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Diagnostic significance of complete blood count in cardiovascular patients

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This article discusses the relationship between parameters of complete blood count (CBC) and cardiovascular diseases (CVD). The main advantages of CBC over other methods of CVD diagnostics are low cost and wide availability. At the same time, the low specificity of CBC is an important disadvantage, limiting its diagnostic value.
After analyzing the results of numerous clinical studies, we concluded that the most important CBC are red cell distribution width, mean platelet volume, total leukocyte count, neutrophil to lymphocyte ratio, platelet-to-lymphocyte ratio, monocyte to high-density lipoprotein ratio. We discuss the diagnostic value of each of the above indicators in CVD. Careful attention to these parameters by clinicians can, to a certain extent, improve the therapeutic and diagnostic process in patients with CVD.

Keywords: complete blood count, cardiovascular diseases, red cell distribution width, mean platelet volume, leukocytes, neutrophil to lymphocyte ratio, platelet-to-lymphocyte ratio, monocyte to high-density lipoprotein ratio.

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Cardiovascular diseases (CVD) are globally characterized by widespread prevalence, high mortality, and disability rate [1-3]. CVDs are usually diagnosed via a clinical examination using relatively expensive methods: functional diagnostics, immunochemical methods determining cardiac biomarkers, such as natriuretic peptides, cardiac troponins, etc. [1, 4]. Along with clinical laboratory and systematic functional studies, doctors also widely use clinical blood testing to assess patients' conditions. Such a test is low in cost and widely available, which provides a suitable approach to analyzing and diagnosing problems such as anemia, the risk of infection and/or hematological malignant neoplasms, inflammatory diseases, and coagulation disorders [5, 6]. However, due to its low specificity for CVD diagnosis, the blood test parameters are sometimes overlooked.

Nowadays, with the improvement of present-day advancements and the presence of programmed hematology counters (automated hematology analyzers), it is possible to measure particular parameters associated with changes in the shape and size of cells, in addition to an accurate quantitative study of blood cells, which makes it possible to calculate several additional indicators using software formulas [7, 8]. These calculated values can facilitate the diagnosis and monitoring of many diseases, including CVD. In this review, based on many foreign studies, we estimate the relationship between some modern clinical blood test parameters to CVD and discuss the possibility of their use to monitor CVD and determine patients' prognosis.

According to current data from international research, the most significant diagnostic/prognostic values among all clinical blood test parameters concerning CVD are the following: red cell distribution width (RDW), mean platelet volume (MPV), total white blood cell count (WBC), neutrophil-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte to high-density lipoprotein ratio (MHR). We considered each of these indicators' diagnostic value and discussed the possible mechanisms underlying the change in reference values.

RDW as an independent predictive biomarker for CVD

RDW is an indicator of the clinical blood test, which makes it possible to characterize the degree of variability in size (volume) of erythrocytes — *anisocytosis* (from the Greek *anisos* — 'unequal', *cytos* — 'cell') [9, 10]. Modern hematology analyzers can calculate RDW and detect anisocytosis much faster and more accurately than the microscopic examination of a blood smear. Normal RDW values are 11,5-14,5% but may vary slightly depending on the type of analyzer. This indicator is commonly used for the differential diagnosis of various types of anemias. There are three types of anisocytosis (increased RDW): anisocytosis due to microcytes (small erythrocytes) — characteristic of iron deficiency anemia; anisocytosis due to macrocytes (large erythrocytes) — observed in megaloblastic anemia and mixed anisocytosis — occurs in newborns (physiological anisocytosis) [11, 12].

