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Research Article

# Hematological and Immunological Alterations in Patients with Rheumatoid Arthritis

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**Key Words**
Autoimmune diseases,
Enzyme-linked immunosorben assay (ELISA),
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**Abstract**: Rheumatoid arthritis is a chronic disease of severe impacts on health status due to various physiological disturbances that linked to disease activity and correlate positively with the severity of the disease. Investigation the relationship between the hematological and serum immunological markers with the disease activity in patients with rheumatoid arthritis. Totally, 50 adult male patients diagnosed clinically and biochemically with rheumatoid arthritis in addition to 25 healthy adult males (HC) were subjected to collection of venous blood samples that used for measurement of hematological parameters using the automatic blood analyzer, as well as for obtaining of sera that tested by specific quantitative ELISA kits to measurement of immune markers. According to disease activity, the study patients were divided into low (LDA), moderate (MDA) and high (HDA) categories. In comparison to HC group, the findings of hematology were shown a significant elevation in values of WBCs and neutrophils among all groups of rheumatoid arthritis patients (LDA, MDA, and HDA) while platelets were increased markedly in MDA and HDA groups. In contrast, the findings of RBCs, hemoglobin and hematocrit were reduced significantly among all patients' groups; whereas, lymphocytes were decreased markedly in MDA and HDA groups. For immunology, the findings of IFN-a, IL-6, IL-8, IL-10, TNF-α and TNF-β were elevated significantly among all groups of study patients; however, elevation in values of IFN-a, IL-10, and TNF-α was more significance in HDA than others; while IL-8 in MDA, and TNF-β in LDA and HDA. This study demonstrates a significant association between the hematological and immune markers with the severity of disease suggesting that these markers can serve as valuable, independent biomarkers. Furthermore, the utility of traditional hematological indices in monitoring disease activity undergoing disease-modifying anti-rheumatic drug therapy has been established, even when acute-phase reactants may appear normal. Also, multifaceted nature of disease necessitates a comprehensive understanding of its pathophysiology to develop effective therapeutic strategies that target both articular and extra-articular manifestations.

## INTRODUCTION

Rheumatoid arthritis is a chronic, systemic inflammatory autoimmune disease which affecting primarily on synovial joints and leading to their eventual destruction[1]. Although the exact etiology of rheumatoid arthritis remains elusive, a complex interplay of genetic, hormonal, and environmental factors are believed to contribute its development[2]. Specifically, genetic predisposition supported by epidemiological evidence demonstrating an elevated vulnerability in individuals with a familial history of rheumatoid arthritis, is a well-established risk factors[3,4]. Furthermore, environmental triggers including chronic infections and certain lifestyles are thought to initiate and perpetuate the autoimmune processes characteristic of the disease[5]. Worldwide, the disease affects approximately 0.2-1% of the global population and represents a significant cause of disability and labor los[6]. This debilitating condition is characterized by immune cell infiltration, synovial hyperplasia, pannus formation, and erosion of cartilage and bone[7]. The disease leads to considerable morbidity, disability, and increased mortality underscoring its significance impact on public health[8]. Thus, the stratification of the disease based on autoantibody status, specifically the presence of anti-citrullinated protein antibodies is critical for understanding its diverse etiologies and prognosis[9].

Hematological markers including novel indices such as the neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, and platelet-to-lymphocyte ratio offer promising, readily available and cost-effective avenues for assessing disease activity[10,11]. These composite scores, derived from routine completed blood counts, reflect the intricate interplay of immune cells during inflammatory processes in autoimmune diseases[12-14]. Moreover, while rheumatoid factor is frequently utilized diagnostic marker, its lack of specificity necessitates the exploration of additional, more precise hematological indicators to enhance diagnostic accuracy in ambiguous cases[15,16]. Beyond these established markers, systemic inflammatory response leads to progressive joint damage, functional impairment and a significant reduction in the quality of life of the patient[17]. Therefore, the accurate and timely identification of immune markers that correlate with disease severity and progression is paramount for effective therapeutic intervention and personalized medicine[18,19]. Nonetheless, current diagnostic indicators often lack the requisite sensitivity and specificity for early detection, and exploration of more precise immune markers can serve as diagnostic biomarkers[20,21].

