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The relationship between hematological parameters and coronary angiographic lesions

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Atherosclerosis is the most important etiology of acute myocardial infarction, which is considered an inflammatory disease with specific cellular and molecular responses. Recent research has linked hematological variables as biomarkers of the severity of coronary artery disease. Studies suggest that nucleated red blood cells (NRBCs), neutrophil to lymphocyte ratio (NLR), and mean platelet volume (MPV) may serve as components of a laboratory model or hematological scoring system for in-hospital surveillance. Atherosclerotic plaques can be graded using scoring systems, such as the SYNTAX score which is used to evaluate the complexity of coronary artery disease. However, there is an open field for research to explain the complex inflammatory mechanism of these plaques. Research has shown that inflammatory processes, such as those seen in coronary atherosclerotic disease, stimulate the bone marrow to release young and immature cells into the systemic circulation, which actively aggregate and, consequently, form thrombotic plaques. This mini review article aims to demonstrate the relationship between hematological parameters and coronary angiographic findings as potential in-hospital prognostic tools for patients with acute myocardial infarction. This expressive relationship between these hematological biomarkers and coronary atherosclerotic plaques may be a target, in addition to prognostic scores, of future therapeutic interventions.

KEYWORDS

hematological parameters, nucleated red blood cells, neutrophil to lymphocyte ratio, mean platelet volume, coronary angiographic lesions, SYNTAX score, prognostic

1 Introduction

Atherosclerosis is mainly a systemic inflammatory disease, and inflammation plays an important role in the pathophysiology of acute coronary syndrome [1]. The inflammatory and hypoxemic etiology of cardiovascular diseases stimulates the bone marrow, leading to an increased production of certain hematological cells or determining the appearance of immature cells [2]. Previous works have shown hematological parameters as potential tools for in-hospital follow-up and prognosis of patients with acute myocardial infarction (AMI) [1–3].

In this approach, all major blood count variables were represented: erythroblasts or nucleated red blood cell (NRBC) (red blood cells), neutrophil to lymphocyte ratio (NLR) (white blood cells), and mean platelet volume (MPV) (platelets) to evaluate the role relationship with coronary angiographic lesions (SYNTAX score) (Figure 1).

The SYNTAX score is used to verify the extent and severity of coronary artery disease (CAD) and has proven to be a good long-term prognostic marker in different scenarios of coronary artery disease, including patients with acute coronary syndromes (ACS) [4].
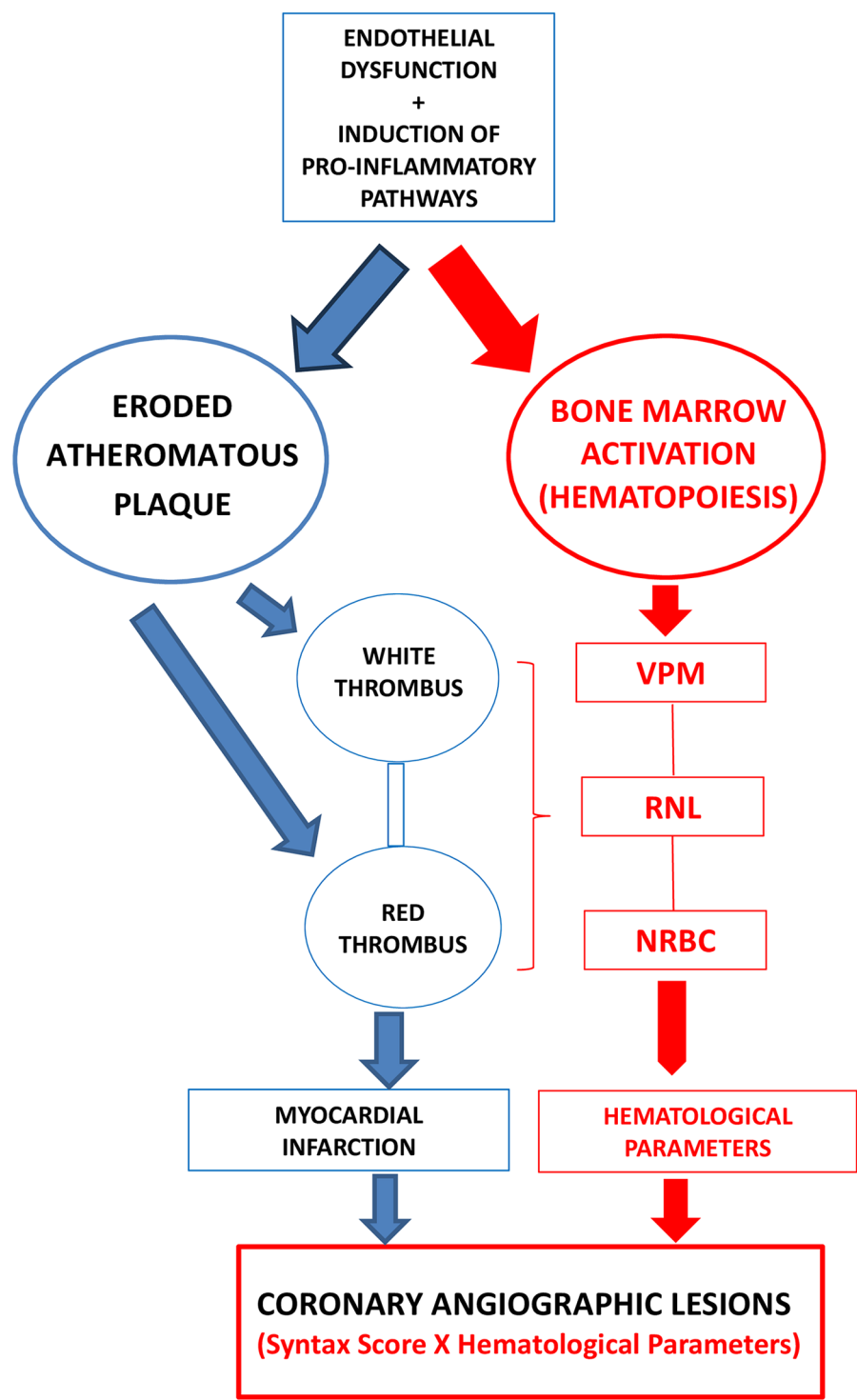
FIGURE 1
The relationship between atherosclerotic plaque and hematological parameters.