Several types of research have mentioned the role of RDW as an independent predictive biomarker in cardiovascular diseases. In particular, it was noted that increased RDW is associated with adverse outcomes and mortality in patients with arterial hypertension, heart failure, stroke, acute myocardial infarction (MI), peripheral arterial disease, and in patients with a history of primary coronary intervention. This relationship can be traced in many studies [13-15]. Nevertheless, the specific pathophysiological mechanisms linking increased RDW to CVD are not completely clear [9, 16]. There are several hypotheses and assumptions about this. Systemic factors such as inflammation increased neuroendocrine system activity, and oxidative stress is the most likely hypothesis to explain the relationship between increased RDW and cardiovascular diseases. Mechanisms such as inflammation, increased activity of adrenergic mechanisms, and the renin-angiotensin-aldosterone system, which are frequent CVD companions, lead to a change in the maturation of erythrocyte precursors and a change in the size of erythrocytes — anisocytosis and an increase in RDW. Oxidative stress also significantly increases RDW in acute inflammatory conditions, causing damage to erythrocyte cell membranes and enhancing the release of immature erythrocytes from the red bone marrow into peripheral blood [10, 12, 16].

A prospective cohort study of 696 adult patients with congenital heart disease (Boston Biobank of Congenital Heart Diseases) discovered a correlation between increased RDW and poor outcomes. The average RDW was 14,0±1,3%. In 81 patients (11,6%), the RDW value exceeded the 15% mark. Mortality among patients with RDW >15% was on average 4,5 times higher than in the rest of the study participants (odds ratio (OR) 4,5 (95% confidence interval (CI) (3,0-6,6)) , p<0,0001) [17].

The diagnostic value of the erythrocyte parameter RDW in CVD has been confirmed in many studies with a relatively large number of examined patients. Almost identical results were obtained across all studies, which support a link between increased RDW and poor CVD outcomes. Also, a decreased RDW has been associated with a favorable prognosis

Table 1

CVD-Associated clinical blood test markers from Clinical Trials

Parameter of the clinical blood test	Diagnosis, number of patients	Clinical data, statistical indicators	Source
RDW	Diabetes (n=3061)	RDW proved to be a significant and independent predictor of death from all causes in these patients	S. Al-Kindi (2017) [13]
	Acute MI, Heart failure, stroke (n=26784)	RDW is associated with the rate of primary hospitalization	Y. Borne (2011) [15]
	Congenital heart disease, congestive heart failure (n=696)	Elevated RDW is an independent predictor of all-cause death in adult patients with chronic heart failure	L. Alshawabkeh (2018) [17]
	Acute heart failure (n=1702)	High RDW was correlated with an increased risk of anemia in patients with acute heart failure	J. Nunez (2011) [27]
MPV	Patients with various diseases (n=206554)	Increased MPV is correlated with a higher risk of death in patients with coronary artery disease	G. Slavka (2011) [28]
	Patients without special conditions (n=25923)	Increased MPV is a predictor of venous thromboembolism	S. Braekkan (2010) [22]
	Patients with venous thromboembolism (n=594)	High MPV is an independent risk factor for death in venous thromboembolism	J. Díaz (2019) [24]
	Patients with acute pulmonary embolism (n=192)	MPV is associated with right ventricular dysfunction and is an independent predictor of early death in acute pulmonary embolism.	M. Kostrubiec (2010) [25]
	Patients with stable coronary artery disease (n=2872)	Low MPV was associated with worse clinical outcomes in patients	H. Wada (2018) [29]
	Portal vein thrombosis (n=855)	As a prognostic biomarker, MPV can be used in patients with portal vein thrombosis	W. Lin (2018) [30]
WBC	Senile patients (73-91) without ischemic heart disease (n=2879)	Increased WBC is associated with a higher risk of congestive heart failure	S. Karino (2015) [32]
	Acute MI (n=975)	Increased WBC is associated with decreased blood flow and higher death rates from new congestive heart failure	H. Barron (2000) [33]
	Ischemic heart disease, ischemic stroke (n=13555)	An increase in WBC is directly related to an increase in CVD mortality (p<0,001)	C. Lee (2001) [37]
NLR	PAOD (n=508)	Higher NLR Associated with Higher CVD Mortality	M. Erturk (2014) [39]
	Acute coronary syndrome (n=400)	Elevated NLR is associated with higher all-cause mortality	Bajari R. (2017) [40]
PLR	MI without ST-segment elevation (n=619)	Higher PLR is a significant independent indicator of long-term patient mortality (p<0,0001)	B. Azab (2012) [46]
	PAOD (n=2121)	Increased PLR is significantly associated with critical limb ischemia in patients at higher risk of CVD endpoints (optimal PLR threshold is 150) (p<0,001)	T. Gary (2013) [47]
MHR	ST-segment elevation MI (n=414)	MHR is an independent predictor of high thrombotic load in patients with ST-segment elevation MI (p<0,001)	A. Arısoy (2017) [43]
	Obstructive sleep apnea syndrome with and without various CVDs (n=1050)	MHR values are significantly higher in patients with CVD compared with patients without CVD (p<0,001)	H. Inonu Koseoglu, et al. [48]

