



Review article

Characteristics of platelet indices and their prognostic significance in selected medical condition – a systematic review

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ABSTRACT

Background: Platelets, also called thrombocytes, are produced in bone marrow and are the second most numerous blood cells which circulate in blood and play a pivotal role in hemostasis, wound healing, angiogenesis. There is a large body of evidence that platelets are likely to contribute to inflammation in multiple diseases. Also, recent studies revealed the association between platelet indices (PI) and inflammation.

Methods: PubMed, Scopus and Google Scholar databases were searched and only papers published in the last 10 years were consequently analyzed.

Results: The most frequently evaluated parameters are mean platelet volume (MPV), platelet diversity index (PDW), plateletcrit (PCT) and the presence of larger platelets (P-LCRs platelet larger cell ratio). The values of platelet indices (PI) were elevated in patients suffering from type 2 diabetes mellitus, myocardial infarction, cancers or acute surgical conditions, such as appendicitis. The measurement of PIs does not generate additional costs and can be performed during routine cell blood count, not requiring additional blood samples.

Conclusions: Platelet indices may have prognostic and predictive value in numerous conditions.

1. Introduction

Platelet indices (PI), markers of platelet activation, are parameters obtained daily as a part of an automatic blood count. PI are related to platelet's morphology and proliferation kinetics. Most commonly assessed PI include the mean platelet volume (MPV), platelet distribution width (PDW), platelet-large cell ratio (P-LCR) and the plateletcrit (PCT) [1]. Blood-based platelet parameters, due to their fairly easy accessibility and inexpensive methods of measurement, seem to be on the rise as potential novel biomarkers of numerous, both acute and chronic, diseases [2]. However, despite numerous attempts to determine the parameters' clinical correlations, their direct association to clinics in terms of both diagnosis and prognosis, is yet to be substantially verified [3].

2. Methods

In September 2019, we searched PubMed, Scopus and Google Scholar for “platelet”, “platelet distribution width”, “platelet indices”, “mean platelet volume”, “plateletcrit”, “platelet larger cell ratio” in combination with “diabetes mellitus”, “acute coronary syndrome”,

“cancer”, “appendicitis”, “cholecystitis”, thrombocytopenia”, investigating a number of studies. Then, we consecutively screened abstracts and, full-text articles published in English. A total of 138 articles were found in PubMed and 9 duplicate papers were excluded. Additionally, 85 articles were excluded as they contained data regarding diseases other than those relevant to the purpose of this review. Finally, 45 papers published in last 10 years were analyzed in this article.

In Fig. 1, we present the schematic diagram on selection of the studies included in this review.

3. Review

3.1. Platelet indices

Mean platelet volume (MPV), the most commonly investigated platelet parameter, signifies the average size of platelets in the blood. In healthy subjects it typically ranges between 7.2 and 11.7 fL [4]. MPV of over 13 fL tends to occur in hyperdestruction, in which case young platelets become bigger and increase in activity, whereas MPV lower than 8 fL is a sign of platelet hypoproduction [4,5]. The changes in MPV

