Clin. Lab. 2023;69:XXX-XXX

REVIEW ARTICLE

Complete Blood Count Test in Rheumatology: Not Just a Screening Test

Saeid Shahrabi [1], Najmaldin Saki [2], Majid Safa [3, 4], Seyed M. S. Pezeshki [2, 5]

[1] *Department of Biochemistry and Hematology, Faculty of Medicine, Semnan University of Medical Sciences, Semnan, Iran*
[2] *Thalassemia & Hemoglobinopathy Research Center, Health Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*
[3] *Department of Hematology and Blood Banking, Faculty of Allied Medicine, Iran University of Medical Sciences, Tehran, Iran*
[4] *Cellular and Molecular Research Center, Iran University of Medical Sciences, Tehran, Iran*
[5] *Blood Transfusion Research Center, High Institute for Research and Education in Transfusion Medicine, Tehran, Iran*

SUMMARY

Background: **Rheumatic disorders are chronic and common diseases, which especially involve connective tissue and may be associated with the damage to vital organs such as heart and kidney. Diagnosis, prognosis, determining the probability of severe complications, monitoring and evaluation of the response to treatment in such patients require specialized, expensive and time-consuming laboratory tests.**
Methods: **In this review article, we assessed the value of parameters of routine, inexpensive, and available Complete Blood Count (CBC) in detecting disease activity and explaining the prognosis of a number of rheumatic disorders, including systemic lupus erythematosus and rheumatoid arthritis by reviewing the results of searching Google Scholar search engine and PubMed databases over 2000 - 2021.**
Results: **Review of previous articles showed that while traditional Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) tests do not have sufficient specificity to appraise disease activity, CBC derived inflammatory biomarker Neutrophil-to-Lymphocyte Ratio (NLR) is able to assess disease activity and response to treatment in Rheumatoid Arthritis (RA). Also, Mean Platelet Volume (MPV) and NLR can determine the prognosis of renal involvement in Systemic lupus erythematosus (SLE).**
Conclusions: **Although CBC-based parameters are not completely specific and sensitive to rheumatic disorders, but based on the results of previous studies, these parameters, particularly red cell distribution width (RDW), MPV, NLR and platelet to lymphocyte ratio (PLR) are inflammatory biomarkers with a prognostic role in rheumatic disorders that can also assess activity of the disease.**
(Clin. Lab. 2023;69:xx-xx. DOI: 10.7754/Clin.Lab.2022.221012)

Correspondence:
Seyed Mohammad Sadegh Pezeshki, PhD
Blood Transfusion Research Center
High Institute for Research and
Education in Transfusion Medicine
Tehran
Iran
Email: s.m.s.pezeshki@gmail.com

Review Article accepted December 12, 2022

KEYWORDS

complete blood count, red cell distribution width, mean platelet volume, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, rheumatology, rheumatoid arthritis, systemic lupus erythematosus

HIGHLIGHTS:

CBC is cost-effective, reliable, and available to patients with rheumatic disorders
ESR and CRP do not have sufficient specificity to appraise disease activity
NLR is able to assess disease activity and response to

treatment in RA
MPV and NLR can determine the prognosis of renal involvement in SLE
PLR is a diagnostic biomarker in OA, Crohn's disease, and Takayasu arteritis

LIST OF ABBREVIATIONS

RA - rheumatoid arthritis
OA - osteoarthritis
SLE - systemic lupus erythematosus
CVDs - cardiovascular diseases
CBC - Complete Blood Count
ESR - Erythrocyte sedimentation rate
CRP - C-reactive protein
RDW - Red blood cell distribution width
MI - myocardial infarction
RPR - RDW to platelet ratio
MPV - mean platelet volume
PDW - platelet distribution width
TLRs - toll like receptors
NLR - neutrophil to lymphocyte ratio
PLR - platelet to lymphocyte ratio
MLR - monocyte to lymphocyte ratio

