

Hematological Parameters as Prognostic Biomarkers in Patients with Cardiovascular Diseases

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Abstract: Cardiovascular diseases are the major causes of preventable health loss from disease in the world and lead to functional disturbances including hematological parameters. The inflammatory and hypoxemic nature of cardiovascular diseases causes a stimulus in the bone marrow and, depending on the intensity of this stimulus, there is a release of immature cells or increase of other cells in the bloodstream. Therefore, their presence in the circulation is an important variable used to diagnose, stratify and predict diseases.

In the last five decades, with the advent of automated counting of immature cells in the peripheral blood, the hemogram was transformed into a clinical tool of great importance in hospital surveillance for demonstrating this daily variability in the hematopoietic response according to the existing injury in the patient. Studies have shown that the presence of nucleated red blood cells and increases in mean platelet volume, immature granulocytes and neutrophil to lymphocyte ratio in the systemic circulation are independent prognostic biomarkers.

This review article has as main objective to demonstrate the association of these hematological parameters to cardiovascular diseases, emphasizing their importance in clinical decision making.

Keywords: Nucleated red blood cells, neutrophil to lymphocyte ratio, mean platelet volume, immature granulocytes, biomarkers, cardiovascular diseases.

1. INTRODUCTION

The cardiovascular diseases (CVD) are among the major causes of preventable health loss from disease in the world, regardless of a country's income socio-demographic status [1]. These diseases are influenced by population aging, genetic predisposition, eating habits, stress, dyslipidemia, diabetes mellitus, systemic arterial hypertension, sedentary lifestyle and risk behaviors such as smoking and alcohol abuse [2]. Studies have demonstrated a strong association between hematological parameters and the risk of adverse outcomes in patients with CDV due to the inflammation and systemic hypoxemia implicated in the pathophysiology mechanisms, and depending on the extent of the injury, causing circulatory failure and, consequently, organic dysfunction [3-5].

The technological advancement of the last five decades and the development of modern automated equipment in the evaluation of blood cells have a great impact on the research of these blood biomarkers, mainly in the prognostic

evaluation in cardiovascular diseases (Table 1). In healthy adults, we did not find immature blood cells in the systemic circulation. Apart from hematological and oncological diseases, the inflammatory and hypoxemic processes are the main stimuli for the greater production by the bone marrow of the constituents of the blood. The presence of these immature young cells in the peripheral circulation is directly associated with the intensity of systemic inflammation and hypoxemia and, consequently, with a poorer prognosis [3, 4].

Previous studies have demonstrated the prognostic value of these hematological parameters in stroke [5, 6], coronary artery disease [7, 8], heart failure [9, 10], systemic arterial hypertension [11, 12], atrial fibrillation [13] and cardiovascular disease associated with septicemia [3, 14]. Therefore, it is important to review these blood cells count as potential clinical analyzers (Table 2) [15].

2. PATHOPHYSIOLOGICAL MECHANISMS

The organ responsible to produce blood cells (red blood cells, leucocytes and platelets) is the bone marrow, a process called hematopoiesis. These cells are originated from a single progenitor cell called the stem cell. These pluripotent

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Table 1. Complete blood count parameters (adapted by Ralph and Sebastian W-Hogiu [18]).

Methodology	Discoverer / Year
Microscope	Vierordt / 1852
Light scattering and absorption measured by eye	Oliver / 1896
Light scattering and absorption measured with a photodetector	Marcandier <i>et al.</i> /1928
Impedance measurement	Coulter / 1953
Impedance measurement and Electrostatic cell sorting	Fulwyler / 1965
Fluorescence-based flow cytometry	Dittrich and Göehde/ 1968
Fluoresce-activated cell sorting	Julius <i>et al.</i> / 1972
Light scattering in flow cytometry	George and Groner / 1973
Parameters	Reporting Units
RBC count	(usually x 10 ¹²)/L
MCV	fL
MCH	pg or fmol
MCHC	g/dL, g/L, mmol/L
RDW	%CV or fL
Hematocrit	% or L/L
Hb concentration	g/dL, g/L, mmol/L
Reticulocyte count	(usually x 10 ⁹)/L
NRBC	(usually x 10 ⁹)/L
WBC count	(usually x 10 ⁹)/L
Lymphocytes	(usually x 10 ⁹)/L
Monocytes	(usually x 10 ⁹)/L
Neutrophil granulocytes	(usually x 10 ⁹)/L
Eosinophil granulocytes	(usually x 10 ⁹)/L
Basophil granulocytes	(usually x 10 ⁹)/L
Platelet count	(usually x 10 ⁹)/L
MPV	fL