The relationship between hematological parameters and anatomical lesions provides new possibilities for hospital monitoring and prognosis of patients with AMI.

2 Hematological parameters

Atherosclerosis is a chronic inflammatory disease involving immune system activation that leads to endothelial dysfunction (5). It is mediated by lipids that induce numerous pro-inflammatory pathways and, together with bone marrow activation, induce myeloid changes, such as synthesis of nucleated red blood cells (NRBCs) and increased neutrophil to lymphocyte ratio (NLR) and mean platelet volume (MPV) in systemic circulation, further contributing to immune cell mobilization and plaque progression (2, 6). Thrombosis superimposed on an eroded or ruptured atherosclerotic plaque is responsible for life-threatening conditions such as acute coronary syndrome and stroke (7). The red thrombus is characterized by a lipid core, plaque rupture, necrotic core, neovascularization, intraplaque hemorrhage, and obstruction (8). Both types of thrombi include platelets and fibrin (9).

Bone marrow produces blood cells, a process called hematopoiesis, which is responsible for the production of red blood cells, leukocytes, and platelets. A single progenitor cell called a stem cell gives rise to all these cells when stimulated by erythropoietin, a glycoprotein produced in 90% of the kidneys, the rest in the liver. Blood exposure to low oxygen concentrations over a long time results in differentiation and increased production of red blood cells (3, 10). Research has shown that hypoxemia and infection trigger differentiation processes into distinct hematological cell lineages (10, 11).

2.1 Nucleated red blood cells

Nucleated red blood cells (NRBCs) are immature erythrocyte cells found in the bone marrow, normally in the peripheral blood of newborns for a few days, but not in adults. Its continuity in the peripheral circulation for children and adults is related to severe hypoxemia and/or infection when hematological diseases, cancer, congestive heart failure, acute and chronic anemias are excluded (12, 13). The presence of NRBCs in the peripheral circulation is associated with high concentrations of erythropoietin, interleukin-3, and interleukin-6 and a worse prognosis (12). Several studies suggest that the detection of NRBCs in hospitalized patients indicates an increased risk of mortality (14).

2.2 Neutrophil to lymphocyte ratio

The neutrophil to lymphocyte ratio (NLR) is composed of two independent markers of inflammation (15). Lymphocytes play an important role in the inflammatory response. Lymphopenia has been linked to progressive atherosclerosis in clinical studies (16). Research has shown an association between NLR and the severity

and extent of coronary disease (17, 18). However, studies have disclosed a strong predictor of short- and long-term mortality in stable and unstable coronary diseases. Azab et al. (19) demonstrated that patients with non-ST-segment elevation myocardial infarction (NSTEMI) with NLR > 4.7 have a mortality rate of 29.8% compared with those with NLR < 3, with a mortality rate of 8.4% ($p < 0.001$).