INTRODUCTION

Rheumatic disorders involve a large number of complications with inflammatory and autoimmune backgrounds as well as generally unknown and multifaceted pathogenesis. These chronic and common diseases affect various tissues, especially connective and skeletal tissues, and may endanger patient's life by involving other vital organs such as kidneys and heart [1]. The prevailing rheumatic disorders such as Rheumatoid Arthritis (RA) and osteoarthritis (OA) are more frequent in the elderly but systemic lupus erythematosus (SLE) mainly affects young women of childbearing age [2]. Given the growing population of elderly in both underdeveloped and developed countries, the costs associated with rheumatic disorders have increased, which essentially require specialized, expensive and time-consuming laboratory tests for diagnosis. Due to the high material and spiritual costs associated with rheumatic disorders in comparison to other complicated conditions such as cancer and cardiovascular diseases (CVDs) [1], treatment planning to diagnose, determine prognosis, evaluate the response to treatment as well as disease severity and activity is inevitable in these disorders. Complete Blood Count (CBC) is a commonly available, routine and inexpensive test in hematology department of a clinical laboratory. Depending on the technology used in automatic cell counters, CBC is able to assess a number of parameters related to blood cells, and the value of this parameter has been previously indicated in CVDs that are life-threatening complications of patients with rheumatic disorders [3]. In this study, previous findings concerning CBC parameters in the most commonly encountered rheumatic disorders will be reviewed to explain the value of these parameters in clinical trials on these diseases, including RA, OA, SLE, Crohn's disease, Takayasu arteritis, and systemic sclerosis.

RDW: a dependable biomarker for assessment of disease activity

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) tests are common markers for laboratory evaluation of inflammation; however, they cannot reflect disease activity and the acute phase of systemic inflammatory diseases because acute phase proteins are only indirectly increased following local inflammation [4]. On the other hand, the abovementioned tests are not specific for inflammatory diseases; for example, ESR is affected by various factors such as age, gender, fibrinogen level and anemia, while CRP is more specific than ESR [5-7]. However, both ESR and CRP may show normal levels at the onset of inflammatory diseases [8, 9], which reduces their value in diagnosis, monitoring, and determining the prognosis of these diseases. Although ESR and CRP are the most frequently used tests to assess the activity of RA, they are only capable of reflecting inflammatory activity in the short term [10]. Rheumatoid arthritis is a chronic autoimmune inflammatory disease that presents with joint involvement and systemic inflammation, eventually causing damage to joint tissue [11-13]. RA is the most important systemic autoimmune rheumatologic disease [14]. A number of disease-related genetic risk factors have been shown as a diagnostic biomarker for RA, particularly HLA-DRB1 [15]. Patients may experience successive periods of recovery and recurrence of the disease or eventually develop disability and a poor quality of life following joint tissue destruction [16,17]. Red blood cell distribution width (RDW) is a reliable laboratory parameter for examining volume changes in RBC and is thus used in the differential diagnosis of anemia [18], which is also considered as an inflammatory biomarker in CVDs with prognostic value [3]. The essential role of RDW in RA is better elucidated when we recognize that the mortality of RA patients is mainly due to CVDs of systemic inflammation origin [19]. Recent studies have noted the increase in RDW among patients with active RA and its correlation with changing levels of other inflammatory parameters, namely ESR and CRP [4,20]. Moreover, the changes in RDW can have prognostic value among RA patients to detect the risk of developing CVDs [18]. In justifying the association between RDW and the occurrence of CVDs, it should be noted that RDW reflects endothelial damage and inflammatory disorder that predispose to atherosclerosis in RA patients, which can lead to life-threatening conditions such as myocardial infarction (MI) [21,22]. On the other hand, the significant increase of RDW in RA patients can be associated with changing cytokine pattern in this disease. The rise in IL-6 and TNF-α levels along with the decrease of IL-10 inhibits erythroid maturation in BM and augments

