × 100) (fL)/MPV (fL) after log transformation of the MPV].

**Statistical Analysis**

In a first step, multiple regression analysis was performed with a Statview 512+ software package on results of platelet parameters in the group of patients with RT. In the regression model, PDW was expressed as a function of both MPV and PLT. Coefficients for each parameter were tested for clinical significance.

In a second step, the regression equation was used to compute for every individual patient an expected PDW value. A new parameter, called PDW residual, was defined (PDW_{residual} = PDW_{observed} − PDW_{expected}).

Values of PLT, MPV, PDW, and PDW residual were compared between RT patients and patients with MPD (both for MPD as a disease group and for each disease entity separately) by Wilcoxon rank sum test.

The discrimination value of PLT, MPV, PDW, and PDW residual was assessed by constructing ROC curves for each parameter with maximum likelihood technique with the LABROC1 program and by comparing the areas under the curves with the Z-score test [13] with the CLABROC program (both programs from C.E. Metz, Department of Radiology, University of Chicago, Chicago, IL).

**Results**

Our data revealed a correlation between PLT, MPV, and PDW (PDW = 79.5 − 0.005 PLT − 3.5 MPV; r = 0.848, R^2 = 0.720) in the RT group. Regression coefficients for both PLT and MPV were highly significant (P < 0.001).

Using the regression equation obtained in the RT group, a PDW_{expected} was computed for each patient, and the PDW_{residual} was determined. For example, patient A (postsplenectomy) had a PLT of 600 × 10^9/L, an MPV of 8.0 fl., and a PDW observed of 48.0. By using the regression equation, PDW expected was 48.5; PDW residual hence was −0.5. Patient B (with PV) had a PLT of 800 × 10^9/L, an MPV of 7.0 fl., and a PDW observed of 55.0. By the regression equation, PDW expected was 51.0; PDW residual therefore was + 4.0.

Comparison of the different categories of MPD vs RT for the three classical platelet parameters was as follows: (a) PLT values were higher in MPD vs RT (P < 0.001), this difference being statistically significant for all categories of MPD except MF (which included only two cases) (Fig. 1A); (b) MPV values were higher in MPD vs RT (P < 0.001), with differences statistically significant in all MPD categories apart from MF (Fig. 1B); (c) PDW values were higher in the PV group than in RT (Fig. 1C). Despite these differences, the overlap between the different groups was too important to allow a differential diagnosis of RT vs MPD.

The use of PDW residual offered a far better discrimination between these groups. In 4 of 6 CML (66%), 8 of 12 ET (66%), 18 of 22 PV (82%), and 2 of 2 MF (100%) [total: 32 of 42 MPD (76%)], PDW residual was well above the 95th percentile value of the RT population. On the other hand,
Fig. 1. Box plots of (A) PLT, (B) MPV, (C) PDW, and (D) PDWresidual values for RT and MPD patients, and for the various subgroups of MPD.

The line inside the box is the median, the limits of the box are the 25th and 75th percentiles, and the whiskers are the smallest and largest values less than 1.5 box-lengths from 25th and 75th percentile.
none of the MPD patients had a negative PDW_{residual} as opposed to 50% of subjects with RT (Fig. 1D).

The area under the ROC curve was significantly higher for PDW_{residual} (0.946 ± 0.018) than for PLT (0.810 ± 0.037, \( P < 0.001 \)), MPV (0.741 ± 0.038, \( P < 10^{-5} \)), and PDW (0.583 ± 0.048, \( P < 10^{-5} \)) (Fig. 2).

**Discussion**

Although platelet parameters such as MPV and PDW have been available now for quite a time, their clinical usefulness hitherto was not obvious \([14]\), especially as they may be influenced by the delay between blood collection and analysis. Furthermore, PDW is calculated differently on various instruments.

The presence of large platelets has been reported in patients with MPD after examination of stained films of peripheral blood \([15]\). The quantification of such platelets, however, remains subjective. Several authors \([9, 12]\) tried to discriminate thrombocytosis in MPD from RT by using platelet parameters provided by blood analyzers. Although significant differences were observed, none was found to provide enough sensitivity to permit satisfactory differentiation between ET and RT in an individual patient.

Our data corroborate previous studies insofar as they concern PLT and PDW \([9, 12]\). In MPD, the value of these parameters tends to be higher than in RT. On the other hand, our findings were in opposition to these authors for MPV results, which in our series were higher in MPD than in RT.