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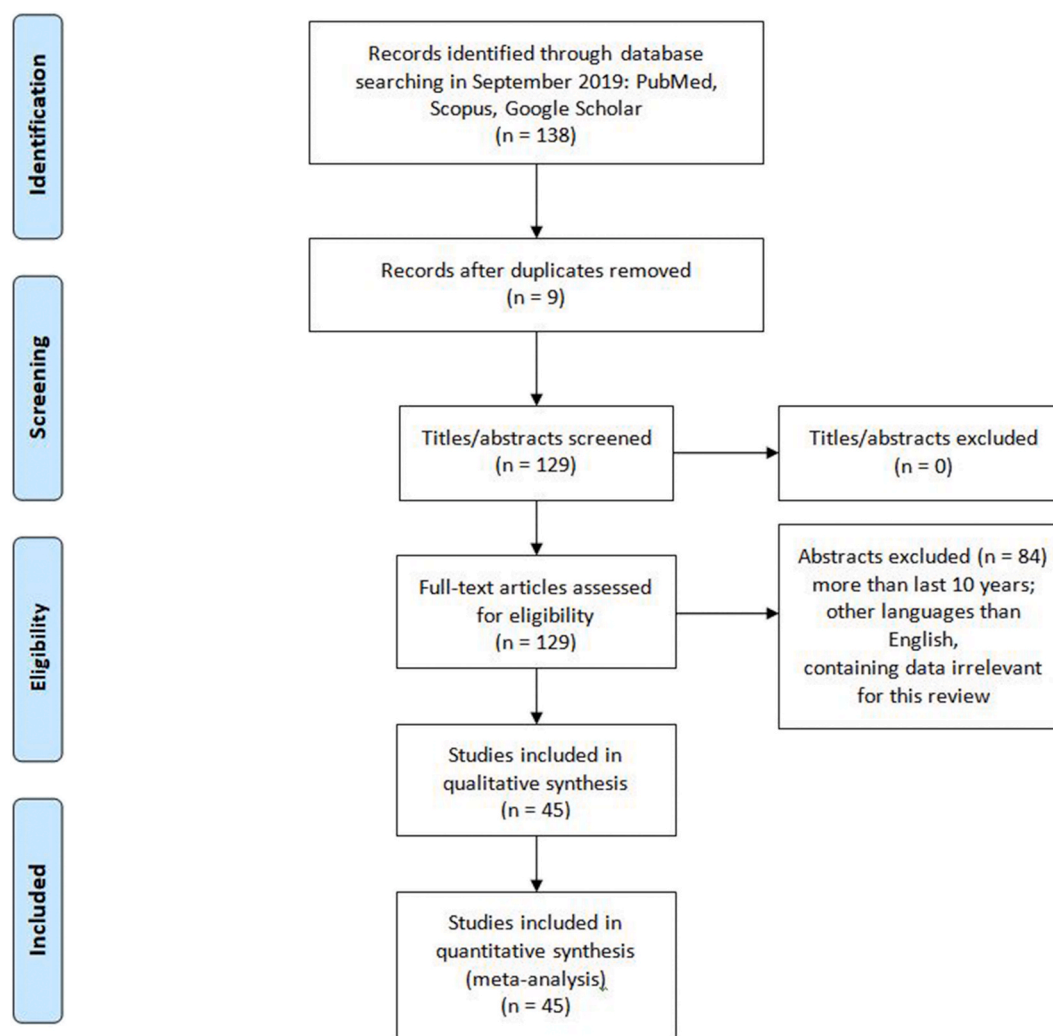


Fig. 1. PRISMA 2009 flow diagram. Adapted from Moher et al. [50].

levels are not only affected by the abnormality in platelet count, but are additionally related to the used method of laboratory analysis [6]. Many factors including race, age, smoking, alcohol consumption, and physical activity can modify MPV [1]. MPV has been analyzed as a potential biomarker of patient's prognosis, with most studies associating its higher value to worse clinical outcome. A study conducted by Lembeck et al. [2], showed a significant association between high MPV and worse prognosis in patients with pancreatic ductal adenocarcinoma regardless of the normalized level of other well-known prognostic markers. This was also observed in patients suffering from myocardial infarction, where those with higher MPV level seemed to be more often associated with poor clinical outcome [6]. Lower MPV level can be related to low-grade inflammation, such as rheumatoid arthritis [7].

Platelet distribution width (PDW) is a marker of platelet anisocytosis, which describes the size distribution of platelets produced by megakaryocytes and increases upon platelet activation [8]. Although review by Budak et al. [1] suggests that PDW reference levels range between 8.3 and 56.6%, there is little to no evidence for such wide variation reported in the literature. Analyzed studies found this parameter to vary between 10 and 18% in healthy individuals [9–12] and observed PDW change in patients suffering from numerous diseases [13–15]. It allows for this parameter to be considered as a potential biomarker. PDW seems to be proportionally related to MPV in healthy individuals [9], however, under non-physiological conditions, such as, threatened preterm labor, they show significant dissonance – a rise in PDW and decrease in MPV [14]. This disrelation was also observed by

Aydogan et al. [16] who compared MPV and PDW levels in patient groups with perforated and non-perforated acute appendicitis. Amin et al. [13] found that higher level of PDW in patients with vaso-occlusive crisis in the course of sickle cell disease can be contributed to megakaryocyte hyperplasia.