the influx of immature RBCs into peripheral blood, which are involved in the process of inflammation and binding of inflammatory agents to surface receptors, leading to heterogeneity in RBC volume and consequent increase in RDW [20,23-26]. RDW also enables the differentiation between similar inflammatory conditions, so that it can be employed to distinguish RA and spondyloarthritis from OA and fibromyalgia, all of which have similar manifestations of articular pain [27], while CRP and ESR are not capable of differentiating between inflammatory conditions [10]. SLE is another common autoimmune disease associated with involvement of various organs [28,29]. The extent of clinical involvement is different in SLE and could be associated with arthritis, vasculitis, damage to the kidneys, skin, and heart [30,31]. Similar to RA patients, those with SLE show an increase in RDW levels, so that there is a correlation between elevated RDW and serum IgM, CRP, and ESR levels of patients [32]. Although the association between other common inflammatory markers (such as CRP and fibrinogen) with increasing RDW has been shown in patients, such correlation does not appear in those SLE patients who are anemic and the effect of anemia on the interpretation of changing RDW levels in SLE patients should be carefully assessed [33]. The increase of RDW in SLE patients seems to not be related with the type of treatment because newly diagnosed SLE patients who have not been treated also show an increase in RDW. However, there is a correlation between increasing levels of this inflammatory biomarker and response to SLE treatment so that patients with higher RDW are more likely than those with normal RDW to have a poor response to treatment and lower one-year flare-free survival rates [34]. RDW to platelet ratio (RPR) is a novel indicator based on CBC data, which is greatly increased in newly diagnosed SLE patients relative to normal individuals, is correlated with ESR, albumin, C3 and C4 levels of the complement system and anti-dsDNA and can be used as a new inflammatory marker in SLE [35]. In patients with Crohn's disease, high RDW levels are associated with the development of CVDs such as MI and atrial fibrillation [36]. In non-anemic patients with Takayasu arteritis, a significant increase in RDW is independently associated with CRP, and RDW can be used in this group of patients to assess the severity of disease similar to patients with Sjogren's syndrome [37,38]. In addition to correlation with ESR and CRP and disease activity, increasing RDW level in patients with systemic sclerosis (SSc) is related with decreased left ventricular ejection fraction and diffusing capacity of lung for carbon monoxide and is thereby a prognostic biomarker associated with cardiac disorder and the likelihood of CVDs [39]. The association between RDW, CRP, and ESR has also been observed in ankylosing spondylitis (AS), in which RDW is a valuable biomarker to evaluate disease activity [40]. Despite the high value of RDW in assessing disease activity and predicting some of the complex clinical consequences of rheumatic disorders, it should be noted that RDW is affected by various conditions such as liver disease, anemia, vitamin B12 and folic acid deficiency [41]. Therefore, in interpreting the changes in RDW levels, it is necessary to pay attention to patient's history and clinical manifestations, especially anemia.

Platelet indices: Indicators of key cells involved in the inflammation process

The need for circulating platelets and pro-inflammatory contents of their granules increases during the acute phase of the inflammatory process because of inflammatory cytokines. As a result of megakaryopoiesis under this pressure, the platelets entering into the blood from BM show changes in size and mean platelet volume (MPV) [42]. The released platelets are younger and larger with a higher ability to produce thromboxane A2 than smaller platelets; therefore, they have a greater ability to aggregate and secrete various agents, thereby contributing to inflammation and tissue damage [43-45]. The direct effect of cytokines on platelets is another reason for the change in platelet size and MPV, which activates platelets by converting their discoid form to spherical shape that increases MPV [46]. In addition to the function of platelets in the inflammatory background of diseases such as RA, increasing platelet-induced thrombotic activity has been addressed in the pathogenesis of RA disease and the study of platelet counts along with routine evaluation of ESR and CRP allows for the assessment of disease activity [47]. Previous studies have indicated an increase in MPV, platelet distribution width (PDW), and platelet count in patients with RA [48,49] (Supplemental table) and have noted the association between MPV and ESR [50]. Consequently, platelet parameters such as PDW and MPV can be routinely used to assess disease activity in RA patients [51]. However, a number of studies have reported conflicting results. For example, unlike most investigations, Kiasacik et al. have reported the decrease in MPV levels among RA and AS patients [52]. This could be attributed to the difference in active disease state and the prescribed treatments for the patients under study, which lead to the difference in final results [53]. An important fact is the relationship between platelet size changes and the risk of CVDs such as MI [3]. On the other hand, a number of studies have pointed to the value of MPV as a marker of hypertension risk and thrombotic events in other diseases, and there may be a link between platelet activation and increased MPV in RA patients at risk of thrombotic events [42,46,54,55]. Through key interactions with endothelium, leukocytes, and selectin receptors, platelets are involved in the development of CVDs, including re-stenosis after tissue damage due to stent implantation to treat coronary artery stenosis [56,57]. Therefore, monitoring of MPV changes can indirectly determine the prognosis of CVDs and thrombotic events in RA patients as well as assessing the inflammatory activity of the disease. Moreover, increasing MPV in patients with Hip OA is a biomarker associated with disease severity [58]. There

