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Complete Blood Count Parameters In Heart Failure

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ABSTRACT

The peripheral blood markers are cheap, easy available and revelant indicators in patients with various diseases including cancer, sepsis, myocardial infarction and renal dysfunction. In recent years, there has been a growing interest of usefulness these biomarkers in heart failure (HF). Many reaearchers confirmed good prognostic value of lymphocyte to total leukocyte ratio (RLC), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and red cell distribution width (RDW), in risk stratification in HF. In the course of HF, inflammation proceses and activation of sympthatetic system may explain deviatation of these biomarkers. The present study is a review of the current knowledge on the role of RDW, NLR, PLR, and RLC in assessment of prognosis in patients with HF.

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INTRODUCTION

Heart failure (HF) is a chronic, progressive condition associated with high morbidity and mortality. Due to the increase of predicted life expectancy of an aging population, the development of advanced therapies for cardiovascular diseases, and significant improvements in the pharmacological treatment of HF, the number of patients with HF is gradually increasing. Therefore, early diagnosis and the inclusion of an appropriate HF treatment have a major impact on the healthcare economy and public health.[1-3]

The biochemical markers, which reflect different components of multifunctional pathophysiology of HF, are thought to perform an important role in early diagnosis and assessment of prognosis in patients with HF. The most commonly used markers include natriuretic peptides, particularly N-terminal pro-B type natriuretic peptide (NT-proBNP).[1,4] In clinical practice, NT-proBNP is commonly used to assist the diagnosis of HF, assess the effect of therapy, and predict the outcomes at different stages of HF.[1,4] Other important markers commonly found in clinical practice include cardiac troponins, used to diagnose myocardial infarction.[1,5]

Simple, cheap, and easily available biomarkers that may be important in the assessment of patients with HF also include peripheral blood markers. Recent researches have demonstrated that peripheral blood markers can be valuable diagnostic and prognostic tools in patients with HF.[4,6,7,8] These indicators are calculated from complete blood count (CBC). Particularly noteworthy are lymphocyte to total leukocyte ratio (RLC), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and red cell distribution width (RDW).[4,6,7,9] The associations between these parameters and HF are being studied with increasing interest.[4,6,7,9]

The present study is a review of the current knowledge on the role of RDW, NLR, PLR, and RLC in risk stratification in patients with HF.

Red blood cell distribution width in heart failure

Red blood cell distribution width (RDW) reflects the variability in the size of circulating erythrocytes. Results above the reference range express higher heterogeneity of cellular volume, called anisocytosis. RDW is measured automatically during CBC. In clinical practice, RDW is presented in morphology as percentages. This indicator is calculated by dividing the standard deviation of the red blood cells by their size and multiplied by 100. RDW is mainly used as an indicator of anemia. Higher RDW can be observed in the early stage of iron deficiency or iron deficiency anemia, due to reduced iron levels.[10] In turn, lower RDW can be observed in patients with ð-thalassemia.[11] However, in recent years, there has been growing interest in the usefulness of RDW in the assessment of prognosis in other diseases, for

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instance in HF, cancer, myocardial infarction, acute pulmonary embolism, cerebrovascular accident, severe sepsis, Hodgkin Lymphoma, and cholecystitis.[6,7,9]

According to the latest researches, elevated RDW is associated with an increased probability of death in patients with HF.[12,13,14,15,16] Felker et al. revealed that RDW is an independent risk factor of morbidity and mortality in patients with chronic HF.[12] Their research group was composed of two large populations, including 2,679 patients from the North American CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) and 2,140 patients from the Duke Databank. Siedlecki et al. also confirmed the good prognostic value of RDW in the assessment of worse prognosis in patients with advanced HF and coexistent diabetes during long-term follow-up.[14]

Salvatori et al. showed that RDW is a useful tool for predicting one-year all-cause mortality in elderly patients with AHF.[15] Furthermore, Targoński et al. indicated a correlation between RDW and higher pulmonary pressure and systemic inflammation in AHF patients.[16]