Abbreviations: IHD — Ischemic heart disease, MI — myocardial infarction, CBC — clinical blood test, AMI — acute myocardial infarction, HF — heart failure, CVD — cardiovascular diseases, MHR — monocyte to high-density lipoprotein ratio, MPV — mean platelet volume, NLR — neutrophil-lymphocyte ratio, PAOD — peripheral arterial occlusive disease, PLR — platelet-to-lymphocyte ratio, RDW — red cell distribution width, WBC — total white blood cell count.

in cardiac patients. Thus, a recent meta-analysis by Abrahan L, et al. (2018), which included 13 studies and 10410 patients, showed that a lower level of RDW is associated with a decrease in the risk of adverse cardiovascular events in patients with the acute coronary syndrome (OR 0,35 (95% CI 0,30 to 0,40), p<0,0001; I^2=53%) both in the short and long term [18]. Several studies have also demonstrated the role of RDW levels in predicting the growth of atherosclerotic plaque of the carotid artery and the relationship between acute heart failure and increased RDW [16, 19]. Red cell distribution width indicator can be considered a valuable independent biomarker for assessing patients' prognosis with heart failure, atherosclerosis, acute MI, and other CVDs.

MPV as an independent risk factor (RF) for CVD

Platelets perform a vital function — they prevent bleeding by forming a thrombus at the site of vascular damage, but their inadequate functioning leads to thrombosis and, as a result, to ischemia of the corresponding tissues and organs. There is a direct relationship between the size of platelets and their activity. Platelet activity can be indirectly measured using MPV (a parameter measuring the size of circulating platelets) [20, 21]. The normal MPV value is from 7 to 10 fL, depending on the type of analyzer and its operating principles. Various studies have found a correlation between an increase in MPV and CVD and noted a predictive role for this biomarker in these diseases. For example, an increase in MPV is associated with acute MI, unstable angina, and stroke. An increase in platelet volume is also associated with an increased risk of death caused by CVD [21, 22]. Another study demonstrated that MPV is the risk factor for unprovoked venous thromboembolism, suggesting that MPV and platelet activity are risk factors for developing arterial and venous thrombosis [23]. In a recent retrospective study, Díaz J, et al. it was found that a high level of MPV (>11,0 fL) is an independent risk factor of death in patients with venous thromboembolism [24]. Kostrubiec M, et al. also reported that elevated MPV levels (>10,9 fL) are independent predictors of early mortality in patients with acute pulmonary embolism during first 7 and 30 days: OR =2,0 (95% CI 1,3-3,0), p<0,001 and OR =1,7 (95% CI 1,2-2,5), p<0,01, respectively. In addition, a correlation was found between MPV and right ventricular diameter (r=0,28, p<0,01), as well as between MPV and right ventricular dysfunction (r=0,19, p<0,02) [25].

Current studies have shown a strong correlation between platelet size and platelet activity, which explains the pathophysiological mechanisms of the relationship between MPV and CVD. Larger platelets are more active than smaller platelets; they also have more storage granules and have a higher capacity to produce prothrombogenic factors such as thromboxane A2. It is believed that MPV increases in CVD due to tissue ischemia, platelet consumption in atherosclerotic plaques, and secretion of cytokines — Interleukin-3 (IL-3) and Interleukin-6 (IL-6), which affect the ploidy of megakaryocytes. IL-3 and IL-6 increase the size and deformation of platelets and promote the release of larger and more active platelets [21, 26], causing additional adhesion and aggregation of platelets through the release of thromboxane A2, adenosine diphosphate (ADP), and adenosine triphosphate (ATP), contributing to the pathogenesis of CVD acute MI [27]. Considering the rapid increase in MPV during the first hours of acute CVD development and its persistence in elevated values for several days after CVD development, this RF can be used as a prognostic/diagnostic biomarker for CVD, especially acute MI and ischemic stroke. The rapidity and stability of the MPV increase are the main advantages of this essential diagnostic/prognostic parameter [28-30].

