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Review

Evaluation of complete blood count parameters in cardiovascular diseases: An early indicator of prognosis?

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ABSTRACT

Background: Studies have been conducted to evaluate the correlation between complete blood count (CBC) indices and cardiovascular diseases (CVDs). Considering the dispersion of these studies as well as reports on prognostic value of CBC parameters in CVDs, we have summarized these findings as a review article for the first time.

Methods: Relevant English language literature was searched and retrieved from Google Scholar search engine and PubMed database (1996–2018). We used "Complete blood count", "Cardiovascular disease", "Red cell distribution width", and "Mean platelet volume" as keywords.

Results: Numerous studies indicated that red cell distribution width (RDW) is an independent prognostic biomarker in relation to CVD diseases. MPV is another considerable prognostic biomarker for CVDs. Elevations of inflammatory markers such as neutrophil to lymphocyte ratio (NLR) in CVD patients (especially in myocardial infarction and heart failure) can be considered as a factor of poor prognosis.

Conclusions: RDW can be used as a valuable independent biomarker to investigate the prognosis of patients with heart failure (HF), atherosclerosis, myocardial infarction (MI), and other CVDs. Rapid and stable increase in MPV makes it a reliable prognostic/diagnostic parameter in CVDs such as MI and unstable angina. Among different inflammatory markers the evaluation of total white blood cell count, NLR, monocyte to high-density lipoprotein ratio (MHR) and platelet to lymphocyte ratio (PLR) may have a high value in predicting the prognosis of different CVDs including MI, HF and atherosclerosis in patients.

1. Introduction

Cardiovascular diseases (CVDs) are common diseases with high mortality rate all over the world. (Haybar et al., 2018). CVDs are generally diagnosed by a physician through clinical examination using expensive methods. Along with other routine tests, complete blood count (CBC) is widely used by physicians to check the status of ill and healthy people. A main trait of this test is its low cost and easy accessibility, which provides an appropriate approach to investigate and diagnose problems such as anemia, the risk of infection and/or hematologic malignancies, and coagulation disorders (Anderson et al., 2007; Dixon, 1997; Walters and Abelson, 1996). CVDs are a main cause of mortality worldwide (Townsend et al., 2015). Nowadays, with the advent of modern technologies, automatic counters measure parameters related to the variation in shape and size of cells in addition to quantitative examination of blood cells, enabling the calculation of several parameters that contribute to the diagnosis and monitoring of many diseases based on a set of software formulas and mechanical rules (Tefferi et al., 2005). Based on previous studies, we will review the relationship between CBC parameters and CVDs and show that CBC can be used to monitor CVDs and also to determine the prognosis of patients (Table 1).

2. RDW as an independent prognostic biomarker for CVDs

Red cell distribution width (RDW) is a quantitative measure of routine CBC, which can reveal anisocytosis by examining size variations in red blood cells (RBCs) (Chen et al., 2009; Wen, 2010). It is an indicator that is typically used for differential diagnosis of various types of anemia (Sharma and Agrawal, 2015). Several studies have mentioned the role of RDW as an independent prognostic biomarker in relation to CVD diseases; for example, increasing RDW values are associated with adverse outcomes and mortality in patients with hypertension, heart failure (HF), stroke, acute myocardial infarction (MI),

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Table 1
Study search strategy.

Inclusion criteria	Exclusion criteria
• Documented quantitative changes in CBC parameters • Confirmation of any type of CVDs diagnosis • Studies with participants ≥400	• Studies without documented quantitative changes in CBC parameters • Studies conducted before 1996 • Studies with < 400 participants

Abbreviations. CBC: Complete blood count; CVDs: Cardiovascular diseases.