The association between RDW and HF is not fully understood and, consequently, more studies are needed to explain this pathophysiology. Some researchers suppose that autonomic dysfunction and inflammation which occur in HF can impair erythropoiesis, which leads to anisocytosis.[16-18] In addition, various factors coexisting with HF, including aging, reduced iron mobilization, decreased hemoglobin levels, and anemias, may also disturb the appropriate formation of red blood cells. [16,18]

Neutrophil to lymphocyte ratio in heart failure

NLR is a ratio of neutrophils to lymphocyte count, which is obtained from easy CBC. Increased NRL indicates systemic inflammation, which is an interdependent process in many conditions such as HF, cancer, chronic kidney disease, and diabetes.[19] In the course of HF, a reduced lymphocytes count and increased leukocytes and neutrophils count may be observed.[20]

Recent researches have emphasized the important role of neutrophils in myocardial apoptosis, remodeling, and fibrotic damage, leading to diastolic dysfunction in patients with HF.[21,22] Moreover, neutrophilia has been associated with the New York Heart Association (NYHA) class, plasma levels of C-reactive protein (CRP), and an increased risk of acute decompensated HF in patients with acute myocardial infarction.[21,23] The pathophysiology of neutrophilia in HF is considered to be a consequence of inflammation and immunologic activation. Simultaneously, activation of pro-inflammatory cytokines, heightened granulocyte-macrophage colony-stimulating factors, and the delay of neutrophils apoptosis lead to the elevated number of these cells.[8,22,24]

In turn, lymphopenia has been correlated with poor prognosis and increased mortality in patients with acute or chronic HF, regardless of etiology.[19,22,23,24] Furthermore, lymphopenia is associated with infections, multiple comorbidities, elevated natriuretic peptide levels, reduced fraction ejection, lower blood pressure, and inadequate HF therapy.[13,24,25] The pathophysiology of lymphopenia is suggested to be associated with systemic stress and inflammation. Due to the activation of the hypothalamic-hypophysis-adrenal axis, there are higher levels of cortisol and catecholamines, which can cause a decrease in the number of lymphocytes.[8,19,26] Moreover, lymphopenia may be explained by lymphocyte apoptosis and increased levels of inflammatory mediators, e.g. tumor necrosis factor 1 (TNF-1) induced by bacterial endotoxin translocated into the circulation due to decompensation of HF.[25,26]

In the light of the above, neutrophilia and lymphopenia are associated with HF and a combined assessment of their prognostic value using a simple NRL indicator may be helpful in a more accurate assessment of patients with HF.

Many studies confirm the importance of increased NLR in the assessment of prognosis in various groups of patients with HF.[8,19,20,23] Durmus et al. demonstrated that NLR is an independent predictor of HF mortality. In addition, they proved that NLR is inversely associated with ejection fraction and it is higher in patients with HF compared to the control group.[19] Furthermore, Cho et al. claimed that NLR is an accurate and independent predictor of severity, as well as short-term and 3-year mortality in patients with AHF.[23] In contradiction, the multivariate analysis conducted by Sadeghi et al. did not show NLR as an independent predictor of prognosis in patients with HF with reduced ejection fraction during a 6-month follow-up. On the other hand, their univariable analysis indicated that elevated NLR was associated with a higher risk of death in their research group.[22]

The predictive value of NRL in the assessment of prognosis in patients with HF may be limited by comorbidities. The study conducted by Argan et al. showed that a higher level of NLR is observed in patients with coexisting atrial fibrillation and renal dysfunction.[27]

It should be emphasized that the current knowledge of NLR in HF is largely based on limited data, and further prospective and widespread studies are needed to confirm the importance of NRL in the assessment of the prognosis in patients with HF.