More interestingly, our data revealed a correlation between both PLT and MPV and PDW. Therefore, we suggest that these three parameters be subjected to a combined interpretation, e.g., through the calculation of a PDW_{residual}. Such an approach enabled us to obtain a far better discrimination than the one revealed by previous studies, which, although showing statistically significant differences, led to a poorly relevant distinction between MPD and RT. In three-fourths of the cases of MPD, the PDW_{residual} on its own was highly suggestive of autonomous thrombocytosis. The differential diagnosis of thrombocytosis is particularly crucial in ET, where an increased PLT is the only abnormality; in our series, in 8 of 12 cases of ET (66%) the autonomous nature of thrombocytosis was revealed by the higher PDW_{residual}. On the other hand, in 50% of cases of thrombocytosis presenting with a negative PDW_{residual}, MPD could virtually be excluded.

The exclusion of 34 patients in the preliminary phase of the study was inspired by the fact that they had a hemopathy other than MPD; the vast majority of them (32 of 34) were recovering from intensive chemotherapy and therefore had also a known etiologic factor for RT. In a subsequent step, we also calculated the PDW_{residual} in this group of patients (data not shown). Of these 34 patients, 30 had a normal PDW_{residual} between \([-2, +2]\); 4 patients, however, presented with markedly increased PDW_{residual}: 1 with chronic myelomonocytic leukemia, 1 with refractory anemia with excess blastosis, and the remaining 2 with acute myeloblastic leukemia recovering from aplasia. No patient with lymphoma or acute lymphoblastic leukemia was found to have an increased PDW_{residual}.

The calculation of PDW_{residual} is of course only one of the possibilities to express the mutual interdependency between PLT, MPV, and PDW. We could have used as well a PLT_{residual} or a MPV_{residual} or an arbitrary discriminant or logistic function of the three parameters. Our choice was inspired by the following reasons. On the one hand, PDW is certainly the forgotten platelet parameter. Every clinician is interested by PLT, some pay attention to MPV, but nobody cares about PDW. To design the hidden information revealed by the combined interpretation of these three parameters, it seemed more obvious to link it to the one parameter that hitherto was disregarded. On the other hand, PDW expresses the distribution of the size of platelets produced by the megakaryocyte. In cases of autonomous platelet hyperproduction, one could expect a diminished control by the megakaryocyte of the platelet size, reflected by a widened dispersion. Intuitively it seemed preferable in such cases to explain that, for a given PLT and MPV value, the PDW was abnormally high, instead of signaling that, for a given PDW, the MPV or the PLT was too low.

We are well aware of the limitations of this study. The linear multiple regression model we propose may not offer an optimal fit; we tried several transformations of the formula (data not shown), without improving the correlation. Probably a more complex model could further

![ROC curves for PDW_{residual} (---), PLT (............. ), MPV (- - - - - - - ), and PDW (--- --- ---) values.](image-url)
enhance the resolution. Nevertheless, linear multiple regression modeling is easily available, and already leads to quite interesting results.

All patients with RT had an obvious cause of thrombocytosis: They were recovering from recent major surgery (65 patients), were infected (53 patients), had a combination of infection and surgery (33 patients), or had a nonhematologic malignancy (23 patients). No systematic follow-up was undertaken for these patients; therefore we cannot formally exclude that some of them developed an MPD later on. Patients with MPD had a positive diagnosis, but were studied at different moments; some were included at time of diagnosis, whereas others already had received different treatments for various periods. Furthermore, the delay between sampling and blood cell counting was not taken into account. It is well possible that at least some of these phenomena might act as confounding variables, leading to an increase in the background noise.

Finally, the increased PDW\textsubscript{residual} probably reflects a dysregulation in thrombopoiesis, which is also translated by the multiple abnormalities of platelet reactivity and the change in platelet membrane and adenine nucleotide content that have been previously described \cite{8–10}. For the reasons mentioned above, we did not compare PDW\textsubscript{residual} with these tests. Physiopathological considerations were well beyond the scope of this study.

By using a parameter such as PDW that, although routinely available, is generally considered an uninterpretable result, we were able to achieve a fairly interesting resolution between reactive and autonomous thrombocytosis. This approach is costless and effortless, and requires only the creation of a laboratory database and the use of a simple linear multiple regression model; it also provides useful assistance in the differential diagnosis of thrombocytosis, which is not always obvious. These preliminary data need to be confirmed by other studies, and should be extended to PDW measured on other automated blood counters. Currently we are investigating whether a similar model can be extended towards patients with normal PLTs.

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