Inflammatory markers that can predict adverse cardiovascular events

Generally, an increase in total white blood cell count (WBC) and an imbalance in the leukocyte formula, expressed as an increase in the percentage of neutrophils and a decrease in lymphocytes, are considered the main laboratory signs of inflammation [31, 32].

Several studies have established a link between inflammation and CVD markers and showed that inflammatory processes play a decisive role in the pathogenesis of atherosclerosis, which predisposes to most CVDs [33, 34]. Hence, measurement and evaluation of inflammation markers play a critical role in determining patients' prognosis with CVD [35].

Neutrophil-lymphocyte ratio (NLR) is an inflammatory marker that can predict the likelihood of death in patients with acute coronary syndrome and arrhythmias. Normal NLR value should not exceed 3.0. An increase in this ratio is associated with an increased risk of CVD and mortality rates from all causes, including congestive heart failure [36]. It has been shown that with NLR >3,15, the risk of atrial fibrillation in patients increases 2,5 times. NLR is an important marker for assessing the prognosis of patients with CVD because it is minimally influenced by physiological conditions of the patient, as a result of which it provides an opportunity to check the balance or imbalance of the immune pathways of inflammation (the number of neutrophils), as well as the body's response to

stress (the number of lymphocytes) [36, 37]. One of the hypotheses of the relative mechanism of an increase in the NLR ratio is a decrease in the number of lymphocytes after programmed cell death (apoptosis) or the movement of lymphocytes from peripheral blood into cardiac tissue followed by its infiltration, which was found in patients with heart failure and acute MI [31]. An increase in NLR is often accompanied by an increase in neutrophils and total leukocyte count, which is also the risk factor of atherosclerosis. Elevation of these parameters is associated with a higher incidence of ischemic heart disease (IHD) and ischemic stroke, since neutrophils and macrophages increase phagocytosis and degradation of vascular tissue and, as a consequence, the progression of atherosclerosis — the growth of atherosclerotic plaque followed by vascular occlusion [38-40]. An increase in total WBC is also associated with decreased blood flow to cardiac tissue [33].

Several studies have shown that inflammation is closely related to lipid metabolism. The total number of leukocytes and numbers of individual subpopulations (neutrophils and lymphocytes) are associated with the concentration of a relatively recently discovered regulator of lipid metabolism — Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) [41-43]. In patients with myocardial infarction (MI) without ST elevation, PCSK9 concentrations were elevated on admission and were associated with neutrophil count (r=0,24; p=0,009). The anti-inflammatory drug tocilizumab, containing the monoclonal antibodies of the cytokine IL-6, reduced both the concentration of leukocytes and the concentration of PCSK9. Presumably, leukocytes, releasing pro-inflammatory factors, increase the formation of PCSK9, which is another additional pathophysiological mechanism of atherosclerosis progression [41, 43].

In a study by Li S, et al. (2014) the relationship between plasma levels of PCSK9 and WBC (r=0,167; p=0,008) were noted in patients with stable coronary artery disease (n=251). Multivariate regression analysis discovered that plasma PCSK9 concentration was significantly and independently associated with WBC and their subpopulations (neutrophils and lymphocytes). Researchers believe that PCSK9 is involved in developing chronic atherosclerotic inflammation in the walls of coronary arteries and promoting coronary artery disease [42].