Studies have shown that higher NLRs are related to a higher SYNTAX score in patients with non-ST-segment elevation acute coronary syndrome and higher numbers of involved coronaries (20, 21). In patients with unstable angina pectoris, NLR proved to be an independent predictor of cardiovascular mortality (22). Kaplangoray et al. (23) published that coronary thrombotic burden correlates with the neutrophil to lymphocyte ratio ($r = 0.335$, $p < 0.001$) and SYNTAX score ($r = 0.351$, $p = 0.001$).

Individuals with drug-eluting stent restenosis (ISR) are more likely to experience serious adverse cardiac events. Patients with higher NLR had higher SYNTAX scores II and greater proportions of vulnerable components of atherosclerotic plaques, demonstrating that NLR is a risk factor for in-stent restenosis (ISR) (24).

2.3 Mean platelet volume

The mean platelet volume (MPV) represents large platelets, which are metabolically and enzymatically more active than small platelets, with an important role in the extension of intravascular thrombus (25). Uysal et al. (26) showed in their study that 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, $p = 0.003$). Therefore, MPV has been appointed as an independent risk factor for acute myocardial infarction in patients with coronary artery disease (27, 28). Studies have shown a positive correlation between VPM and SYNTAX score (29, 30).

2.4 Hematological score

The hematological score is composed of nucleated red blood cells (NRBC), mean platelet volume (MPV), and neutrophil to lymphocyte ratio (NLR), which represent the constituents of the blood count and whose changes are associated with all causes of hypoxemia and inflammation during hospitalization of patients with acute myocardial infarction. This scoring system was developed to monitor these variables, serving as a prognostic parameter. This hematological score, on a scale ranging from 0 to 49, has been shown to be associated with an increased risk of mortality (sensitivity of 89.1%, specificity 67.2%, negative predictive value of 97.9%, positive predictive value of 26.8% and area under the ROC curve of 86.8%). This work was published in 2020 by our research group, but still needs validation (2).

3 Angiographic lesions

The coronary angiographic lesions are classified by considering a scoring system, which is a tool for grading the complexity of

coronary artery disease (31, 32). It specifies information on location, characteristics, tortuosity, and other factors for each lesion, which allowed the online calculator and a Kaplan–Meier curve to show what the cumulative event rate would have been for a patient at a similar risk level in the SYNTAX trial (33, 34). This score classifies coronary lesions into low SYNTAX score (0–22 points), intermediate (23–32 points), and high (≥33 points). Patients with low scores are ideal for percutaneous coronary intervention (PCI), while those with an intermediate or high SYNTAX score are preferentially eligible for surgery (34). Özmen et al. (35) demonstrated a significant relationship between the SYNTAX score and patients with diabetes mellitus.

3.1 SYNTAX score

The SYNTAX score originated from the work published by Patrick Serruys's group in 2009, which compared surgical revascularization with angioplasty using the first-generation *Taxus* drug-eluting stent (Boston Scientific, USA) in patients with a multi-arterial lesion pattern. The study was non-inferiority, and what was seen is that the primary outcome (death from any cause, stroke, myocardial infarction, or repeated revascularization) was more common in the angioplasty group (17.8% × 12.4%, $p = 0.002$). Mortality and infarction were similar in 1 year, and the surgical group experienced a higher incidence of stroke. Therefore, the SYNTAX score is an angiographic severity score of coronary lesions, assessing the difficulty and chance of success of the percutaneous intervention (PCI) (31).

3.2 SYNTAX score II

However, a second version (SYNTAX score II) was shown by Bo Xu's group in 2014, which consisted of adding clinical variables, which enlarged its performance in predicting mortality. The study examined 1,528 patients who underwent angioplasty of the unprotected left main coronary artery. The primary outcome was the ability of SYNTAX score II to predict mortality. Patients were divided into three tertiles: ≤21 points with 508 patients, >21 and ≤28 points with 480 patients, and >28 points with 540 patients. Those in the highest tertile were older, were more likely to be female, had a higher prevalence of prior heart attack and stroke, lower ejection fraction, reduced creatinine clearance, and more extensive coronary disease with complex lesions involving two or three vessels. At the 4-year follow-up, the rates of death, cardiac death, myocardial infarction, and target vessel revascularization were 4.4%, 5%, 7.5%, and 9.5%, respectively, which were significantly higher in the highest and intermediate tertiles. In the multivariate analysis, the SYNTAX score II was associated with an increased mortality rate (HR = 1.76, 95% CI: 1.1–2.82, $p = 0.02$) in patients receiving angioplasty in the unprotected main left coronary artery. The results suggest that SYNTAX score II has greater power to predict mortality compared with the classic SYNTAX angiographic score (36).