Abbreviations: RBC, red blood cell; MCH, mean cell Hb; MCHC, mean cell Hb Concentration; RDW, red cell distribution width; MPV, Mean platelet volume; %CV, % coefficient of variation; fL: femtoliter (x 10⁻¹⁵L); fmol: femtomol (x 10⁻¹⁵mol); pg: picogram (x 10⁻¹²g).

Table 2. Potential clinical measures of hematological parameters analyzers (adapted by Thomas Pierre and Michael Bernimoulin [15]).

Blood Cells	Parameters	Clinical Measures
Red blood cells		
	% hypochromic red blood cells	Assessment of iron-restricted erythropoiesis
	Low hemoglobin density	Assessment of iron-restricted erythropoiesis
	Red cell distribution width	Anisocytosis
	Immature reticulocyte fraction	% Immature erythrocytes
	Reticulocyte hemoglobin content	Iron deficiency anemia
	Nucleated red blood cells	Bleeding disorders, hypoxemia
	Schistocytes	Hemolytic anemia
White blood cells		
	Immature granulocyte	Infections
	White cell volume	Infections
	High fluorescent lymphocytes	Atypical lymphocytes
Platelets		
	Immature platelet fraction	% immature platelet and thrombocytopenia
	Platelet distribution width	thrombocytopenia
	Mean platelet volume	Platelet activation and thrombocytopenia
	Large cell ratio	Bleeding disorders and thrombocytopenia
	Platelet dry mass	Histogram of platelet
	Plateletcrit	Platelet activation

stem cells can reproduce when necessary and lead to differentiation processes in distinct hematological cell lines [16] (Fig. 1). There are proteins responsible for the induction of cell multiplication and other proteins are responsible for cellular differentiation, called differentiation inducers, which are controlled by factors external to the bone marrow. For example, blood exposure to low oxygen concentrations over a long period results in the induction of growth, differentiation and production of an increased number of red blood cells. This stimulus to the bone marrow is produced by erythropoietin, a glycoprotein produced in 90% by the kidneys, the rest being formed, for the most part, in the liver, in the presence of hypoxemia [16].