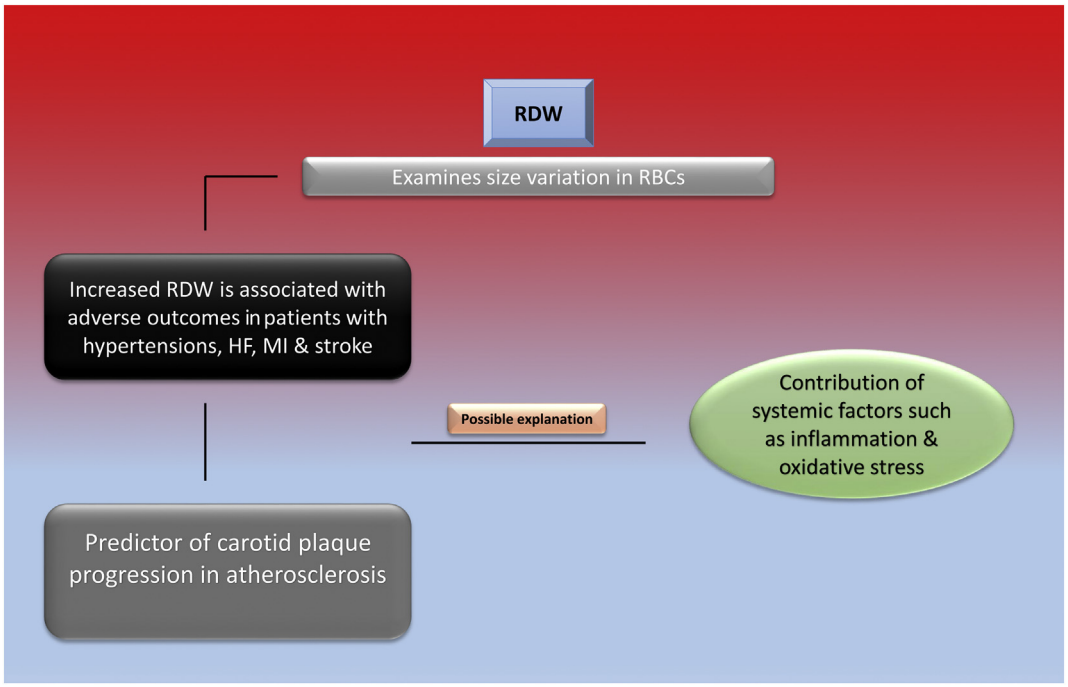

Fig. 1. RDW as an independent prognostic biomarker in patients with CVDs. RDW: Red cell distribution width; RBC: Red blood cell; HF: Heart failure; MI: Myocardial infarction.

peripheral artery disease, as well as patients with a history of primary coronary intervention (Al-Kindi et al., 2017; Özcan et al., 2013; Sharma and Agrawal, 2015) (Fig. 1). For the first time, Felker referred to the prognostic role of this indicator in the prediction of mortality rates (Borné et al., 2011). RDW is a marker to check the prognosis of patients with CVD; however, the mechanism of RDW relationship with these disorders has not been elucidated (Chen et al., 2009; Lappegård et al., 2015). Contribution of systemic factors such as inflammation and oxidative stress is the most likely hypothesis on the relationship between RDW with CVDs. It seems that inflammation, increased activity of adrenergic and neuroendocrine systems, as well as activation of renin-angiotensin system lead to changing maturation process of RBCs, anisocytosis, and increased RDW. Oxidative stress is also effective in increasing RDW in acute inflammatory conditions by causing damage to RBC membranes and inducing bone marrow (BM) to release immature RBCs into peripheral blood (PB)(Borné et al., 2011; Sharma and Agrawal, 2015; Wen, 2010). The relatively large population under study in numerous investigations and almost identical results of them confirm the association between RDW and the adverse outcomes of CVDs compared to other CBC parameters (Table 2). Also recently, a meta-analysis showed that lower RDW is associated with lower risk for major adverse cardiovascular events in patients with acute coronary syndromes (Abrahan et al., 2018). Given that earlier studies have demonstrated the role of RDW in predicting the progression of carotid plaque in atherosclerosis and considering the association between acute HF and increased RDW (Lappegård et al., 2015; van Kimmenade et al., 2010), RDW can be deemed as a valuable independent biomarker to investigate the prognosis of patients with HF, atherosclerosis, MI, and other CVDs.

3. MPV as an independent risk factor for CVDs

Platelets prevent bleeding by creating thrombus, and their abnormal function in inducing thrombosis of various vessels can lead to tissue ischemia. There is a direct relationship between platelets size and activity. Platelets activity can be indirectly measured using mean platelet volume (MPV), a parameter that represents the size of platelets in circulation (Demirkol et al., 2012; Erhart et al., 1999). Various studies have highlighted the correlation between the increase in MPV with CVDs and the prognostic role of this biomarker in these diseases; for example, it has been shown that increasing MPV is associated with MI and unstable angina, and rising platelets volume is related with an increased risk of mortality due to CVDs (Braekkan et al., 2010; Demirkol et al., 2012) (Fig. 2). Another study examining the relationship between increased MPV and unprovoked venous thromboembolism (VTE) has demonstrated that MPV is a risk factor for VTE in addition to being an independent risk factor associated with MI and stroke, which suggests that platelet activity is a risk factor for development of arterial and venous thromboses (Vizioli et al., 2009). With regard to the relationship between MPV and CVDs, studies have shown that due to the correlation between the size and activity of platelets, larger platelets are more active, have more granules as well as a higher capacity for the production of pro-thrombotic factors such as thromboxane A2. Therefore, MPV is increased in CVD patients probably due to tissue ischemia, consumption of platelets in atherosclerotic plaques, and secretion of cytokines affecting megakaryocyte ploidy such as interleukin IL-3 and

Table 2
Summary of clinical trials and observations studying the association of CBC parameters with CVD patients.