Relative lymphocyte count in heart failure

Relative lymphocyte count (RLC) is calculated as the ratio of absolute lymphocyte count to total white blood cell (WBC) count and multiplied by 100. In the literature, many studies have emphasized the importance of RLC in risk stratification in different populations of patients with HF.[13,25,26,28,29,30] Low RLC is associated with HF progression, the need for an urgent transplant, or an increased risk of all-cause mortality. [13,25,26,28,29,30]

As a consequence of the fast normalization of lymphopenia, some researchers suppose that RLC is a more accurate predictor in short-term observation than in long-term observation.[25,26] Vaduganathan et al. claimed that RLC is useful in the assessment of poor prognosis in the early post-discharge period in patients hospitalized for the decompensation of HF.[25] Similarly, Núñez et al. showed that RLC is a significant marker of one-year mortality in patients with AHF.[26]

Although, several authors have indicated that RLC is an independent predictor of mortality in patients with HF with a longer follow-up, e.g. three years.[13,28,29,31] Acanfora et al. confirmed that RLC is an independent risk factor of poor

outcomes in elderly patients with congestive HF during a three-year follow-up.[29] In turn, Rudiger et al. indicated the good prognostic value of RLC in predicting long-term mortality in patients with AHF.[31]

RLC is a marker that reflects quantitative disturbances of lymphocytes and WBC. In patients with HF, the three main deviations of CBC include leucocytosis, neutrophilia, and lymphopenia. Therefore, RLC is thought to be a significant marker in HF. Researchers have indicated two major causes of association between PRL and HF, both of which lead to lymphopenia, namely inflammatory system activation and increased secretion of cortisol.[26,29]

Platelet to lymphocyte ratio in heart failure

Platelet to lymphocyte ratio (PLR) is well known as an inflammatory marker. PLR is calculated by dividing the absolute platelet count by the absolute lymphocyte count. Platelets are significant mediators in hemostasis and have an impact on inflammation, atherogenesis, and pathological thrombosis.[32,33,34] They can be activated by ADP, thromboxane A2, serotonin, epinephrine, collagen, and thrombin.[34]

In the course of an increased inflammatory response in HF, platelets interact with endothelial cells and WBCs, and as a result, additional inflammatory factors are released.[32,33] Inflammation can cause cardiac remodeling, fibrosis, hypertrophy, and endothelial dysfunction. Endothelial activation leads to a persistent inflammatory state within the vascular wall and a decrease of NO, which may contribute to diastolic dysfunction.[35] Therefore, the inflammatory process and endothelial dysfunction are associated with the development and prognosis of HF.[32,33,35,36]

Thrombocytosis may be explained by increased proliferation of bone marrow megakaryocytes as a result of sympathetic activation. Additionally, intensified maturation of megakaryocytes induced by cytokines present in HF such as IL-6 and IL-1b contributes to an elevated level of platelets [37,38,39]. Due to these processes related to the disturbances in the number of lymphocytes and platelets, there are deviations of PLR in HF.

In recent years there has been a growing interest in the correlation between PLR and HF. Several authors reported that PLR is a useful marker in the assessment of poor prognosis in patients with HF.[8,14,32,40]

Ye et al. indicated that PLR is a significant and independent risk factor in patients with AHF.[32] In addition, Siedlecki et al. showed that PLR is a predictor of long-term mortality in patients with advanced HF and coexisting diabetes.[14] On the other hand, the multivariate analysis performed by Heidarpour et al. did not show PLR as an independent prognostic factor in patients with decompensated AHF, although the authors did reveal a trend towards significance (p value = 0.054).[2] In turn, Haybar et al. claimed that PLR is a valuable tool for the assessment of prognosis in patients with myocardial infarction, HF, and atherosclerosis.[40]

However, it should be emphasized that PLR – similar to other inflammatory markers – may be increased in patients with various conditions such as inflammation, cancer, myocardial infarction, renal dysfunction, and obstructive sleep apnoea syndrome.[41]

CONCLUSION

In recent years, RDW, NLR, RLC, and PLR have received much attention in HF. These parameters are calculated from CBC, which is a simple, fast, and routine test. The latest researches have shown that RDW, NRL, RLC, and PLR may be significant tools in the assessment of the prognosis in patients with HF. However, the prognostic value of these markers in risk stratification of HF patients may be limited by comorbidities such as congestive kidney diseases, liver disorders, or neoplastic disease. Further prospective studies are needed to confirm the usefulness of these biomarkers in the assessment of the prognosis in patients with HF.

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