are contradictory results on the relationship between MPV and disease activity in SLE as another common rheumatic disorder. Some studies have reported a reduction in the level of this parameter in active phase SLE patients compared to those in the remission phase and the healthy control group [59,60], while other investigations have noted increasing MPV levels in active SLE patients compared to inactive phase SLE patients. For instance, a study mentioned an increase of MPV in SLE patients having renal involvement compared to SLE patients without renal involvement [61]. Other researchers have reported a similar relationship between MPV changes and renal complications in patients [62,63]. A recent meta-analysis that found no significant difference in MPV between active and inactive SLE patients rejected the value of MPV as a biomarker to assess and determine disease activity, citing the discrepancy between the above findings and the heterogeneity of previous clinical studies [64]. In SLE patients, immune complexes cause systemic and tissue inflammation and increase platelet aggregation, activate endothelial cells, and enhance inflammation through FcgRIIA receptors and toll like receptors (TLRs), especially TLR4, thereby playing a role in the development of CVD in patients [65,66]. SLE patients in the active phase also show hypercoagulability, which can be due to platelet activation and subsequent endothelial damage [67]. In explaining the reason for increasing MPV in a number of the abovementioned researches, we can mention the relationship between increasing inflammatory activity of platelets with rising MPV, and the decrease in MPV patients can be attributed to the discharge of pro-inflammatory agents from platelet granules and the release of smaller platelets from BM under stress conditions [64, 68]. Despite the differences in results, the mentioned studies have introduced MPV as a biomarker to evaluate disease activity. However, it seems that further investigations are needed in relation to SLE to determine the exact relationship between MPV changes and disease activity. Research has also revealed an association between other inflammatory diseases and MPV. For example, patients with Crohn's disease show an increase in MPV relative to healthy population and the response to infliximab treatment can be evaluated in them by monitoring MPV changes [69,70]. Therefore, MPV can potentially be used as a marker to assess intestinal inflammation and the response to therapy in patients. In Systemic Sclerosis (SSc) patients, the MPV parameter is significantly increased and is prognostic of macrovascular (CVDs) and microvascular (digital ulcers) complications and is also associated with disease activity [71]. There are different results concerning AS so that in some cases the increase of MPV has been reported in patients while there have been reports of the decrease in MPV or no significant change of it in AS patients compared to the control population in other investigations [52,72,73]. Patients with Behcet's disease also show changes in MPV levels, while the results of studies have not been conclusive. A number of investigations have linked an increase or decrease of MPV levels in patients with disease activity and clinical findings [74-76]. Takayasu arteritis is a rare but progressive inflammatory disease [77], and MPV is significantly decreased in patients afflicted with this disease compared to the control group, which correlates with ESR and CRP levels and can be used as an indicator to evaluate remission in patients [78].

CBC derived inflammatory biomarkers: New useful determinants

In recent years, combined parameters based on main parameters of CBC test have been introduced to assess the activity of inflammatory diseases and their predictive value has been mentioned in complex CVDs [3]. Among these parameters, more emphasis has been placed on the prognostic role of neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) because of the role neutrophil and platelet play in inflammation. RA patients experience leukocyte count changes at different stages of the disease, may experience a relative or absolute increase in neutrophil count, and some patients can show increasing eosinophil counts. However, so far only a link between increasing neutrophil counts and disease activity has been shown, so that several studies have appraised the value of NLR index in determining disease severity and even the evaluation of the response to treatment in patients [79,80]. For example, in RA patients treated with an anti-TNF-α agent, the increase in NLR levels is associated with a higher risk of unfavorable response to treatment, and the changes of this parameter along with PLR are correlated with ESR and CRP values and disease severity [81]. While CRP and ESR were not able to fully evaluate the response to treatment in RA patients who received tocilizumab, the NLR parameter was well correlated with response to therapy through significant changes in its values among patients with flare [82]. The association between NLR, PLR, and monocyte to lymphocyte ratio (MLR) has been demonstrated in patients with clinical symptoms of polymyalgia arteritis, which can be used to diagnose and assess disease activity [83]. Considering the direct relationship between higher activity of RA and increasing NLR levels in patients compared to controls and the correlation of this parameter with CRP, ESR, platelet counts and platelet parameters [47,48], NLR can be used to diagnose the disease, estimate disease activity and response to treatment among patients. In patients with Hip OA, the increase in PLR is a biomarker to assess the severity of the disease [58]. These combined indicators can be used to prevent the occurrence of complex events in SLE patients. Of SLE patients, 25 - 50% are subject to infection that may endanger their life, so it is important to diagnose and evaluate the infection in such patients. Although CRP is not sufficiently specific for this purpose, the use of NLR in addition to CRP has acceptable specificity for the assessment of these patients [84]. In SLE patients, 50% may develop glomerulonephritis, which is