Parameter	Participants conditions	M/F (%)	Median Age	Patient No.	Nationality	Clinical findings	Statistical significance (95% confidence interval)		Ref.
							Hazard ratio (HR)	p-Value	
RDW	Participants with no history of CVDs	62/38	66	17802	Multinational	RDW was associated with all-cause mortality	-	-	(Horne et al., 2005)
	MI, HF and stroke	39/61	-	26784	Sweden	RDW was associated with incidence of hospitalization for the first time because of HF	1.33 (1.07-1.66)	< 0.02	(Borné et al., 2011)
	AHF	50/50	73	1702	Spanish	Higher RDW was associated with increased risk for developing anemia in AHF patients	1.1 (1.03-1.18)	0.002	(Nunez et al., 2011)
	Diabetes mellitus	50/50	61	3061	American	RDW was a strong marker of CVDs and all-cause mortality in these patients	2.39 (1.3-4.38)	0.005	(Al-Kindi et al., 2017)
	CHF	50/50	39	696	American	Elevated RDW is an independent predictor of all-cause mortality in adult patients with CHF	1.8 (1.5-2.2)	< 0.0001	(Alshawabkeh et al., 2018)
MPV	CADs including STEMI; NSTEMI and etc.	-	-	-	Multinational	Higher MPV was associated with CAD and patients with higher MPV (≥7.3 fL) had greater odds of having CAD than patients with lower MPV	-	-	(Sansanayudh et al., 2014)
	Admitted individuals for determination of MPV	43/57	50	206554	Austrian	Increased MPV was associated with higher risk of death due to ischemic heart disease	1.8	< 0.01	(Slavka et al., 2011)
	Participants with no specific condition	-	47	25923	Norwegian	An increasing MPV is predictive of total VTE event	1.2 (1.0-1.6)	0.09	(Braekkan et al., 2010)
	Stable CAD	83/17	67	2872	Japanese	A low MPV was associated with worse clinical outcomes in patients	1.43 (1.10-1.86)	0.009	(Wada et al., 2018)
	PVT	55/45	57	855	Multinational	MPV can be used as a predictive biomarker in PVT patients	-	< 0.0001	(Lin et al., 2018)
Total WBC	Japanese-American men aged 71-93 years free of CHD at baseline	100/0	78	2879	Japanese-American	Higher total WBC counts were associated with higher risk of CHD incidence in elderly Japanese-American men	1.75 (1.18-2.62)	0.006	(Karino et al., 2015)
	MI	-	-	975	American	Elevated total WBC count was associated with reduction of blood flow and a higher incidence of death due to new congestive heart failure	-	0.002	(Barron et al., 2000)
	CHD and ischemic stroke	44/56	54	13555	American	Elevation of WBC is directly associated with increased mortality caused by CVDs in black and white men and women	-	< 0.001	(Lee et al., 2001)
NLR	PAOD	81/19	65	508	Turkish	An elevated NLR was related to higher CVDs mortality in patients (NLR was determined as 3)	2.04 (1.2-3.3)	0.004	(Erturk et al., 2014)
	ACS	72/28	61	400	Indian	Elevated NLR was independently associated with higher all-cause mortality in patients (NLR was determined as 5.25)	-	< 0.001	(Bajari and Tak, 2017)
	stable CAD	78/22	67	500	Italian	NLR in higher tertile can independently predict major adverse effects [NLR was determined 2.5 (tertile 1) 3.2 (tertile 2) 4.4 (tertile 3)]	1.65 (1.07-2.55)	0.024	(Bressi et al., 2018)
PLR	NSTEMI	67/33	64	619	American	The higher PLR is a significant independent predictor of long-term mortality for patients (PLR was determined 118.4 to 176)	1.03 (1.02-1.04)	< 0.0001	(Azab et al., 2012)
	PAOD	59/41	71	2121	Austrian	Increased PLR is significantly associated with critical limb ischemia in patients with higher risk for CVD endpoints (Optimal cut off determined as 150)	-	< 0.001	(Gary et al., 2013)
MHR	Obstructive sleep apnea syndrome patients with and without CVDs	66/34	48	1050	Turkish	Values of MHR were significantly higher in CVDs patients with CVD compared with those without CVDs	-	< 0.001	(Inonu Koseoglu et al., 2018)
	STEMI	76/24	63	414	Turkish	MHR is an independent predictor of high thrombus burden in STEMI patients	-	< 0.001	(Arısoy et al., 2017)

