Review Article

The Role of Hematological Indices in Patients with Acute Coronary Syndrome

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An increased systemic and local inflammation plays a key role in the pathophysiology of acute coronary syndrome (ACS). This review will discuss the role of hematological indices: white blood cells (WBC), neutrophil to lymphocyte ratio (NLR), red cell distribution width (RDW), and platelet indices, that is, platelet to lymphocyte ratio (PLR), mean platelet volume (MPV), and platelet distribution width (PDW) in the case of ACS. In recent years, strong interest has been drawn to these indices, given that they may provide independent information on pathophysiology, risk stratification, and optimal management. Their low-cost and consequent wide and easy availability in daily clinical practice have made them very popular in the laboratory testing. Furthermore, many studies have pointed at their effective prognostic value in all-cause mortality, major cardiovascular events, stent thrombosis, arrhythmias, and myocardial perfusion disorders in terms of acute myocardial infarction and unstable angina. The most recent research also emphasizes their significant value in the combined analysis with other markers, such as troponin, or with GRACE, SYNTAX, and TIMI scores, which improve risk stratification and diagnosis in ACS patients.

1. Introduction

Coronary heart disease (CHD), most commonly caused by atherosclerosis, is the leading cause of death worldwide. Atherosclerosis is a systemic, lipid-driven immune inflammatory disease [1]. Inflammation, one of the factors leading to coronary artery disease (CAD), can be not only local but also systemic. Research carried out by Dutta et al. [2] proved that myocardial infarction is linked to an increased myeloid activity. Interestingly, it has also been shown that in the case of mice with an induced myocardial infarction, the sympathetic nervous system (SNS) becomes activated. This, in turn, induces the release of hematopoietic stem cells (HSPCs) from bone marrow niches, which consequently causes the further systemic stimulation of atherosclerotic plaques.

The chronic low-grade inflammation plays a key role in the initiation and development of the atherosclerotic plaque, which subsequently leads to the plaque’s instability with a thrombus formation. Inflammation is also considered to be one of the main causes of diabetes, hyperlipidemia, metabolic syndrome, and endothelial dysfunction [3]. The inflammation leading to ACS encourages research into the clinical usage of new inflammatory biomarkers.

In this review, we shall describe the main hematological indices and their prognostic and diagnostic value in patients with ACS. In recent years, strong interest has arisen in these indices, given that they may provide independent information on pathophysiology, risk stratification, and optimal management.

The main advantage of hematological indices is that they are relatively inexpensive and thus widely and easily available in daily clinical practice. They have also proven their diagnostic and prognostic value in many cardiovascular diseases including CAD, atrial fibrillation following...
the coronary artery bypass graft (CABG) procedure, acute and chronic cardiac insufficiency, cardiac arrhythmias, and pulmonary hypertension.

2. White Blood Cell Count (WBC)

Leukocytes play a key role in the pathophysiology of ACS, given their effect on the instability of atherosclerotic plaques. In the initial stage, leukocytes permeate endothelial cells and become activated when reaching the tunica intima. They induce the formation of microvascularity there and, as a result, make plaques more susceptible to rupture [4]. Many studies have indicated that leukocytosis is related to an increased cardiovascular mortality rate. What is more, leukocytosis also proved to be of prognostic value when assessing adverse clinical outcomes [5–7].

In the study of Sabatine et al., the elevated WBC count was found to be a relevant death risk factor during the first 30 days and 6 months following the myocardial infarction among patients with ACS (UA, NSTEMI). Furthermore, the elevated level of WBC was also related to a more advanced CAD as well as epicardial and myocardial perfusion disorders [8]. In another study, the WBC > 10,000 pointed to increased mortality among AMI and UA patients. [9] Many prospective studies have shown that the increased concentration of leukocytes on admission was connected not only to the development of worse microvascular injury, congestive heart failure, and shock but also to the elevated mortality rate in patients with ACS [10].

3. Neutrophil to Lymphocyte Ratio (NLR)

NLR is easily measured by dividing neutrophil count by lymphocyte count in a differential white blood cells (WBC) sample. It is one of the best-assessed hematological biomarkers, which provides prognostic and diagnostic information in ACS. Its role in cardiovascular diseases has been studied extensively in the past few years [11, 12].