Platelet larger cell ratio (P-LCR), another marker of platelet activity, is a percentage of all platelets with a volume measuring over 12 fL circulating in the bloodstream. It normally ranges between 15 and 35% [17]. In the study of Baig [5] direct relation of P-LCR to PDW and MPV, and its inverse relation to platelet count in patients with thrombocytopenia could be observed. P-LCR seems to be more susceptible to alterations in platelet size in comparison to MPV, despite their correlation [18].

Plateletcrit (PCT) measures total platelet mass as a percentage of volume occupied in the blood. The normal range for PCT is 0.22–0.24% [1,18]. It seems to play an effective screening role in detecting platelet quantitative abnormalities [5]. The PCT is nonlinearly correlated to the platelet count and indicates comparable clinical implication [18]. Tang et al. [19] investigated PCTs potential as a novel biomarker of active Crohn's disease in patients with low high sensitivity C-reactive protein (hs-CRP).

Platelet indices are currently under thorough investigation to be applied as potential novel biomarkers in terms of diagnostics and prognosis in various, both acute and chronic diseases. PI can be measured inexpensively and are accessible at hand during routine blood counts [19]. Despite many attempts to establish both significant and

Table 1
Platelet indices with their normal range and their diagnostic and prognostic value in selected conditions.

Platelet Indices (PI)	Normal range	Conditions with platelet indices above normal range	Conditions with platelet indices below normal range
MPV	7.2–11.7 fL	- immune thrombocytopenia purpura (ITP) [45] - diabetes mellitus [18,19] - DM related retinopathy and nephropathy [22,23] - septic shock [16] - heart disease [25] - malignant tumors [31]	- non-complicated acute appendicitis [39] - acute cholecystitis [40,41] - low-grade inflammation ex. rheumatoid arthritis [11] - threatened preterm labor [10]
PDW	8.3–56.6%	- complicated acute appendicitis [39] - DM related retinopathy and nephropathy [22,23] - ST-elevation myocardial infarction [25] - acute cholecystitis [40] - threatened preterm labor [10] - vaso-occlusive crisis sickle cell disease [8]	- non-malignant tumors [31]
P-LCR	15–35%	- immune thrombocytopenia purpura (ITP) [45] - DM related retinopathy and nephropathy [22,23]	- myeloid insufficiency [45]
PCT	0.22–0.24%	- acute cholecystitis [40] - active Crohn's Disease with low hs-CRP [17]	- immune thrombocytopenia purpura (ITP) [45]

applicable clinical correlations, these parameters are still not used extensively mainly because of the methodological problems in terms of standardization and determination of reference values [3]. Several studies evaluated the lack of consistency in PIs measurements when analyzed using different techniques. This acts as a serious limitation for obtaining comparable results between laboratories. Considering numerous factors that impact the change in platelet parameters, further multicenter prospective studies should be performed in order to establish uniformity of measurement that will allow for the recognition of platelet indices as biomarkers [1].

In Table 1, we present platelet indices with their normal range and conditions in which PI could be used as diagnostic and prognostic biomarkers.

3.2. Cardiovascular diseases

Due to low cost of standard peripheral blood smear and a great need for new biomarkers of inflammation, platelet indices have been the subject of numerous analyses.

The conducted analyses confirm the importance of changes in platelet indices in the course of diabetes mellitus (DM).