Abbreviations: M/F: Male to female ratio; CBC: complete blood count; CVDs: cardiovascular diseases; RDW: red cell distribution; AHF: Acute heart failure; MI: Myocardial infarction; HF: Heart failure; CHF: congenital heart disease; MPV: mean platelet volume; CADs: Coronary artery disease; STEMI: ST-segment elevation myocardial infarction; NSTEMI: Non-ST-segment elevation myocardial infarction; fL: Femtoliters; VTE: Venous thromboembolism; WBC: White blood cell; PVT: Portal vein thrombosis; NLR: neutrophil to lymphocyte ratio; PAOD: Peripheral arterial occlusive disease; ACS: Acute coronary syndrome; PLR: Platelet to lymphocyte ratio; MHR: monocyte to high density lipoprotein.

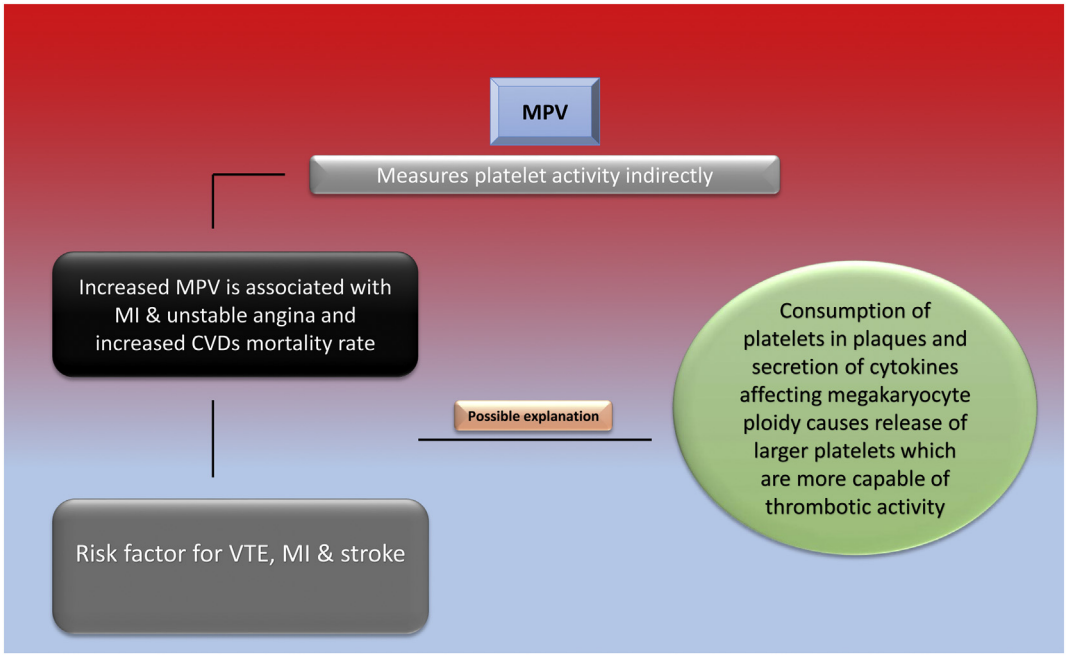

Fig. 2. MPV as an independent risk factor in CVDs with prognostic/diagnostic value in predicting CVDs status. MPV: Mean platelet volume; MI: Myocardial infarction; CVD: Cardiovascular disease; VTE: Venous thromboembolism.

IL-6 which increase platelet size and deformation as well as release of active platelets (Assiri et al., 2012; Demirkol et al., 2012). These larger platelets, which are more active than smaller ones, cause further adhesion and aggregation of platelets through the release of thromboxane A2, adenosine diphosphate (ADP), and adenosine triphosphate (ATP), contributing to the pathogenesis of CVDs, including MI (Nunez et al., 2011). Due to the rapid increase of MPV during initial hours of CVD events and its persistence up to several days after CVD events (Assiri et al., 2012), this risk factor can be used as a prognostic/diagnostic biomarker for CVDs, especially MI and ischemic stroke. Rapid and stable increase in MPV is the main advantage of this important prognostic/diagnostic parameter.