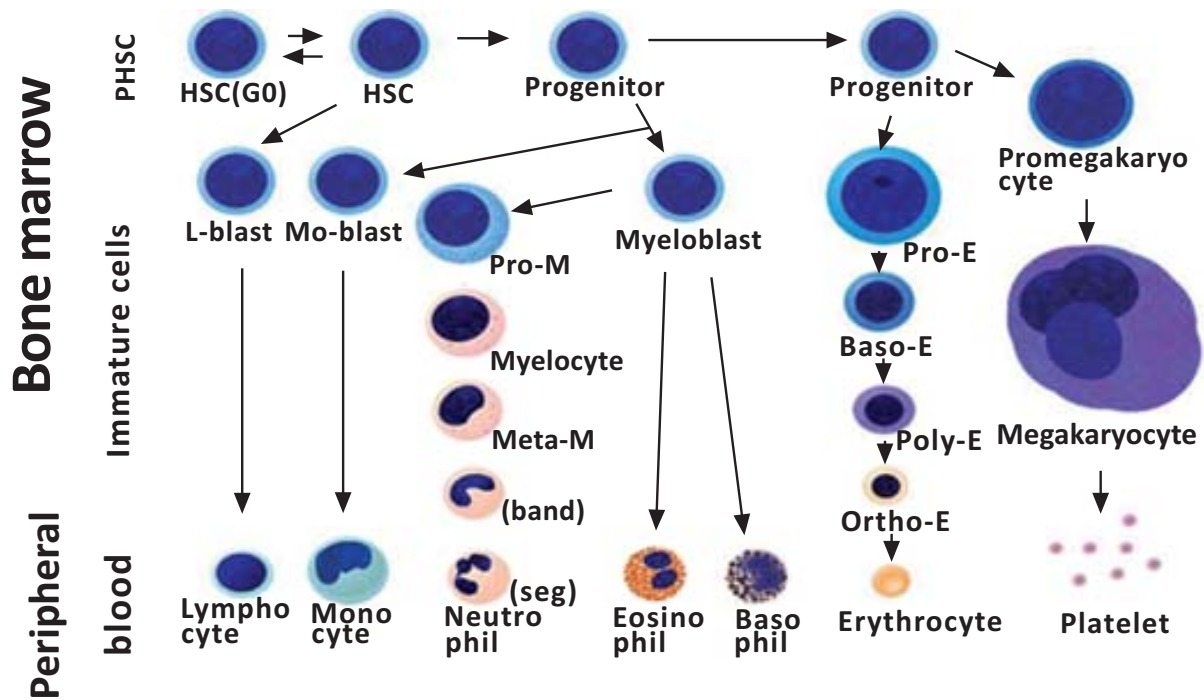


Fig. (1). Formation of blood cell differences from pluripotent hematopoietic stem cell (PHSC) in bone marrow.

Infectious diseases cause growth, differentiation and final formation of specific types of leukocytes for each pathogen. Therefore, in the inflammatory process caused by bacteria, trauma, chemical agents, heat or any other phenomenon, there is a specific cellular differentiation at the spinal level. In relation to platelets, which are cells formed in the bone marrow from megakaryocytes, there are small fragments of anucleated cells that have a characteristic discoidal form and vary from 1 to 3 μm in diameter, which have an important role in hemostasis, inflammation and innate immunity [16, 17].

3. HEMOGRAM: NEW PARAMETERS

The development of microscopy over more than 300 years ago by Van Leeuwenhoek was a milestone in laboratory medicine. Consequently, experimental research was boosted due to the observation that the blood is formed by small red blood cells and their sizes were eventually determined. In 1870, due to the improvement of optical microscopy with objective corrective lenses by Paul Ehrlich, it was possible to distinguish between different types of white blood cells. However, despite this differentiation in morphology, it was observed that the number of cells changed in many diseases; therefore, the need for the quantitative measurement of these cells. A laborious manual measurement was introduced as it was counted cell-by-cell, attempting to quantify and describe the volume and geometry of cells [18].

Another method of automated measurement based on electrical impedance has been developed since the work of Wallace Coulter in 1940. Therefore, with technological advances in optics, electronics and microfluidics, new improvements are being directed towards the development of new agents and contrast methods, which will allow greater accuracy and precision in the automated analysis [18].

3.1. Nucleated Red Blood Cells

Nucleated red blood cells (NRBCs), also known as erythroblasts, are immature erythrocyte cells present in the bone marrow in the process of hematopoiesis. It is normal to find NRBCs in the peripheral blood of newborns for a few days. However, its permanence in the systemic circulation of children and adults is associated with serious diseases, mainly hematological and oncological. Prior studies have shown that severe hypoxemia and/or infection are responsible for the presence of NRBCs in peripheral blood, when hematological diseases, cancer, congestive heart failure, acute and chronic anemias are excluded [19-21]. It has also been demonstrated that patients with serum NRBCs (NRBCs present in the peripheral circulation) have high concentrations of erythropoietin, interleukin-3 and interleukin-6 suggestive of an important role of tissue oxygenation and/or inflammation, caused by local or systemic disorders, and presenting a poorer prognosis [19].

Therefore, the presence of serum NRBCs in hospitalized patients with cardiovascular diseases is associated with increased mortality and the need for these patients to stay in the intensive care unit even with clinical improvement [3]. In a study published by our research group [3], we observed that the inclusion of the NRBCs in the model including the APACHE II score would result in an increase in the area under the ROC curve from 0.7668 to 0.7929, $p = 0.011$ (Fig. 2).