The study of Sezer et al. proved that the increased number of neutrophils and MPV in patients with a front wall myocardial infarction is strongly and independently connected to the development of microvascular reperfusion injury after recanalisation of infarct-related artery [13]. In another study, activated neutrophils called polymorphonuclear cells (PMN) were found in coronary thrombi in patients with myocardial infarction who were undergoing primary percutaneous coronary intervention (PCI). PMN release neutrophil extracellular traps (NETs) at the culprit lesion site. NETs are highly proinflammatory and prothrombotic fibers which can entrap leucocytes and propagate thrombosis. NETs proved to be correlated negatively with ST-segment resolution (STR) and positively with infarct size [14]. By contrast, lymphocytes, especially B2 and T helper, as the elements of the adaptive immune system, could mute and limit inflammation. The lower lymphocyte counts were associated with atherosclerosis progression and adverse clinical outcomes in patients with heart failure and ACS [15–17].

The combination of neutrophil and lymphocyte parameters has a better prognostic value than each parameter separately [18]. Kalay et al. demonstrated that NLR is related to the progression of coronary atherosclerosis, the process which is a strong and independent predictor of future coronary events [19]. In Wang et al. meta-analysis, NLR was a predictor of all-cause mortality and cardiovascular events in patients undergoing angiography or cardiac revascularization [20].

In the study of Tamhane et al., the admission NLR was described as a predictor of in-hospital and 6-month mortality in patients who undergo PCI. In the same study, it was proved that higher NLR was associated with diabetes and heart failure [21].

In recent years, numerous papers have been published regarding the value of NLR in predicting short- and long-term mortality in patients with ST-segment elevation (STEMI) [22–25] and with non-NSTEMI [26]. Preprocedural elevated NLR was also linked to an increased risk of significant ventricular arrhythmias during PCI [27].

NRL enables a clinician to predict stent thrombosis and the high mortality rate among patients with STEMI. NLR > 4.9 had 70% accuracy and 65% specificity in predicting in-hospital mortality. In a multidimensional analysis, NLR was strongly linked to stent thrombosis [28]. Furthermore, NRL itself is referred to the complexity and severity of ACS assessed by SYNTAX score, GRACE scale, and TIMI score [29–31].

4. Red Cell Distribution Width (RDW)

RDW which is a part of a standard complete blood count (CBC) is a measure of variations in the volume of red blood cells. An elevation in RDW is known as anisocytosis. An increased level of RDW has been found in patients with vitamin B12, iron, and folate deficiency. RDW has also been observed after blood transfusion and hemolysis [32].

In the study of Patel et al., the RDW values above 14.0% were significantly related to a decreased red blood cell deformability, which can impair the blood flow through microcirculation. The resultant diminution of oxygen supply at the tissue level may help to explain the increased risk of adverse cardiovascular events associated with elevated RDW [33]. In 2007, Felker was one of the first authors who proved that the elevated RDW is a useful biomarker of morbidity and mortality among patients with heart failure [34]. In the study of Arbel et al., the RDW level of 12% and above is associated with an increased risk of cardiovascular morbidity and all-cause mortality in both anemic and nonanemic patients [35].

Many studies have highlighted that the increased RDW has also been linked to peripheral artery disease (PAD) [36], chronic obstructive pulmonary disease (COPD) [37], renal failure [38], sepsis and shock sepsis [39], cerebral atherosclerosis [40], stroke [41], and pulmonary hypertension [42]. Tonelli et al. indicated a relationship between higher levels of RDW and the risk of death and adverse cardiovascular outcomes in people with prior myocardial infarction but without symptomatic heart failure [43]. Moreover, it was shown that the elevated RDW was connected to a higher
mortality rate in patients with a myocardial infarction (with or without anemia) [44–47].

In their study, Lippi et al. showed that the combined measure of RDW and troponin T (cTnT) increased diagnostic sensitivity to 99%, which meant that the combined measure was more effective in diagnosing ACS than the measure of cTnT alone [48]. Moreover, it was proved that RDW is an essential predictor of CAD severity among patients with acute myocardial infarction (AMI) [49].

5. Platelet Indices: PLR, PDW, and MPV

Regardless of their role in the general (systemic) inflammatory response, platelets have been closely related to the activation and coordination of endothelium. It has recently been observed that there is a close relation between cardiovascular mortality and the number of platelets or their ability to aggregate. Platelets play a key role in the pathophysiology of ACS. Compounded with fibrin, platelets form coronary thrombus [1]. The CADILLAC study has shown that the level of platelets (which does not affect the effectiveness of percutaneous interventions) is significantly correlated with the incidence of restenosis and stent thrombosis [50], given the function of platelets in the local as well as general inflammatory response and their aspirin resistance [51, 52].

Platelets participate in the creation of blood clots and deliver mediators which develop and sustain a local inflammatory response [53]. MPV and PDW are important and simple markers which significantly increase during platelet activation [54]. Furthermore, these indices are helpful in the evaluation of thromboembolic diseases.