4 Hematological parameters and angiographic lesions

The relationship between hematological parameters and angiographic lesions is quite evident in studies published in the literature, especially the neutrophil to lymphocyte ratio and mean platelet volume (Table 1). However, there are still no studies evaluating the relationship between erythroblasts and angiographic lesions.

Prospective cohort study by Rostami et al. (37) included the SYNTAX score and the TIMI flow grade before and after primary percutaneous coronary intervention (pPCI), describing the NLR as an independent predictor of postprocedural no reflow, but not a predictor of the SYNTAX score and the preprocedural TIMI flow grade in patients with ST-segment elevation myocardial infarction (STEMI). However, Maleki et al. (20) demonstrated that higher NLR was significantly associated with higher SYNTAX score ($\beta = 0.162$, $p = 0.021$), and with the same conclusion, Li et al' (22) described that the level of NLR, among other variables, in patients with high SYNTAX score is significantly higher than that in patients with the low SYNTAX score. Zuin et al. (38) demonstrated that the NLR significantly correlated with SYNTAX score with 1-year cardiovascular mortality in patients with ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI) treated with percutaneous coronary intervention (PCI) within 24 h (OR = 2.85, 95% CI: 1.54–5.26, $p = 0.001$ and OR = 2.57, 95% CI: 1.62–4.07, $p < 0.0001$ for STEMI and NSTEMI, respectively). Kurtul et al. (39) demonstrated that NLR was significantly lower in patients with a low SYNTAX score compared with that in patients with an intermediate or high SYNTAX score (3.7 ± 4–4.6 ± 2 and 7.9 ± 4, $p < 0.001$), and linear regression analysis revealed that NLR (coefficient $\beta = 0.380$, 95% CI: 1.165–1.917, $p < 0.001$) was significantly associated with the SYNTAX score in patients with NSTEMI.

The residual SYNTAX score (rSS) is used to determine the severity of obstructive coronary atherosclerosis after initial PCI, and in multivariate logistic regression analysis, the NLR was an independent predictor of high rSS (OR = 3.933; 95% CI: 2.419–6.393; $p < 0.001$) (40). Highly sensitive troponin T and NLR were significantly correlated with angiographic severity of acute coronary syndromes (ACS) assessed by SYNTAX score (41). Therefore, many studies have demonstrated the relationship between NLR and the severity of coronary angiographic lesions represented by the SYNTAX score (42–49).

Previous studies have demonstrated the importance of the participation of mean platelet volume (MPV) as a biomarker of coronary atherosclerotic plaque instability and, consequently, in the relationship with angiographic lesions (SYNTAX score). Vogiatzis et al. (29) described that mean platelet volume (MPV) is a primary indicator of platelet activation. It was significantly correlated to SYNTAX score ($r = 0.658$, $p < 0.001$) and was found to be an independent predictor factor of major advanced cardiac event (MACE) with HR = 6.8 (95% CI: 1.46–33.36). Sahin et al. (50) demonstrated that the association with the extent and complexity of coronary artery disease in diabetic patients with ST-elevation

TABLE 1 Hematological parameters and SYNTAX score in clinical studies.