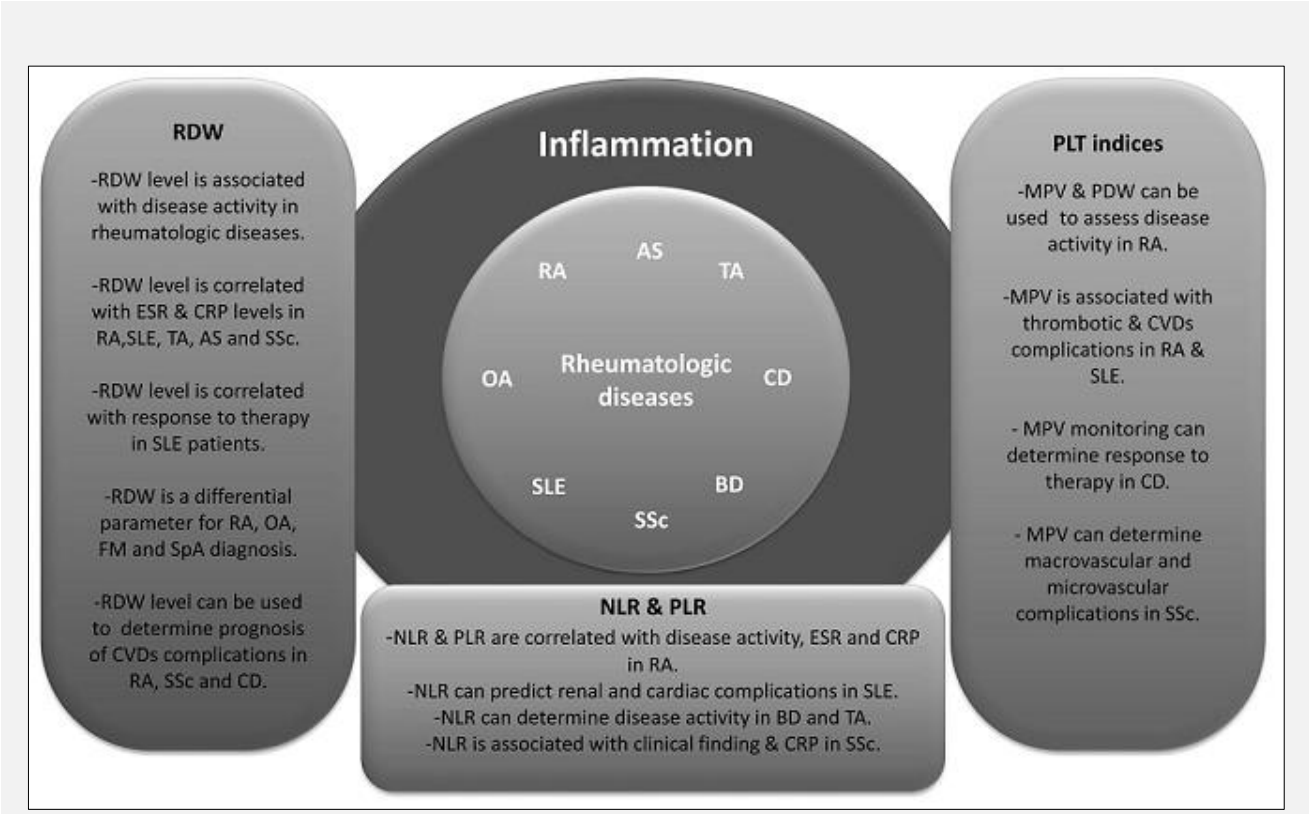

Figure 1. CBC parameters value in rheumatologic diseases.