MHR can also be considered a valuable indicator retrieved from clinical and biochemical blood tests. A massive study by Zhang Y, et al. (2016) showed that MHR is an independent marker of major adverse cardiovascular events, including death, acute MI, heart failure, unstable angina, and stroke. This is because high-density lipoproteins (HDL) play an antiatherogenic and anti-inflammatory role by inhibiting CD11b integrin activation, which is involved in the adhesion migration and regulation of the inflammatory activity of monocytes/macrophages [34]. Consequently, an increase in the MHR ratio, characterized by an increase in the number of monocytes and/or a decrease in HDL, indicates inhibition of the protective anti-inflammatory and antiatherogenic mechanisms.

Arisoy A, et al. (2017) assessed the relationship of MHR with angiographic thrombotic load calculated on the basis of thrombolysis in patients with ST-segment elevation MI (STEMI) who underwent primary percutaneous coronary intervention (n=414). In patients with a high thrombotic load, the MHR index was significantly higher than in patients with a low thrombotic load (25,4 (13,5-44,6) vs. 16,0 (9,2-22,1); p<0,001) [44]. Thus, the MHR index is an independent predictor of high thrombotic load in patients with ST-segment elevation myocardial infarction who underwent primary percutaneous coronary intervention.

Similar to the ratios of NLR and MHR, platelet-to-lymphocyte ratio (PLR) is another marker of inflammation with a significant predictive value. An increase in it correlates with increased functional activity, platelet count, decreased lymphocyte count, and a poor prognosis in patients with CVD [45]. A study by Azab B, et al. (2012) found that PLR is a significant independent predictor of long-term (4-year) mortality after MI [46]. Interestingly, mortality at a PLR value of >176 in patients treated with one antiplatelet drug was significantly higher than in patients receiving dual antiplatelet therapy: 50% vs. 32%, p=0,0018 [46].

In another clinical study with Gary T, et al. (2013) investigated the PLR value in patients (n=2121) with the peripheral arterial occlusive disease (PAOD). The optimal PLR value was 150 or less, and patients with PLR >150 developed critical limb ischemia much more often (OR 1,9 (95% CI 1,7-2,1)). An increase in PLR was associated with critical limb ischemia even after adjusting for all other well-known CVD risk factors [47].

Clinical blood test parameters and clinical application

Table 1 summarizes the clinical studies results that showed the relationship between clinical blood test parameters and various CVD parameters. It is worth noting that the clinical blood test parameters' exact reference values may differ depending on the type of analyzer, its principles of operation, and units of measurement. Therefore, we avoided excessive use of specific numerical indicators when analyzing individual clinical studies. Specific hospitals

should make empirical (experimental) estimates, particularly on retrospective patient data, for the optimum use of the clinical blood test for tracking and predicting CVD.

Conclusion

The diagnostic/prognostic value of clinical blood test parameters for CVD is an important research area. Clinical blood testing is an inexpensive, widespread, and at the same time, a valuable additional prognostic tool for patients with CVD.

After analyzing the results of clinical studies, we concluded that such blood testing parameters as red cell distribution width, the mean platelet volume, the total white blood cell count, the neutrophil-lymphocyte ratio, the platelet-to-lymphocyte ratio, the monocyte to high-density lipoprotein ratio are reliable in monitoring and assessing the prognosis of various cardiovascular diseases. Such diseases include atherosclerosis, MI, stroke, heart failure, venous thromboembolism, and PAOD. These parameters represent the most accessible and easy-to-use tools for assessing the prognosis of patients' life, which is their undoubted advantage over complicated, expensive, and time-consuming examination methods. Further research is required in this area, both of a fundamental (the study of specific pathophysiological mechanisms) and clinical types, to study the possibilities of widespread use of these indicators in real clinical practice.

Relationships and Activities: none.