Another important parameter in clinical practice is the measurement of erythrocyte size variability in the systemic circulation, the RDW (Red Blood cell distribution range), which, in healthy adults, is about 4.0 to $6.0 \times 10^6 / \text{mm}^3$ but high levels, according to some studies, are associated with poorer prognosis in heart failure and coronary disease [22, 23]. Another variable also well studied is the aggregation of erythrocytes, which is associated with cardiovascular

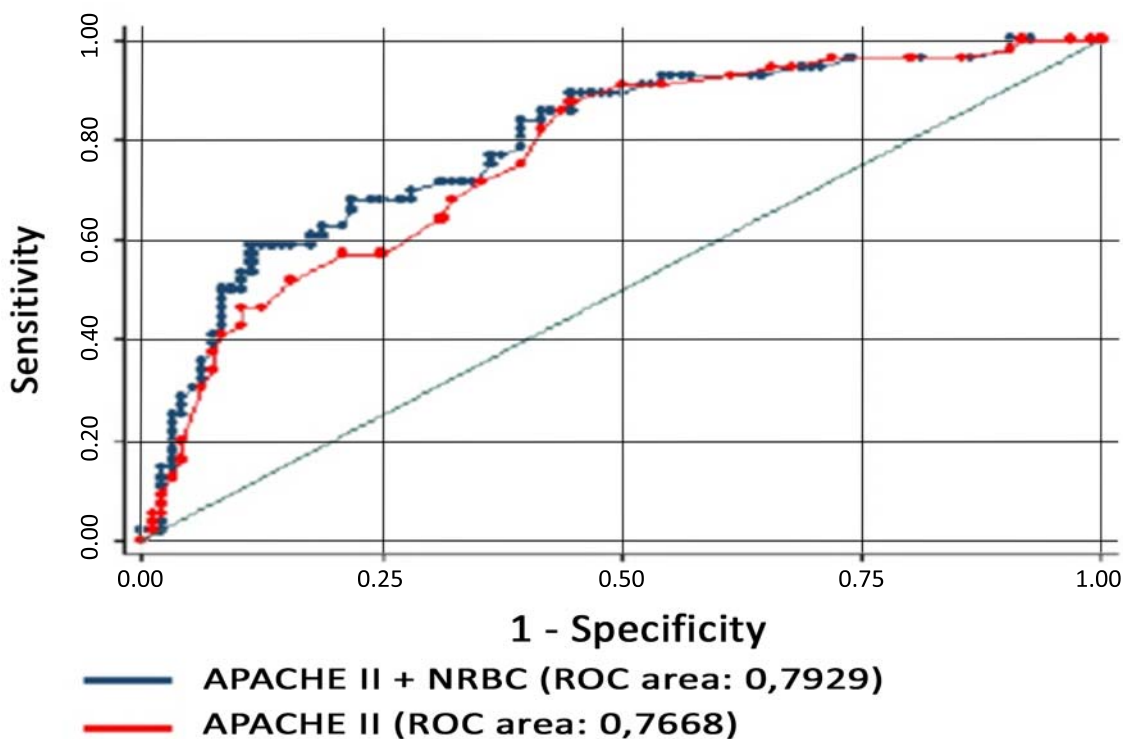


Fig. (2). comparison of the ROC curves, $p = 0.01$.

diseases [24]. Several studies conditions increased erythrocyte's aggregation with myocardial ischemia and infarction [25], cerebral ischemia and infarction [26] and peripheral vascular diseases [27].

3.2. Neutrophil to Lymphocyte Ratio

In the investigation of atherosclerosis, we have focused on inflammation, which participates articulately in all stages, from the beginning of the lesion to the progression and destabilization of the plaque, which determined studies evaluating certain inflammatory factors in the prognosis of cardiovascular risk [28]. C-reactive protein (CRP) has been the most studied and most applicable in clinical practice. However, its predictive value was recently questioned and the need for new complementary markers is evident [29].

The blood count is performed routinely on admission and carries important prognostic information. The neutrophil to lymphocyte ratio (NLR), a combination of two independent markers of inflammation, is considered a simple and non-specific marker of inflammation [30]. White blood cells, particularly lymphocytes, cause an important modulation in the inflammatory response. Lymphopenia has been associated with progressive atherosclerosis in clinical and experimental studies [31].