Abbreviations: CBC - complete blood count, RA - Rheumatoid arthritis, AS - Ankylosing spondylitis, TA - Takayasu arteritis, CD - Crohn's disease, BD - Behcet's disease, SSc - Systemic sclerosis, SLE - Systemic lupus erythematosus, OA - Osteoarthritis, RDW - red cell distribution, ESR - Erythrocyte sedimentation rate, CRP - C-reactive protein, PLT - Platelet, MPV - Mean platelet volume, PDW - Platelet distribution width, CVDs - Cardiovascular diseases, NLR - Neutrophil to lymphocyte ratio, PLR - Platelet to lymphocyte ratio.

associated with a higher risk of complications such as renal failure and CVDs [85,86]. NLR levels in this group of patients are higher than in SLE patients without glomerulonephritis and may have prognostic value [61]. In SSc patients, the level of NLR and MLR inflammatory parameters is higher than the control population and is associated with clinical manifestations of cardiac and digital ulcers as well as disease severity in addition to correlation with CRP [87]. In patients with Takayasu arteritis, NLR, MLR, and PLR indicators increased significantly compared to the control group, correlated with CRP and ESR levels and could be used to assess remission conditions of patients [78]. Similar to patients with Behcet's disease, those with Takayasu arteritis show an increase in NLR, and this indicator can be employed to determine disease activity in them [53]. Patients with Crohn's disease have shown an increase in NLR and PLR levels as well as correlation with CRP and ESR compared to the healthy control group [88], and NLR is likely to be used for diagnosis and differentiation of patients from healthy individuals [89]. However, further studies may be needed to determine the value of the abovementioned inflammatory biomarkers in Crohn's disease [90].

DISCUSSION AND FUTURE PERSPECTIVES

Previous studies have examined the prognostic/diagnostic utility of genetic biomarkers including HLAs, which are among the risk factors for RA and SLE [15]. Compared to these biomarkers, CBC parameters are easier, more accessible and less expensive to evaluate. Rheumatic disorders are generally multidimensional diseases with unknown pathogenesis, and the physician needs specialized and expensive laboratory investigations to diagnose these disorders, differentiate them from each other and evaluate the response to therapy and prognosis of patients. In addition to their ability to assess patients' inflammatory conditions, CBC parameters have the potential to determine prognosis and assess the severity and activity of the disease in some of the most

common rheumatic disorders (Figure 1). ESR and CRP do not have sufficient specificity to appraise disease activity, especially ESR that is affected by various factors. Compared to ESR and CRP, the RDW parameter is more specific for disease activity and the incidence of CVDs in RA but the effect of anemia on its interpretation should be considered. RDW in RA is also correlated with ESR and CRP levels. In SLE, in addition to the association of RDW with CRP and ESR, RDW can be used to rate disease activity and response to treatment. RDW in patients with Crohn's disease predicts the occurrence of CVDs and is associated with disease activity in Takayasu arteritis, Sjogren's syndrome and SSc. There are different results in relation to changes of MPV levels in rheumatic disorders. To justify the contradictions of these studies, the effect of additional factors such as thrombocytopenia and BM stress activity on MPV should be considered. Overall, larger platelets are more active, so the findings of investigations indicating increasing MPV levels, higher disease activity and the incidence of CVDs seem to be more plausible. Given the chronic nature of rheumatic disorders and sustained activity of BM under stress to produce platelets, the reason for the decrease of MPV in patients with active disease conditions as well as higher incidence of complications may be the compensatory release of smaller platelets to peripheral blood. Among the CBC-based combination parameters, NLR has the ability to assess disease activity and response to treatment in RA and is correlated with ESR and CRP. Along with MPV, the NLR index can determine the prognosis of renal involvement in SLE. An increase in NLR relative to healthy individuals is evident and has diagnostic value in Behcet's disease, Takayasu arteritis, and Crohn's disease. The inflammatory index of PLR also increases in OA, Crohn's disease, and Takayasu arteritis relative to healthy subjects and is thus a diagnostic biomarker.

CONCLUSION

In this study, for the first time, we comprehensively examined the value of CBC parameters in the most common rheumatic disorders and finally showed that these parameters are capable of assessing disease activity and determining the prognosis of cardiac complications and can be employed as prognostic/diagnostic laboratory factors that are cost-effective, reliable, and available to patients with rheumatic disorders.

Source of Funds:
There is no funding to report.

Ethical Approval and Consent to Participate:
This manuscript does not contain human and/or animal studies.

Human and Animal Rights:
This manuscript does not contain human and/or animal studies.

Consent for Publication:
Agreed.

Statement of Availability of Data and Materials:
There is no data and materials to share.

Declaration of Interest:
The authors declare no conflict of interest.

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