6. Platelet to Lymphocyte Ratio (PLR)

It turns out that the platelet to lymphocyte ratio is a useful parameter describing the systemic inflammatory response. Thus, it has become an important prognostic factor in numerous diseases. It has been shown that PLR correlates with the prognosis in esophageal, ovarian, rectal, and hepatocellular carcinoma as well as glioma multiform [55].

The roles of PLR and other complex markers of systemic inflammatory response have been primarily described in relation to the prognosis of ACS. It has been shown that PLR correlates with a greater overall mortality in patients with NSTEMI [56]. In the recently published (prospective) study involving 5886 patients, the same relation for STEMI has been presented [57]. The same study also showed that high PLR correlates with the recurrence of myocardial infarction, stroke, and subsequent heart failure. It seems that PLR is also helpful in predicting long-term results of percutaneous interventions and it can help select patients with a higher risk of no-reflow syndrome after pPCI [58, 59].

7. Platelet Distribution Width (PDW)

Platelet distribution width (PDW) indicates a varied size of platelets. The number of large immature platelets in patients with ACS is caused by an increased bone marrow activity during the process known as thrombocytopenia.

PDW measured on admission is a cheap and generally available biomarker which allows for predicting the development of heart failure in patients with ACS after PCI [60]. Bekler et al. showed that an increased level of PDW (>17%) was related to the severity of CAD in patients with ACS. In the same study, an elevated PDW, diabetes mellitus, and myocardial infarction (MI) were positively correlated with a high Gensini score [61]. In a different study, PDW was greater in patients with STEMI than in those with stable CAD [62]. PDW also serves as a useful prognostic factor for long-term mortality in patients after AMI [63, 64].

8. Mean Platelet Volume (MPV)

MPV is a useful, indirect, and easily marked biomarker of platelet activity. Numerous studies support the association of MPV with adverse cardiac outcomes in patients with ACS.

MPV was a strong and independent predictor of impaired reperfusion and 6-month mortality in STEMI patients who underwent PCI [65, 66]. A similar correlation was found in NSTEMI patients [67, 68]. Moreover, Chu et al. showed that in patients who underwent PCI, the elevated MPV occurred in patients who developed restenosis [69]. Similarly, Huczek et al. proved that MPV was significantly higher in patients with ACS who developed an early stent thrombosis. It correlated with a poor dual antiplatelet responsiveness [70]. In another study of 462 patients with CAD who underwent PCI, higher MPV levels were independently associated with high residual platelet reactivity after both aspirin and clopidogrel treatments [71]. This is due to the fact that larger platelets are more often reticulated than smaller platelets containing more prothrombotic material (thromboxane A2, platelet factor 4, alpha-granules, P-selectin, and platelet-derived growth factor), which is an independent predictor of a poor response to dual antiplatelet therapy [72].

MPV turned to be independently responsible for the slow coronary flow (SCF) occurrence and its extent [73]. In the recent years, the correlation of WBC to MPV has been named as the WBC/MPV ratio (WMR). The relationship between WMR and major adverse cardiovascular events (MACE) in patients with NSTEMI [74] and STEMI [75] was more prominent than with WBC and MPV, respectively.

9. Conclusions

There is a high demand for a reliable, accessible, noninvasive, and hematological prognostic marker in ACS, which would identify patients of high cardiovascular risk in secondary prevention and tailor the therapy to their needs. Many of the indices presented here reflect the complex pathophysiology of ACS. The inflammatory processes play a key role in the development of atherosclerosis, destabilisation of atherosclerotic plaques and formation of clots on the plaque surface [76]. The significance of NLR, PLR, PDW, MPV, and RDW in the prognosis of ACS has been indicated in many studies as it has been shown above. The most crucial studies concerning hematological indices have been summarized in Table 1.
### Table 1: Summary of some studies investigating diagnostic and prognostic role of the most important hematological indices.