Studies have shown that the NLR is a strong predictor of short and long-term mortality in stable and unstable coronary insufficiency. Patients with non-ST-segment elevation myocardial infarction with $NLR > 4.7$ have a mortality rate of 29.8% compared to those with $NLR < 3$, with a mortality rate of 8.4 ($p < 0.001$) [32]. In another study, using a 2.54 cut-off point, NLR was a predictor of severe atherosclerosis

with a sensitivity of 74% and specificity of 53% (ROC curve 0.627; 95% CI: 0.545-0.704, $p = 0.004$) [33]. There are also studies demonstrating the association between NLR and the extent and severity of coronary artery disease [34, 35].

3.3. Plaquetogram

The multiple quantitative and qualitative platelet parameters, evaluated by the electronic counters, justify applying the term plaquetogram, in analogy to the other subdivisions of the hemogram. Parameters evaluated included platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), cross-linked platelets (RT) and platelet-cell ratio (P-LCR) [36, 37].

Platelets are found in the systemic circulation with a concentration between 150,000 and 450,000 mm^3 , 70% of which are present in the circulation for approximately 10 days and 30% in the spleen [38]. Platelet counts represent a dynamic equilibrium of many simultaneous processes, including altered capillary permeability and inflammatory cascades, as well as the coagulation process [39]. An abnormal fall in the number of platelets in the bloodstream, known as thrombocytopenia ($< 150 \times 10^9/\text{L}$), may result in increased bleeding. Studies have associated this decline in platelet count with unfavorable clinical outcomes [39-41]. In a recent publication of our research group [42], we categorized patients for serum platelet count as mild ($100-149 \times 10^9/\text{L}$), moderate ($50-99 \times 10^9/\text{L}$) and severe ($< 50 \times 10^9/\text{L}$) associated with mortality during hospitalization period (Fig. 3).

Large platelets are metabolically and enzymatically more active than small platelets and they are reflected by elevation

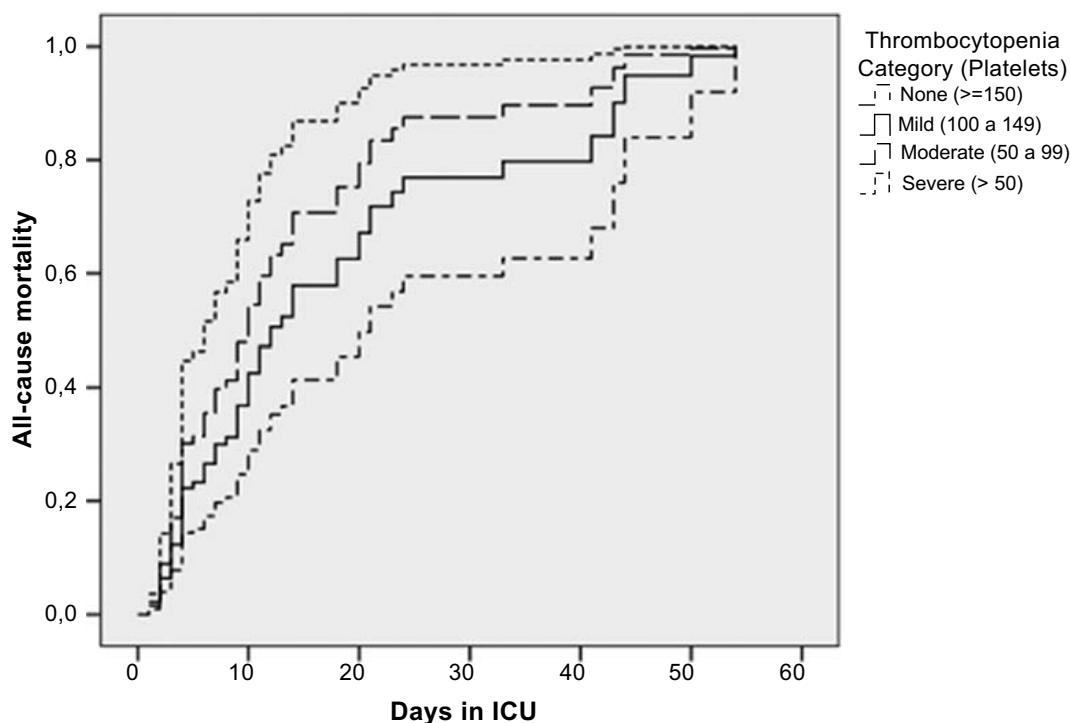


Fig. (3). Kaplan-Meier curve for mortality (death). Patients categorized by platelet count during the period of hospital stay (days).