References

1. Chaulin AM, Karslyan LS, Grigoriyeva EV, et al. Clinical and Diagnostic Value of Cardiac Markers in Human Biological Fluids. Kardiologiia. 2019;59(11):66-75. (In Russ.). doi:10.18087/cardio.2019.11.n414.
2. Alieva AM, Nikitin IG, Starodubova AV, et al. Diagnostic and Prognostic Value of Natriuretic Peptides in Cardiac Patients. Lechebnoye delo. 2016;3:78-84. (In Russ.)
3. Chaulin AM, Duplyakov DV. Increased cardiac troponins, not associated with acute coronary syndrome. Part 1. Cardiology: News, Opinions, Training. 2019;7(2):13-23. (In Russ.) doi:10.24411/2309-1908-2019-12002.
4. Kremneva LV, Suplotov SN, Shalaev SV. Modern high-sensitive troponin diagnostic methods in assessment of myocardial ischemia and prognostical value for chronic coronary heart disease. Russian Journal of Cardiology. 2017;(3):160-4. (In Russ.) doi:10.15829/1560-4071-2017-3-160-164.
5. Dixon LR. The complete blood count: physiologic basis and clinical usage. J Perinatal Neonatal Nurs. 1997;11(3):1-18. doi:10.1097/00005237-199712000-00003.
6. Anderson JL, Ronnow BS, Horne BD, et al. Usefulness of a complete blood count-derived risk score to predict incident mortality in patients with suspected cardiovascular disease. Am J Cardiol. 2007;99(2):169-74. doi:10.1016/j.amjcard.2006.08.015.
7. Blindar VN, Zubrikhina GN, Matveeva II, Kushlinsky NE. Hematological research methods. The clinical significance of blood counts. M.: Publishing House Medical Information Agency LLC, 2013. p. 96. (In Russ.) ISBN: 978-5-9986-0135-4.
8. Novikova IA, Khoduleva SA. Clinical and laboratory hematology. Minsk "Higher School Publishing House", 2013. p. 445. (In Russ.) ISBN: 978-985-06-2226-6.
9. Chen PC, Sung FC, Chien KL, et al. Red blood cell distribution width and risk of cardiovascular events and mortality in a community cohort in Taiwan. Am J Epidemiol. 2009;171(2):214-20. doi:10.1093/aje/kwp360.
10. Wen Y. High red blood cell distribution width is closely associated with risk of carotid artery atherosclerosis in patients with hypertension. Exp Clin Cardiol. 2010;15(3):37-40.
11. Walters MC, Abelson HT. Interpretation of the complete blood count. Pediatr Clin North Am. 1996;43(3):599-622. doi:10.1016/s0031-3955(05)70424-7.
12. Sharma R, Agrawal VV. The relationship between red blood cell distribution width (RDW CV) and C reactive protein (CRP) with the clinical outcomes in non-ST elevation myocardial infarction and unstable angina pectoris: a 6 months follow up study. Int Cardiovasc Forum J. 2015;2:27-31. doi:10.17987/icfj.v2i1.68.
13. Al-Kindi SG, Refaat M, Jayyousi A, et al. Red cell distribution width is associated with all-cause and cardiovascular mortality in patients with diabetes. Biomed Res Int. 2017:5843702. doi:10.1155/2017/5843702.