<table>
<thead>
<tr>
<th>Study type</th>
<th>Study</th>
<th>Sample size</th>
<th>Main findings</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>WBC</td>
<td></td>
<td>WBC count of $&gt;10,000$ was associated with increased 30-day and 10-month mortality. Elevation in WBC count was associated with reduced epicardial blood flow and myocardial perfusion, thromboresistance, and a higher incidence of new congestive heart failure and death.</td>
<td>[9]</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Cannon et al. (2001)</td>
<td>7651 patients with ACS</td>
<td>WBC count of $&gt;10,000$ was associated with increased 30-day and 10-month mortality. Elevation in WBC count was associated with reduced epicardial blood flow and myocardial perfusion, thromboresistance, and a higher incidence of new congestive heart failure and death.</td>
<td>[9]</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Barron et al. (2000)</td>
<td>975 patients with MI</td>
<td>Higher baseline WBC count was associated with impaired epicardial and myocardial perfusion, more extensive CAD, and higher six-month mortality rates.</td>
<td>[8]</td>
</tr>
<tr>
<td>Prospective</td>
<td>Sabatine et al. (2002)</td>
<td>2220 patients with UA/NSTEMI</td>
<td>Elevation in WBC count was associated with reduced epicardial blood flow and myocardial perfusion, thromboresistance, and a higher incidence of new congestive heart failure and death.</td>
<td>[10]</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Gurm et al. (2003)</td>
<td>4450 patients</td>
<td>A low or an elevated preprocedural WBC count in patients undergoing PCI is associated with an increased risk of long-term death.</td>
<td>[11]</td>
</tr>
<tr>
<td>Prospective</td>
<td>Chia et al. (2009)</td>
<td>363 patients with STEMI</td>
<td>Elevated leucocyte and neutrophils are predictors of adverse cardiac events.</td>
<td>[12]</td>
</tr>
<tr>
<td>NLR</td>
<td>NLR</td>
<td></td>
<td>The NLR was an independent significant predictor of long-term mortality in patients who have undergone coronary angiography.</td>
<td>[18]</td>
</tr>
<tr>
<td>Prospective</td>
<td>Duffy et al. (2006)</td>
<td>1046 patients who underwent PCI</td>
<td>The NLR was an independent significant predictor of long-term mortality in patients who have undergone coronary angiography.</td>
<td>[18]</td>
</tr>
<tr>
<td>Prospective</td>
<td>Tamhane et al. (2008)</td>
<td>2833 patients with ACS</td>
<td>NLR was a predictor of in-hospital and 6-month mortality in patients who undergo PCI.</td>
<td>[21]</td>
</tr>
<tr>
<td>Prospective</td>
<td>Núñez et al. (2008)</td>
<td>515 patients with STEMI</td>
<td>NLR was a useful marker to predict subsequent mortality in patients admitted for STEMI, with a superior discriminative ability than total WBC.</td>
<td>[22]</td>
</tr>
<tr>
<td>Prospective</td>
<td>Azab et al. (2010)</td>
<td>1345 patients with NSTEMI</td>
<td>NLR is an independent predictor of short-term and long-term mortalities in patients with NSTEMI.</td>
<td>[26]</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Chatterjee et al. (2011)</td>
<td>30,798 records who have undergone coronary angiography</td>
<td>A preprocedural NLR, elevated WBC count, and neutrophils were predictors of significant ventricular arrhythmias in patients undergoing PCI.</td>
<td>[27]</td>
</tr>
<tr>
<td>Prospective</td>
<td>Akpek et al. (2012)</td>
<td>418 patients with STEMI who underwent PCI</td>
<td>The NLR was independently associated with the development of no-reflow and in-hospital MACEs in patients with ST-segment elevation myocardial infarction undergoing primary PCI.</td>
<td>[23]</td>
</tr>
<tr>
<td>Prospective</td>
<td>Sahin et al. (2013)</td>
<td>840 patients with STEMI who underwent PCI</td>
<td>NLR was the independent predictor for SYNTAX score in patients with STEMI. NLR based on an optimal cut-off value of 7.4 was an excellent predictor of short- and long-term survival in patients with revascularized STEMI.</td>
<td>[24]</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Sawant et al. (2014)</td>
<td>250 consecutive STEMI patients</td>
<td>NLR was the independent predictor for SYNTAX score in patients with STEMI. NLR based on an optimal cut-off value of 7.4 was an excellent predictor of short- and long-term survival in patients with revascularized STEMI.</td>
<td>[31]</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Ayça et al. (2015)</td>
<td>102 patients with stent thrombosis and 450 patients with STEMI</td>
<td>There is a graded independent association between higher RDW values and adverse outcomes in patients with ACS.</td>
<td>[45]</td>
</tr>
<tr>
<td>Prospective</td>
<td>Yaylak et al. (2016)</td>