in mean platelet volume (MPV). Therefore, platelets are heterogeneous in relation to platelet volume and density, biological variables that determine platelet function and activity, with an important role in the development of intravascular thrombus [38]. In the study by Uysal *et al.* [33], the value of the MPV above 10.4 is a predictor of severe atherosclerosis with a sensitivity of 39% and specificity of 90% (ROC curve: 0.631, 95% CI: 0.549-0.708, $p = 0.003$), and can be used as a predictor and cardiac risk identifier in patients with coronary artery disease. Therefore, MPV has been identified as an independent risk factor for acute myocardial infarction (AMI) in patients with coronary artery disease [43, 44].

Recent studies have demonstrated that immature platelets, also known as reticulated platelets, because they are analogous to reticulocytes, immature red blood cells, contain measurable amounts of cytosolic messenger ribonucleic acid (mRNA) that, unlike normal mature platelets, continue in protein synthesis and aggravate their prothrombotic potential in acute coronary syndrome (ACS) [45]. In addition, the response of these immature platelets to the ticlopidine clopidogrel and prasugrel is significantly decreased and obviously related to the serum level [46]. Therefore, these findings indicate that there is a justification for the evaluation of these platelets, cross-linking for risk stratification in patients with ACS who receive dual antiplatelet therapy with aspirin and thienopyridines [46, 47].

3.4. Immature Granulocytes

Immature granulocytes (IG), which comprise the sum of metamyelocytes, myelocytes and promyelocytes, are cells released into the systemic circulation resulting from bone marrow stimuli, such as bacterial infection, acute inflammatory diseases, cancer (particularly spinal metastasis),

tissue necrosis, acute transplant rejection, surgical trauma, orthopedic trauma, myeloproliferative disease, steroid use and pregnancy (especially in the third trimester). However, in the elderly, neonates or immunosuppressed individuals, $IG > 2\%$ may be indicative of acute infection, even if the patient does not have neutrophilia or neutropenia [48].

Therefore, the counting of immature cells by automation is faster, more accurate, and determined while the other blood count parameters are released. This means agility in the knowledge of diagnostic hypotheses and patient care. Ansari-Lari *et al.* [49] observed that the $IG > 3\%$ is a specific predictor of sepsis. According to the Surviving Sepsis Campaign: the International Guidelines for the Management of Severe Sepsis and Septic Shock (2012), the inflammatory variables below are part of the diagnostic criteria of sepsis: 1 - Leukocytosis (leukocytes $> 12 \times 10^3 / \mu\text{L}$), 2 - Leukopenia (leukocytes $< 4.0 \times 10^3 / \mu\text{L}$) and 3 - Normal leukocyte count and $IG > 10\%$ [50].

4. CLINICAL IMPLICATIONS

The appearance of nucleated red blood cells and increases in mean platelet volume, neutrophil to lymphocyte ratio and immature granulocytes in peripheral blood are directly associated with the intensity of systemic inflammation and hypoxemia. These two mechanisms are directly implicated in the pathophysiology of organic dysfunction, according to clinical studies (Table 3).

Ischemic stroke (IS) is one of the leading causes of disability and death around the world. Fan *et al.* [5] hypothesized that the prognostic value of these routine hematological parameters can be explained by inflammation and stress. This study indicated that routine hematological parameters, including NLR, eosinophil and RDW are useful

Table 3. Hematological parameters in clinical studies.