In Iraq, several researchers among various geographical areas have been identified the incidence rate of rheumatoid arthritis[22] as well as the biological manifestation[23], isotypes[24] and demographic, clinical, serological, genetic, immune, and molecular markers[25,26] however, limited data have been provided by recent studies in Wasit province[27,28]. Hence, the current study aims to investigate the relationship between the hematological and serum immunological markers with the disease activity in patients with rheumatoid arthritis.

## MATERIALS AND METHODS

Ethical Approval: The license of this study was obtained from the Scientific Committee in the Biology Department at the College of Education for Pure Sciences (University of Wasit).

**Samples:** An overall 50 adult male patients diagnosed clinically and biochemically with rheumatoid arthritis were attended to the private rheumatology clinics in Al-Kut city (Wasit province, Iraq) during February to May (2025) and divided into three levels according to disease activity; low (LDA), moderate (MDA) and high (HDA). In addition, a total of 25 healthy adult males were selected as a control group (HC). Under aseptic conditions, 10ml of venous blood was collected from all individuals of study population (diseased and healthy) using a disposable syringe and divided into two tubes; 8ml into free-anticoagulant glass gel tube for sera and 2ml into EDTA-plastic for hematology. After centrifugation, the obtained sera were collected into 1.5ml labeled Eppendorf tube and saved frozen at -20°C until be tested serologically.

**Hematology and Serology:** For hematology, the collected samples were tested directly and automatically using the Cellagon 3 Device (Diagon, Hungary) for detecting the values of total RBCs, hemoglobin, hematocrit, total WBCs, neutrophils, lymphocytes, and platelets. For serology, quantitative ELISAs' kits (Sunlong Biotech, China) were served for measurement immune markers including IFN-a (Cat.No:SL0957Hu), IL-6 (Cat.No:SL1001Hu), IL-8 (Cat.No:SL1004Hu), IL-10 Cat.No:SL0967Hu), TNF-a (Cat.No:SL1761Hu) and TNF-β (Cat.No:SL1762Hu). Briefly, the contents of each kit in addition to serum samples of study population were prepared at room temperature, processed, and the optical density (OD) was read at an absorbance 450nm.

Finally, concentrations of each one were calculated in serum samples based on the concentrations and ODs of the Standard diluents as well as ODs of the serum samples through utilization the standard curve in the Microsoft Office Excel (version 2016)[29].

**Statistical Analysis:** GraphPad Prism Software was served to identify significant differences between the findings of study groups (control, low-disease activity, moderate-disease activity, and high-disease activity) at $p<0.05$ throughout the one-way ANOVA and 95% confidence interval (95%CI)[30].

## RESULTS AND DISCUSSIONS

**Hematological Parameters:** The findings of total WBCs count were shown a significant elevation ($p<0.0001$; 95%CI: 2.961 to 17.76) in values of all groups of rheumatoid arthritis patients; LDA ($8.11\pm0.84\times10^3/\times L$), MDA ($11.77\pm0.88\times10^3/\times L$), and HDA ($16.14\pm1.43\times10^3/\times L$) when compared to findings of HC ($5.42\pm0.71\times10^3/\times L$). However, values of HDA were significantly ($p<0.05$) higher than the findings of LDA and MDA (Figure 1).