A meta-analysis conducted by Zaccardi et al. [20] shows that the MPV of people with DM type 2 (T2DM) is significantly higher compared to the healthy individuals but not in metabolic syndrome. Platelet distribution width was wider in T2DM. Platelet count was higher in impaired fasting glucose and metabolic syndrome. The aim of the study by Razak et al. [21] was to measure the MPV in patients with T2DM and its correlation with albuminuria, duration of DM, hypertension, stroke, ischemic heart disease (IHD), and glycated hemoglobin (HbA1c) level. Regarding HbA1c, 68% of patients had poorly controlled DM. MPV were higher in the uncontrolled group with a statistically significant association. There was a statistically significant positive correlation between MPV and albuminuria, duration of DM, hypertension, stroke and HbA1c.

A prospective analysis, conducted on over 38,200 participants, the largest group so far, confirmed the increased risk of T2DM in the population with elevated MPV [22]. This study showed that MPV positively correlates with the value of fasting glucose and the elevated value of glycated hemoglobin. The results were confirmed by an analysis conducted by Demirtunc et al. [23], which compared two groups of patients with T2DM. Patients were randomized depending on the value of glycated hemoglobin: group A: A1c < 7% and group B: A1c > 7%. Higher MPV values were observed among patients with worse glycemic control. In addition, MPV value decreased within 3 months among 86% of patients in group B, aligning glycemia with appropriate diet and pharmacotherapy [23]. It is interesting that the platelets parameters such as: MPV, PDW and P-LCR are elevated in patients with diabetic

retinopathy (DR) and diabetic nephropathy (DN) in comparison to patients in whom the above-mentioned complications have not yet been observed [15,24]. Therefore MPV, PDW and P-LCR can serve as inexpensive and routinely assessed risk factors for micro- and macrovascular complications. In a meta-analysis conducted by Liu et al. [25] the authors investigated the correlation of neutrophil to lymphocyte ratio (NLR), MPV, and PDW with DN and DR. Compared to patients with T2DM and without DR, NLR, MPV, and PDW were higher in patients with DR. Compared to patients with T2DM and without DN, NLR, MPV, and PDW were higher in patients with DN. These findings suggest that NLR, MPV, and PDW could be recommended as inexpensive diagnostic biomarkers for DN and DR.

Platelets are cytoplasmic fragments of megakaryocytes that enter the circulation. They contribute to the formation of atherosclerotic plaque, blood clots, leading to acute coronary syndromes. In case of damage of vascular endothelium, platelets are activated and adhere to the site of injury. Thrombocytes become a source of biologically active substances that participate in chemotaxis and exacerbate the local inflammatory process. Presence of acute phase proteins and proinflammatory cytokines increases the risk of cardiovascular events.

PDW, also known as an indicator of platelet cell diversity, increases in the case of cardiac events, as a result of platelet activation. What is more, the low grade inflammation precedes incidents of cardiovascular events. In this case bone marrow produces larger platelets with increased activity and releases them into circulation. It was demonstrated that PDW with sensitivity of 81% and specificity of 39% may serve as a predictor of left ventricular failure, in patients with acute coronary syndrome (ACS) undergoing coronary angioplasty [26]. In another study, PDW was higher in patients with ST segment elevation myocardial infarction (STEMI) compared to those with stable coronary artery disease [27]. PDW (> 17 fL) and P-LCR (38.1%) have been shown to correlate with higher mortality in patients undergoing ACS [28]. What is more, in the literature review carried out by Korniluk et al. [29], increased MPV was observed in cardiovascular diseases, cerebral stroke, respiratory diseases, chronic renal failure, and rheumatoid diseases. MPV ≥ 11.6 fL can also be an independent risk factor of heart infarction in patients with coronary disease and designate patients threatened with acute cardiac incidents. Patients with high MPV were shown to be more at risk of acute stroke in comparison with normal MPV, while decreased MPV was noted in tuberculosis during disease exacerbation, ulcerative colitis, and systemic lupus erythematosus (SLE) in adults [29].