<td>A total of 213 subjects with inferior STEMI</td>
<td>NLR was an independent predictor of RVD in patients with inferior STEMI undergoing primary PCI.</td>
<td>[25]</td>
</tr>
<tr>
<td>RDW</td>
<td>RDW</td>
<td></td>
<td>In patients with STEMI, preprocedural high NLR was associated with both stent thrombosis and higher mortality rates.</td>
<td>[28]</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Nabais et al. (2009)</td>
<td>1796 patients with ACS</td>
<td>There is a graded independent association between higher RDW values and adverse outcomes in patients with ACS.</td>
<td>[45]</td>
</tr>
<tr>
<td>Study type</td>
<td>Study</td>
<td>Sample size</td>
<td>Main findings</td>
<td>References</td>
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<tr>
<td>Prospective</td>
<td>Lippi et al. (2009)</td>
<td>456 patients with ACS</td>
<td>RDW at admission might be considered with other conventional cardiac markers for the risk stratification of ACS patients admitted to emergency departments.</td>
<td>[48]</td>
</tr>
<tr>
<td>Prospective</td>
<td>Dabbah et al. (2010)</td>
<td>1709 patients with AMI</td>
<td>RDW is a predictor of mortality after AMI. Moreover, an increase in RDW during hospitalization also portends adverse clinical outcome.</td>
<td>[44]</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Uyarel et al. (2011)</td>
<td>2506 STEMI patients</td>
<td>RDW at admission was a predictor of in-hospital and long-term cardiovascular mortality.</td>
<td>[46]</td>
</tr>
<tr>
<td>Prospective</td>
<td>Isik et al. (2012)</td>
<td>135 patients with STEMI</td>
<td>RDW is a marker indicating long-term prognosis.</td>
<td>[47]</td>
</tr>
<tr>
<td>Prospective</td>
<td>Timóteo et al. (2015)</td>
<td>787 patients with ACS</td>
<td>Combination of RDW with GRACE score improves the predictive value for all-cause mortality.</td>
<td>[80]</td>
</tr>
<tr>
<td><strong>PLR</strong></td>
<td><strong>Observational study</strong></td>
<td><strong>Azab et al. (2012)</strong></td>
<td>619 patients with NSTEMI</td>
<td>PLR is a significant independent predictor of long-term mortality after NSTEMI.</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Acet et al. (2016)</td>
<td>800 patients with STEMI</td>
<td>PLR, RDW and monocyte were associated with GRACE score in patients with STEMI.</td>
<td>[81]</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Yildiz et al. (2015)</td>
<td>287 patients with STEMI</td>
<td>High preprocedural PLR and NLR levels are significant and independent predictors of no-reflow in patients undergoing primary PCI. Higher PLR was associated with recurrent myocardial infarction, heart failure, ischemic stroke, and all-cause mortality in patients with STEMI.</td>
<td>[58]</td>
</tr>
<tr>
<td>Prospective</td>
<td>Sun et al. (2017)</td>
<td>5886 patients with STEMI</td>
<td>PLR and NLR were associated with no-reflow phenomenon in patients with STEMI treated with pPCI.</td>
<td>[59]</td>
</tr>
<tr>
<td>Prospective</td>
<td>Vakili et al. (2017)</td>
<td>215 patients with STEMI</td>
<td>PLR and NLR were associated with no-reflow phenomenon in patients with STEMI treated with pPCI.</td>
<td>[59]</td>
</tr>
<tr>
<td><strong>PDW</strong></td>
<td><strong>Prospective</strong></td>
<td><strong>De Luca et al. (2010)</strong></td>
<td>1882 patients undergoing coronary angiography + IMT in 359 patients</td>
<td>PDW is not related to the extent of CAD and carotid IMT. PDW positively correlated with age, weight, waist circumference, and prevalence of diabetes.</td>
</tr>
<tr>
<td>Prospective</td>
<td>Rechciński et al. (2013)</td>
<td>538 patients who underwent primary PCI in acute MI</td>
<td>PDW and P-LCR are prognostic predictors after MI.</td>
<td>[63]</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Celik et al. (2015)</td>
<td>306 patients with STEMI</td>
<td>Baseline PDW and MPV are independent correlates of no-reflow and in-hospital MACEs among patients with STEMI undergoing pPCI.</td>
<td>[64]</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Bekler et al. (2015)</td>
<td>502 patients with ACS were enrolled.</td>
<td>The group with PDW &gt; 17% had significantly higher Gensini score.</td>
<td>[61]</td>
</tr>
<tr>
<td><strong>MPV</strong></td>
<td><strong>Prospective</strong></td>
<td><strong>Huczek et al. (2005)</strong></td>
<td>398 patients with STEMI</td>
<td>MPV is a predictor of impaired reperfusion and mortality in STEMI treated with pPCI.</td>
</tr>
</tbody>
</table>
The authors declare no conflicts of interest.

Conflicts of Interest

The authors declare no conflict of interests.


M. Cetin, E. M. Bakirci, E. Baysal et al., "Increased platelet distribution width is associated with ST-segment elevation..."