4. Inflammatory markers derived from CBC can predict bad CVD events

Generally, the increase in neutrophils and total white blood cell (WBC) as well as decrease in lymphocytes are common laboratory findings during inflammation (Horne et al., 2005). A relationship has been reported between inflammation and inflammatory markers with CVDs, and it has been shown that atherosclerosis has a basic inflammatory background as a multifactorial disease predisposing to most CVDs (including MI and HF) (Table 2) (Barron et al., 2000; Zhang et al., 2016). Therefore, the evaluation of inflammatory markers is expected to have a high value in predicting the prognosis of CVD patients, although the relationship between inflammation and CVDs is not precisely determined (Afari and Bhat, 2016) (Fig. 3). Neutrophil to lymphocyte ratio (NLR) is an inflammatory marker that can predict the probability of death in patients with acute coronary syndromes and the occurrence of cardiac arrhythmias, and the increase of this marker is related to mortality rates associated with congestive heart failure (Bhat et al., 2013). NLR is an excellent marker for the prognosis of patients with CVD because it is less likely to be affected by physiological conditions, providing an opportunity to check the balance or imbalance of immune pathways of inflammation (neutrophil count) as well as stress response (lymphocyte count) (Lee et al., 2001). One hypothesis regarding the mode of increase in NLR is the reduction of lymphocytes following increased programmed cell death (apoptosis) or the infiltration of lymphocytes from PB to cardiac tissue, which has been previously reported in patients with HF and MI (Horne et al., 2005). At the same time, total WBC increase is also a risk factor for atherosclerosis, and the increase in this marker is associated with a higher incidence of coronary heart diseases (CHDs) and ischemic stroke since the phagocytes, especially macrophages and neutrophils, are likely to result in the progression of atherosclerosis with tissue degradation (Balta and Ozturk, 2015). The increase in total WBC is also associated with decreased blood flow in the cardiac tissue (Afari and Bhat, 2016). A study has shown that monocyte to high-density lipoprotein ratio (MHR) is a marker that can independently determine the prognosis for adverse CVD events, including acute MI, HF, and stroke because high-density lipoprotein (HDL) plays an anti-inflammatory role by inhibiting the activation of CD11b integrin, which has a role in the adhesion, migration, and regulation of inflammatory activity of monocyte/macrophage (Barron et al., 2000). Therefore, the increase in MHR, which is a prognostic and inflammatory marker indicating an increase in monocytes and inflammation, is related with a poor prognosis in CVD patients. Similar to NLR and MHR, platelet to lymphocyte ratio (PLR) is another marker of inflammation with prognostic value, the increase of which is correlated with elevated number and function of platelets and decreased lymphocytes as well as a poor prognosis in CVDs patients because it is indicative of enhanced inflammatory function of platelets via secretion of pro-inflammatory cytokines such as IL-6 and exacerbation of inflammation (Kivimäki and Steptoe, 2018).

5. CBC parameters and clinical application

We reviewed application of CBC parameters in previous section with details (Table 2). Not only these parameters are reliable in predicting prognosis of different cardiac complications (specially MI, HF, stroke and atherosclerosis), but they are easy-to-access and affordable to use. As far as we know, our study is the first to summarize CBC parameters value in cardiovascular diseases. We tried to discuss each parameter individually and specifically to determine its real value in clinical applications for our colleagues. In order to do so, we included data from past studies (Table 1). Some of these studies included more than one parameter in their survey to evaluate risk score while others had