3.3. Cancers

In the study conducted by Kurtoglu et al. [30] the prognostic value of MPV and PDW was assessed in 105 women with benign endometrial

lesions and in 114 women in different stages of endometrial adenocarcinoma. In the group diagnosed with malignancies, MPV (> 7.54) was significantly increased, while PDW was significantly decreased (< 37.8) compared to the group of women with benign endometrial lesions. A total of 11 studies were analyzed in a meta-analysis performed by Xia et al. [31]. The results suggest that high PDW level is related to poor overall survival, especially for breast cancer and pharyngolaryngeal cancer, and it is obviously associated with lymph node metastasis.

In the study by Karateke et al. [32], the authors confirmed the prognostic value of platelet indices in gynecological conditions. The highest MPV, PDW and PCT values were observed in patients with endometrial cancer identified by histopathological examination, compared to the control group. According to the authors, the above platelet indices allow for the selection of patients suspected of developing malignant tumor, even before performing histopathological examinations.

A retrospective analysis of 294 patients with gastric cancer showed that the decreased PDW correlated positively with the age of patients, the elevated value of carcinoembryonic antigen (CEA) and the stage of tumor-node-metastasis (TNM) classification for gastric cancer. Moreover, reduced PDW significantly correlated with a shorter overall survival of gastric cancer patients [33]. The prognostic value of PDW in gastric cancer metastases assessment was demonstrated also in the study by Gunaldi et al. [34]. Therefore, PDW can be considered as an important factor influencing surgical treatment and chemotherapy in gastric cancer patients.

3.4. Acute surgical conditions

In the Ceylan et al. [35] study, changes in MPV and PDW were analyzed in people with appendicitis. The study included 362 patients, of whom 170 constituted a control group. Complications occurred in 66 patients with appendicitis. MPV was lower among patients with appendicitis without complications compared to those with complicated appendicitis and the control group (MPV: 9.78 ± 0.99 vs. 10.20 ± 1.21 and 10.14 ± 1.03 , respectively). In contrast, PDW levels did not differ between the three groups [35]. In further four retrospective studies, it was also observed that the MPV was decreased in patients with acute appendicitis compared to healthy individuals [12,36–38]. However, the analysis carried out by the team of Narci et al. [39] revealed that the MPV value was statistically significantly higher among patients with acute appendicitis compared to the control group ($p < 0.001$). The MPV cut-off point was 7.87 fL and allowed for the diagnosis of acute appendicitis with 66% sensitivity and 51% specificity. Another retrospective analysis focused on the diagnostic value of MPV and PDW. The study compared the platelet indices of 202 patients, divided into two groups. The first group consisted of patients with acute appendicitis, the second group consisted of patients in whom the acute condition was complicated by perforation. Platelet counts, MPV and PDW were statistically significantly higher among patients with perforation compared to the group of patients without complications of appendicitis. It was noted that MPV and PDW can be used as markers of perforation risk in the early stages of acute appendicitis [16].

In the study by Sayit et al. [40], MPV values were significantly lower among 60 patients with acute cholecystitis compared to the healthy control group. However, PCT values and PDW were significantly higher in patients with acute cholecystitis compared to healthy subjects. The group headed by Seker et al. [41], analyzed cases of 33 people with acute cholecystitis, 32 patients with chronic cholecystitis and 28 healthy individuals. The research proved that the value of MPV was significantly lower in patients with acute inflammation compared to chronic cholecystitis and a control group. Prospective studies, conducted on a large group of patients, would provide a lot of important information on the prognostic value of platelet parameters in acute cholecystitis.

The study by Türkoğlu et al. [42] included 95 patients who underwent emergency surgery due to acute mesenteric ischemia and 90 healthy control subjects. MPV was statistically significantly higher in the experimental group compared to the control group ($p < 0.001$). As a result, high MPV values determined in routine blood counts confirmed the resolution of mesenteric ischemia among patients with uncharacteristic abdominal pain.