Clinical studies (First Author / Year)	Hematological Parameters (Results)
ISCHEMIC STROKE	
Lou Fan / 2017	Eosinophil: OR 0.74 (95% CI: 0.67-0.82) Neutrophil: OR 0.76 (95% CI: 0.67-0.84) WBC: OR 0.72 (95% CI: 0.64-0.81) RDW: OR 0.65 (95% CI: 0.56-0.73) NLR: OR 0.76 (95% CI: 0.68-0.84) Monocyte: OR 0.67 (95% CI: 0.59-0.76) Lymphocyte: OR 0.75 (95% CI: 0.67-0.83) RDW: Total stroke: HR 1.31 (95% CI: 1.11-1.54) Cerebral infarction: HR 1.32 (95% CI: 1.10-1.58) Intracerebral hemorrhage: Adjusted HR 1.44 (95% CI: 0.90-2.30) Subarachnoid hemorrhage: Adjusted HR 0.94 (95% CI: 0.43-2.07)
Martin Söderholm / 2015	
ATHEROSCLEROSIS (CORONARY DISEASE)	
Jan Budzianowski / 2017	Review article: WBC >10.000; NLR >4.9; RDW >14.0%; PDW >17%; MPV > 7.1% provide risk stratification, pathophysiology and optimal management.
José Gildo / 2018	NRBC: HR 2.42 (95% CI: 1.35-4.36) NLR: HR 5.02 (95% CI: 1.68-15.0) MPV: HR 2.97 (95% CI: 1.15-7.67)
HEART FAILURE	
Guoxing Wan / 2018	NLR \geq 3.96 Gene SLC22A4: OR 5.219 (95% CI: 1.762-15.458) Gene ILIR2: OR 5.228 (95% CI: 1.560-17.515) Gene VNN3: OR 3.478 (95% CI: 1.322-9.195)
Sem Liu / 2016	RDW: OR 2.531 (95% CI: 1.371-4.671)

SYSTEMIC ARTERIAL HYPERTENSION	
Marzieh Emamian / 2017	Multivariate OR: WBC: 1.01 (95% CI: 0.94-1.09) RBC: 0.92 (95% CI: 0.66-1.28) HCT: 1.02 (95% CI: 1.003-1.04) MCV: 0.98 (95% CI: 0.96-1.002) RDW: 0.98 (95% CI: 0.94-1.02)
Bamlaku Enawgaw / 2017	Median (IQR) value with p <0.005: WBC, RBC, Hgb, HCT, MCV Mean (SD) vakue with p <0.005: MCHC, RDW, MPV, PDW Median (IQR) value p=0.262: PLT
ATRIAL FIBRILLATION	
Alexander Weymann / 2017	Systematic review with meta-analysis: 22 studies were analyzed including a total of 6098 patients. Weighted mean difference (preoperative): PC: -7.07 x 10 ⁹ /L and p <0.001 MPV: 0.53 FL and p <0.001 WBC: 0.130 x 10 ⁹ /L and p <0.001 NLR: 0.33 and p <0.001 RDW: 0.36% p <0.001 Weighted mean difference (postoperative): WBC: 1.36 x 10 ⁹ /L and p <0.001 NLR: 0.74 and p <0.001
SEPTICEMIA	
José Gildo / 2015	NRBC: Univariate model: OR 3.37 (95% CI: 1.64-6.89) Multivariate model: OR 1.81 (95% CI: 0.79-4.12)

Abbreviations: OR, Odds ratio; HR, Hazard ratio; WBC, white blood cell; RBC, red blood cell; PDW, platelet distribution width; HTC, hematocrit; Hgb, hemoglobin; MCV, mean corpuscular volume; MCH, mean cell Hb; MCHC, mean cell Hb Concentration; RDW, red cell distribution width; NRBC, nucleated red blood cell; MPV, Mean platelet volume; NLR, neutrophil to lymphocyte ratio; PDW, platelet distribution width; PLT, platelet count.

and independent prognostic factors for IS. Another study by Martin Söderholm *et al.* [6] demonstrated the association between high RWD with an increased incidence of total stroke and cerebral infarction, but there was no significant association between RDW and incidence of intracerebral or subarachnoid hemorrhage.