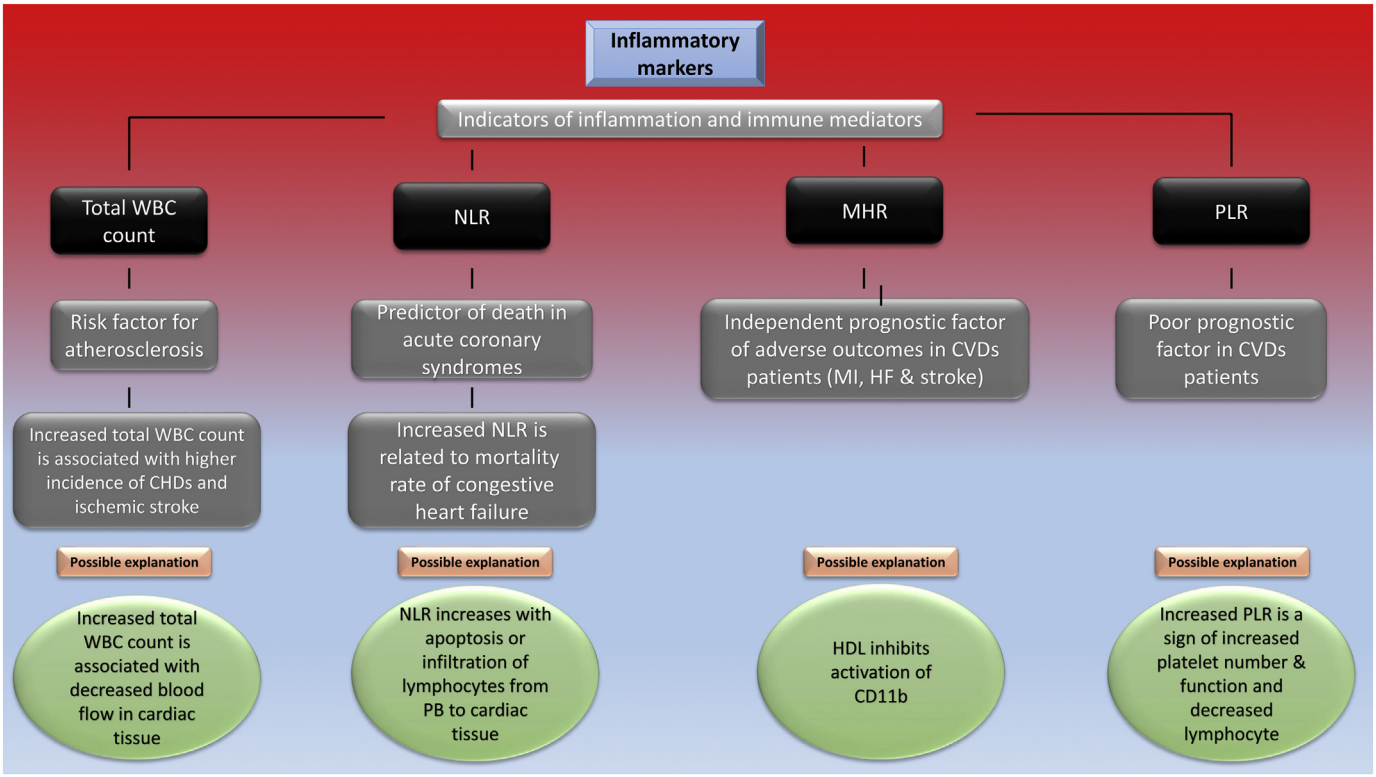

Fig. 3. Inflammatory markers including total WBC count, NLR, MHR and PLR provide prediction of outcomes in CVDs. WBC: White blood cell; CHD: Coronary heart disease; NLR: Neutrophil to lymphocyte ratio; PB: Peripheral blood; MHR: Monocyte to high-density lipoprotein ratio; CVD: Cardiovascular disease; MI: Myocardial infarction; F: Heart failure; PLR: Platelet to lymphocyte ratio.

focused on specific parameters (such as RDW, MPV and etc.)

6. Conclusion and future perspective

The prognostic and sometimes diagnostic value of CBC parameters in CVDs is a major research topic. It seems that the inexpensive but valuable CBC test can be used as a new prognostic tool for CVD patients. CBC is a cost-effective test since it has a low setup and staff training expense as well as because the physician can refer to CBC results in determining prognosis and later therapeutic measures with more confidence by observing the standard procedure in clinical hematology laboratory. According to the history of studies and their results, four CBC parameters of RDW, MPV, WBC count, and NLR appear to be more relevant and efficient than other parameters. However, we suggest the study of other parameters such as MHR in larger populations to determine their exact prognostic value more efficiently. Moreover, due to the stability of RBC indices like mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) in different populations regardless of race, we suggest the study of these parameters separately or together with inflammatory and platelet parameters.

Authors' contributions

N.S. conceived the manuscript and revised it; H.H. and S.M.S.P. wrote the manuscript and prepared the tables; S.M.S.P. designed and performed figures.

Declaration of Competing Interests

The authors declare no conflict of interest.

Research involving human participants and/or animals

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

For this type of study, informed consent is not required.

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