At the same time, MPV can be used as a prognostic factor for acute mesenteric ischemia. A retrospective study conducted by Altintoprak et al. [43] in 30 patients confirmed that MPV values are significantly higher in patients who died of acute intestinal ischemia compared to survivors. Thus, the MPV parameter can be taken into account as the factor of worse prognosis and the need to carry out a second surgery.

Bilgiç et al. [44], studied 61 cases of patients with acute mesenteric ischemia by dividing them into two groups: patients who survived and patients who died of intestinal perfusion disorders. MPV values and other prognostic factors in the above two groups were compared. Statistically significantly higher values of MPV were observed among patients who did not survive acute mesenteric ischemia. High MPV values at admission may be indicative of more intense mesenteric ischemia and a greater risk of mortality.

3.5. Thrombocytopenia

One of the analyzed studies was performed on 40 patients with diagnosed immune thrombocytopenia purpura (ITP; excessive peripheral platelet destruction) and 40 patients with thrombocytopenia due to myeloid failure (10 patients with aplastic anemia, 17 patients with acute leukemia, 3 patients with myelodysplastic syndrome and 10 patients undergoing chemotherapy). The study proved that MPV values were statistically significantly higher among patients with ITP compared to patients with bone marrow failure secondary to the above-mentioned conditions. In the same study, the P-LCR index was significantly higher in patients with ITP compared to the control group and significantly lower in patients with myeloid insufficiency compared to the control group [45].

A bone marrow biopsy can provide important information about the cause of thrombocytopenia. However, it is a costly and invasive procedure that carries a risk of complications. Therefore, the assessment of platelet indices may help in differentiating the causes of thrombocytopenia, allowing resignation from time-consuming and requiring considerable experience, bone marrow biopsy. A prospective study on 83 patients, including 33 patients with ITP showed that all the platelet parameters (PDW, MPV, P-LCR) were significantly higher among patients with ITP compared to patients with insufficient bone marrow production. MPV, PDW and P-LCR can be used as biomarkers to explain the cause of thrombocytopenia and to avoid invasive bone marrow biopsy [12].

4. Discussion

Platelet indices are potentially useful markers of various diseases, yet their utility does not come without certain limitations. Preanalytical factors, such as, with- or without stasis vein puncture, anticoagulant used ethylenediamine tetraacetic acid - EDTA or citrate, temperature of blood sample or time between blood sampling and testing can influence the measurements of PIs [29]. For example, EDTA causes the platelets to shift from discoid to spherical shape resulting in variations of MPV value [46]. Also, low sample temperature causes the platelets to decrease their volume, whereas warming causes MPV to increase [29]. However, extended sample storage time causes PDW decrease [47]. Additionally, different methods used (optical, impedance) and calibrations of analyzers affect the outcome of measurements, which points out the urging need of PI measurements standardization [48,49]. Despite discussed limitations, platelet indices offer additional diagnostic, as well as, prognostic value. Moreover, the measurement of PIs does not

generate additional costs and can be performed during routine cell blood count not requiring additional blood samples.

5. Conclusions

In summary, the use of automatic hematological analyzers allows for easy assessment of platelets indices in complete blood count. The platelet indices are the subject of numerous investigations due to the pivotal role of platelets in hemostasis, inflammation, defense against pathogens, wound healing and angiogenesis. What is more, changes in platelet indices have been confirmed as having significant prognostic and diagnostic value in multiple diseases such as thrombocytopenia, sepsis, myocardial ischemia, trauma and others. However, further investigations should be performed to fully assess the role of platelet indices in numerous conditions.

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The Author contribution

Study Design: Karolina Pogorzelska, Anna Krętowska, Maryna Krawczuk – Rybak, Małgorzata Sawicka – Żukowska.

Data Collection: Karolina Pogorzelska, Anna Krętowska, Maryna Krawczuk – Rybak, Małgorzata Sawicka – Żukowska.

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Data Interpretation: Karolina Pogorzelska, Anna Krętowska, Maryna Krawczuk – Rybak, Małgorzata Sawicka – Żukowska.

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Declaration of competing interest

The authors declare no conflict of interests.

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