Atherosclerosis is currently considered as a chronic inflammatory disease, leading to an endothelial dysfunction associated with the activation of the immune system. Coronary disease is most commonly caused by atherosclerosis. In the review article by Jan Budzianowski *et*

al. [7], the authors shall describe the main hematological parameters and their prognostic and diagnostic values in patients with the acute coronary syndrome. For examples, $NLR > 4.9$ enabled a clinician to predict stent thrombosis and the high mortality rate among patients with acute myocardial infarction (70% accuracy and 65% specificity in predicting in-hospital mortality) and MPV was a strong and independent predictor of impaired reperfusion and 6-month mortality in patients with acute myocardial infarction who underwent primary percutaneous coronary intervention. They conclude the article referring to the importance of these hematological parameters in the identification of high cardiovascular risk in secondary prevention and tailor the therapy to their needs. Monteiro Junior *et al.* [8] associated increased NRBC, MPV and NRL in peripheral blood with higher in-hospital mortality in patients with acute myocardial infarction. Therefore, they considered these variables an important in-hospital tool of clinical surveillance.

Heart failure, commonly the end-stage of most cardiovascular diseases, is a complex inflammatory neuroendocrine syndrome not merely an exclusive problem of low cardiac output [9]. Wan *et al.* [9] described the association between NLR and three genes SLC22A4, IL1R2 and VNN3 with heart failure. NLR is considered a useful prognostic index for many cardiovascular diseases. The current study is the first to investigate the potential decisive factors associated with elevated NLR in heart failure by microarray assay of genes. The researcher Liu *et al.* [10] demonstrated in patients with heart failure, the elevated RDW with an independent risk factor for mortality.

Atrial fibrillation is one of the most critical common complications after cardiovascular surgery such as thromboembolism, cerebrovascular events, prolonged hospital stay and readmissions to the intensive care unit (ICU) and hospital, organ failure, as well as an increase in health care costs and mortality [13]. In this study, the authors concluded that hematological parameters may predict the risk of postoperative atrial fibrillation before surgery and these exams should be evaluated in all patients submitted to myocardial revascularization and valvular surgical or combined procedures.

In septicemia, the immature granulocyte is associated with the bacterial infectious process. Therefore, it helps the clinician in differentiating whether the inflammation is due to an infectious process or not. In addition, it is a prognostic marker of severity in patients with infectious disease. Musher *et al.* [14] recently published a review article associating acute infection and myocardial infarction. This study has confirmed that acute bacterial and viral infections are associated with an increased risk of myocardial infarction in the short, intermediate and long term. However, we will need to discuss the mechanisms that might explain this association.

Therefore, the presence of nucleated red blood cells and increases in neutrophil to lymphocyte ratio, mean platelet volume and immature granulocyte in peripheral blood are an important tool of daily monitoring of the clinical response after treatment. Persistence or worsening of these variants in the bloodstream is associated with poorer prognosis.

CONCLUSION

These new hematological parameters derived from the hemogram, obtained in an automated way, simple and low cost, need to be valued as a daily tool of prognostic surveillance of hospitalized patients. As we have seen, there is much evidence in the medical literature that corroborates that nucleated red blood cells, neutrophil to lymphocyte ratio, mean platelet volume and immature granulocyte are independent biomarkers of cardiovascular death risk.

However, more research on these biomarkers is necessary to establish these variables in daily practice, helping the clinician in the diagnosis and prognostic evaluation of cardiovascular diseases.

LIST OF ABBREVIATIONS

ACS	=	Acute Coronary Syndrome
AMI	=	Acute Myocardial Infarction
APACHE II	=	Acute Physiology and Chronic Health Evaluation II
CVD	=	Cardiovascular Diseases
CRP	=	C-Reactive Protein
IG	=	Immature Granulocytes
ICU	=	Intensive Care Unit
MPV	=	Mean Platelet Volume
NLR	=	Neutrophil to Lymphocyte Ratio
NRBCs	=	Nucleated Red Blood Cells
PDW	=	Platelet Distribution Width
P-LCR	=	Platelet-Cell Ratio
PLT	=	Platelet Count
PROCAPE	=	Pernambuco Cardiac Emergency Hospital
RDW	=	Red Blood Cell Distribution Range
ROC	=	Receiver Operating Characteristic
RT	=	Cross-linked Platelets

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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