Clinical studies	SYNTAX score	
Author (year)	Results	
Neutrophil to lymphocyte ratio (NLR)		
Rostami et al. (2021)	After adjustments for age and sex, the NLR and the SII were independent predictors of postprocedural no reflow. However, the NLR and the SII are not predictors of the SYNTAX score and the preprocedural TIMI flow grade.	
Maleki et al. (2021)	Higher NRL was significantly associated with higher SYNTAX score ($\beta = 0,162$, $p = 0,021$).	
Li et al. (2023)	The level of NLR, PLR, and hsCAR and SII in patients with high SYNTAX score are significantly higher than those in patients with low SYNTAX score.	
Tanındı et al. (2023)	Cutoff NLR to predict moderate to severe CAD according to SYNTAX score was 2.26, with 72% sensitivity and 71% specificity (AUC: 0.772, 95% CI: 0.679–0.865, $p < 0.001$).	
Li et al. (2022)	NLR was positive and linearly correlated with SYNTAX score ($r = 0.270$).	
Pan et al. (2022)	The NLR correlated with the Gensini and SYNTAX scores in male CAD patients (both $p < 0.001$).	
Kahraman et al. (2021)	NLR with a cutoff value of 2.59 had good predictive value for increased rSS (area under the curve = 0.707, 95% CI: 0.661–0.752, $p < 0.001$). In conclusion, higher NLR was an independent predictor of increased rSS in patients with STEMI.	
Mean platelet volume (MPV)		
Emre et al. (2020)	The rSS ($p = 0:01$) value of the high WMR group was higher than that of the low WMR group. A higher WMR value on admission was associated with worse outcomes in patients with P-PCI.	
Vogiatzis et al. (2019)	MPV was significantly correlated to SYNTAX score ($r = 0.658$, $p < 0.001$) and was found to be an independent predictor factor of MACE with HR = 6.8 (95% CI: 1.46–33.36). The cutoff value of MPV was 7.5 with a sensitivity of 98% and a specificity of 30.8%.	
Jiang et al. (2019)	Receiver operating characteristic analysis showed a good diagnostic value for MPV at predicting long-term cardiac mortality (area under the curve: 0.735, 95% CI: 0.590–0.880, $p = 0.01$). Elevated MPV was a significant risk factor for 2-year cardiac mortality (hazard ratio: 2.091, 95% CI: 1.075–4.070, $p = 0.030$) in multivariable Cox regression analysis.	
Sivri et al. (2019)	In receiver operating characteristics (ROC) analysis, WMR > 960 predicted a SYNTAX score ≥23 with 80.6% sensitivity and 67.6% specificity (AUC: 0.756; 95% CI: 0.685–0.818; $p < 0.0001$), and a WMR > 1,360 predicted a SYNTAX score ≥33 with 71.4% sensitivity and 93% specificity (AUC: 0.840; 95% CI: 0.777- 0.892; $p < 0.0001$). Higher WMR was associated with a greater SYNTAX score in patients with NSTEMI. WMR may be used to predict the severity of the CAD and to implement risk stratification in patients with NSTEMI.	
Demir et al. (2023)	After adjustment for age, sex, eGFR, troponin levels, and the Global Registry of Acute Coronary Events (GRACE) score in Cox regression models, the association of high WMR with the cumulative incidence of MACE was preserved (overall patients (HR = 1.85, 95% CI: 1.1–3.12, $p = 0.02$) and patients with a SYNTAX score <22 (HR = 2.06, 95% CI 1.15–3.67, $p = 0.01$).	

NRBC, nucleated red blood cell; MPV, mean platelet volume; NLR, neutrophil to lymphocyte ratio; SII, systemic inflammatory immunologic index; PLR, platelet–lymphocyte ratio; hsCAR, high-sensitivity C-reactive protein–albumin ratio; CAD, coronary artery disease; rSS, residual SYNTAX score; WMR, white blood cell counts to mean platelet volume ratio; P-PCI, primary percutaneous coronary intervention; MACE, major advanced cardiac event; HR, hazard ratio; AUC, area under the curve; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

myocardial infarction (STEMI) was stronger than that in non-diabetic STEMI patients ($r = 0.473$, $p < 0.001$ vs. $r = 0.129$, $p = 0.001$). A recent study by Abalı et al. [51] described the relationship between MVP and the severity of coronary atherosclerosis in patients with diabetes mellitus, and they found that MPV has a positive correlation with the SYNTAX score. Ekici et al. [52] were quite categorical in clarifying that a positive correlation between MPV and SYNTAX score ($p < 0.001$, $r = 0.504$).

Therefore, numerous studies have explored the relationship between these hematological variables (NLR and MPV) with the SYNTAX score [53–55]. However, there is limited research examining the nucleated red blood cells (NRBC) with a biomarker in relation to the SYNTAX score. These biomarkers may have great applicability in clinical practice.

5 Discussion

Hematological variables (NRBC, NLR, and MPV), representing the entire spectrum of blood counts in the peripheral circulation, are associated with inflammation and hypoxemia. Coronary angiographic lesions have eminently inflammatory and hematological components, suggesting a likely association between the severity of coronary atherosclerotic plaques (SYNTAX score) and hematological variables. There is substantial evidence in the literature supporting the relationship between mean platelet volume and neutrophil to lymphocyte ratio with coronary angiographic lesions (SYNTAX score), which has not yet been demonstrated with the nucleated red blood cells (NRBC).

These hematological parameters (NRBC, MPV, NLR) have shown potential as valuable tools for in-hospital surveillance of all-cause mortality in patients hospitalized with acute myocardial infarction. However, there is a need for further studies to demonstrate the relationship between these hematological variables and coronary angiographic lesions. In addition to being easy to measure and low-cost, they could serve as useful components of a prognostic scoring system.

Author contributions

TR: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. JM: Conceptualization, Investigation, Methodology, Writing – original draft, Writing –

review & editing. VF: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. DS: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing.

Funding

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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