14. Ozcan F, Turak O, Durak A, et al. Red cell distribution width and inflammation in patients with nondipper hypertension. Blood Press. 2013;22(2):80-5. doi:10.3109/08037051.2012.707336.
15. Borne Y, Smith JG, Melander O, et al. Red cell distribution width and risk for first hospitalization due to heart failure: a population-based cohort study. Eur J Heart Fail. 2011;13(12):1355-61. doi:10.1093/eurjhf/hfr127.
16. Lappegard J, Ellingsen TS, Vik A, et al. 2015. Red Cell Distribution Width and Carotid Atherosclerosis Progression: The Tromsø Study. Thromb Haemost. 2015;113(3):649-54. doi:10.1160/TH14-07-0606.
17. Alshawabkeh L, Rajpal S, Landzberg MJ, et al. Relationship of Red Cell Distribution Width to Adverse Outcomes in Adults With Congenital Heart Disease (from the Boston Adult Congenital Heart Biobank). Am J Cardiol. 2018;122(9):1557-64. doi:10.1016/j.amjcard.2018.07.019.
18. Abrahan LL 4th, Ramos JDA, Cunanan EL, et al. Red Cell Distribution Width and Mortality in Patients With Acute Coronary Syndrome: A Meta-Analysis on Prognosis. Cardiol Res. 2018;9(3):144-52. doi:10.14740/cr732w.
19. van Kimmenade RR, Mohammed AA, Uthamalingam S, et al. Red blood cell distribution width and 1-year mortality in acute heart failure. Eur J Heart Fail. 2010;12(2):129-36. doi:10.1093/eurjhf/hfp179.
20. Erhart S, Beer JH, Reinhart WH. Influence of aspirin on platelet count and volume in humans. Acta Haematol. 1999;101(3):140-4. doi:10.1159/000040940.
21. Demirkol S, Balta S, Unlu M, et al. Evaluation of the mean platelet volume in patients with cardiac syndrome X. Clinics (Sao Paulo). 2012;67(9):1019-22. doi:10.6061/clinics/2012(09)06.
22. Braekkan S, Mathiesen EB, Njolstad I, et al. Mean platelet volume is a risk factor for venous thromboembolism: the Tromsø study. J Thromb Haemost. 2010;8(1):157-62. doi:10.1111/j.1538-7836.2009.03498.x.
23. Vizioli L, Muscari S, Muscari A. The relationship of mean platelet volume with the risk and prognosis of cardiovascular diseases. Int J Clin Pract. 2009;63(10):1509-15. doi:10.1111/j.1742-1241.2009.02070.x.
24. Díaz JM, Boietti BR, Vazquez FJ, et al. Mean platelet volume as a prognostic factor for venous thromboembolic disease. Rev Med Chil. 2019;147(2):145-52. doi:10.4067/s0034-98872019000200145.
25. Kostrubiec M, Łabyk A, Pedowska-Włoszek J, et al. Mean platelet volume predicts early death in acute pulmonary embolism. Heart (British Cardiac Society). 2010;96(6):460-5. doi:10.1136/hrt.2009.180489.
26. Assiri AS, Jamil AM, Mahfouz AA, et al. Diagnostic importance of platelet parameters in patients with acute coronary syndrome

admitted to a tertiary care hospital in southwest region, Saudi Arabia. J Saudi Heart Assoc. 2012;24(1):17-21. doi:10.1016/j.jsha.2011.08.004.
27. Nunez J, Minana G, Bodi V, et al. Low lymphocyte count and cardiovascular diseases. Curr Med Chem. 2011;18(21):3226-33. doi:10.2174/092986711796391633.
28. Slavka G, Perkmann T, Haslacher H, et al. Mean platelet volume may represent a predictive parameter for overall vascular mortality and ischemic heart disease. Arterioscler Thromb Vasc Biol. 2011;31(5):1215-8. doi:10.1161/ATVBAHA.110.221788.
29. Wada H, Dohi T, Miyauchi K, et al. Mean platelet volume and long-term cardiovascular outcomes in patients with stable coronary artery disease. Atherosclerosis. 2018;277:108-12. doi:10.1016/j.atherosclerosis.2018.08.048.
30. Lin WY, Lu X, Fan FJ, et al. Predictive Effect of Mean Platelet Volume in Patients with Portal Vein Thrombosis: A Meta-analysis of Case-control Studies. Curr Med Sci. 2018;38(4):575-81. doi:10.1007/s11596-018-1916-z.
31. Horne BD, Anderson JL, John JM, et al. Which white blood cell subtypes predict increased cardiovascular risk? J Am Coll Cardiol. 2005;45(10):1638-43. doi:10.1016/j.jacc.2005.02.054.
32. Karino S, Willcox BJ, Fong K, et al. Total and differential white blood cell counts predict eight-year incident coronary heart disease in elderly Japanese-American men: the Honolulu Heart Program. Atherosclerosis. 2015;238(2):153-8. doi:10.1016/j.atherosclerosis.2014.12.003.
33. Barron HV, Cannon CP, Murphy SA, et al. Association between white blood cell count, epicardial blood flow, myocardial perfusion, and clinical outcomes in the setting of acute myocardial infarction: a thrombolysis in myocardial infarction 10 substudy. Circulation. 2000;102(19):2329-34. doi:10.1161/01.cir.102.19.2329.
34. Zhang Y, Li S, Guo YL, et al. Is monocyte to HDL ratio superior to monocyte count in predicting the cardiovascular outcomes: evidence from a large cohort of Chinese patients undergoing coronary angiography. Ann Med. 2016;48(5):305-12. doi:10.3109/07853890.2016.1168935.
35. Afari ME, Bhat T. Neutrophil to lymphocyte ratio (NLR) and cardiovascular diseases: an update. Expert Rev Cardiovasc Ther. 2016;14(5):573-7. doi:10.1586/14779072.2016.1154788.
36. Bhat T, Teli S, Rijal J, et al. Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. Expert Rev Cardiovasc Ther. 2013;11(1):55-9. doi:10.1586/erc.12.159.
37. Lee CD, Folsom AR, Nieto FJ, et al. White blood cell count and incidence of coronary heart disease and ischemic stroke and mortality from cardiovascular disease in African-American and white men and women: atherosclerosis risk in communities study. Am J Epidemiol. 2001;154(8):758-64. doi:10.1093/aje/154.8.758.
38. Balta S, Ozturk C. The platelet-lymphocyte ratio: A simple, inexpensive and rapid prognostic marker for cardiovascular events. Platelets. 2015;26(7):680-1. doi:10.3109/09537104.2014.979340.
39. Erturk M, Cakmak HA, Surgit O, et al. Predictive value of elevated neutrophil to lymphocyte ratio for long-term cardiovascular mortality in peripheral arterial occlusive disease. J Cardiol. 2014;64(5):371-6. doi:10.1016/j.jjcc.2014.02.019.
40. Bajari R, Tak S. Predictive prognostic value of neutrophil-lymphocytes ratio in acute coronary syndrome. Indian Heart J. 2017;69 Suppl 1(Suppl 1):S46-S50. doi:10.1016/j.ihj.2017.01.020.
41. Ueland T, Kleveland O, Michelsen AE, et al. Serum PCSK9 is modified by interleukin-6 receptor antagonism in patients with hypercholesterolaemia following non-ST-elevation myocardial infarction. Open Heart. 2018;5(2):e000765. doi:10.1136/openhrt-2017-000765.
42. Li S, Guo YL, Xu RX, et al. Association of plasma PCSK9 levels with white blood cell count and its subsets in patients with stable coronary artery disease. Atherosclerosis. 2014;234(2):441-5. doi:10.1016/j.atherosclerosis.2014.04.001.
43. Chaulin AM, Duplyakov DV. PCSK9: modern views about biological role and possibilities of use as a diagnostic marker for cardiovascular diseases. Part 1. Cardiology: News, Opinions, Training. 2019;7(2):45-57. (In Russ.) doi:10.24411/2309-1908-2019-12005.
44. Arısoy A, Altunkas F, Karaman K, et al. Association of the Monocyte to HDL Cholesterol Ratio With Thrombus Burden in Patients With ST-Segment Elevation Myocardial Infarction. Clin Appl Thromb Hemost. 2017;23(8):992-7. doi:10.1177/1076029616663850.
45. Kivimaki M, Steptoe A. Effects of stress on the development and progression of cardiovascular disease. Nat Rev Cardiol. 2018;15(4):215-29. doi:10.1038/nrcardio.2017.189.
46. Azab B, Shah N, Akerman M, et al. Value of platelet/lymphocyte ratio as a predictor of all-cause mortality after non-ST-elevation myocardial infarction. J Thromb Thrombolysis. 2012;34(3):326-34. doi:10.1007/s11239-012-0718-6.
47. Gary T, Pichler M, Belaj K, et al. Platelet-to-lymphocyte ratio: a novel marker for critical limb ischemia in peripheral arterial occlusive disease patients. Plos One. 2013;8(7):e67688. doi:10.1371/journal.pone.0067688.
48. Inonu Koseoglu H, Pazarli AC, Kanbay A, et al. Monocyte Count/HDL Cholesterol Ratio and Cardiovascular Disease in Patients With Obstructive Sleep Apnea Syndrome: A Multicenter Study. Clin Appl Thromb Hemost. 2018;24(1):139-44. doi:10.1177/1076029616677803.