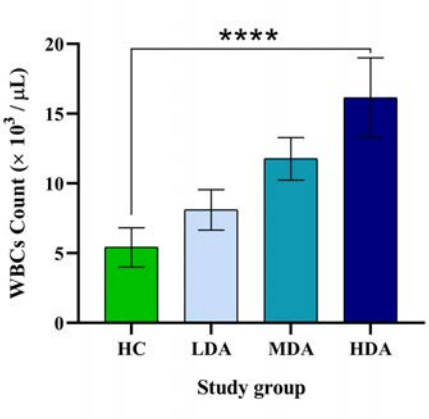


Fig. 1: Levels of total WBCs count among the groups of study population

Subsequently, the findings of neutrophils were elevated significantly ($p<0.0009$; 95%CI: 49.83 to 81.32) among all groups of rheumatoid arthritis patients; LDA (59.9±9.76%), MDA (69.67±8.17%), and HDA (77.4±2.29%) when compared to findings of HC (55.33±1.8%). However, values of HDA were significantly ($p<0.05$) higher than the findings of LDA and MDA (Figure 2).

In contrast, the findings of lymphocytes were reduced significantly ($p<0.0124$; 95%CI: 10.59 to 40.76) among the MDA (18.67±3.84%), and HDA (16.6±1.2%) groups when compared to findings of HC (35.85±0.81%) as well as LDA (31.57±9.24%) groups (Figure 3).

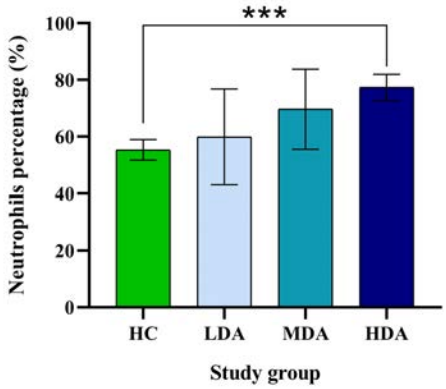


Fig. 2: Percentage of neutrophils among the groups of study population

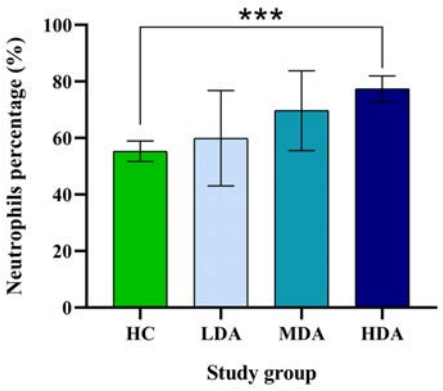


Fig. 3: Percentage of lymphocytes among the groups of study population

The findings of total RBCs count were recorded a significant reduction ($p<0.0003$; 95%CI: 3.713 to 5.202) in values of all groups of rheumatoid arthritis patients; LDA ($4.48\pm0.2\times10^6/\times L$), MDA ($4.15\pm0.14\times10^6/\times L$), and HDA ($4.09\pm0.06\times10^6/\times L$) in comparison with those of HC ($5.11\pm0.23\times10^6/\times L$). However, insignificant variation ($p>0.05$) was seen between values of all groups of rheumatoid arthritis patients (Figure 4).

Significant decreases ($p<0.0001$; 95%CI: 12.38 to 15.82) in values of hemoglobin were reported among all groups of rheumatoid arthritis patients; LDA (14.17±1.58g/dL), MDA (13.85±1.09g/dL), and HDA (12.88±0.39g/dL) when compared to those of HC (15.5±0.47g/dL). However, values of hemoglobin were significantly ($p<0.05$) less in individuals HDA group than those of LDA and MDA groups (Figure 5).

Relation to findings of hematocrit, there were significant decreases ($p<0.0002$; 95%CI: 35.73 to 48.34) in values of rheumatoid arthritis patients; LDA (41.43±5.17%), MDA

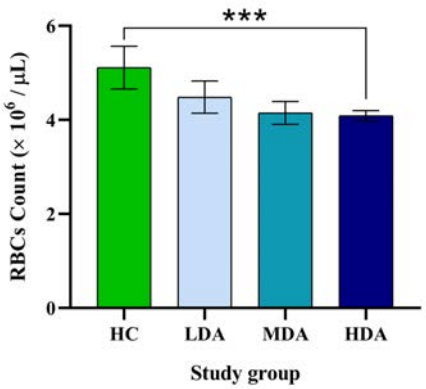


Fig. 4: Levels of total RBCs count among the groups of study population

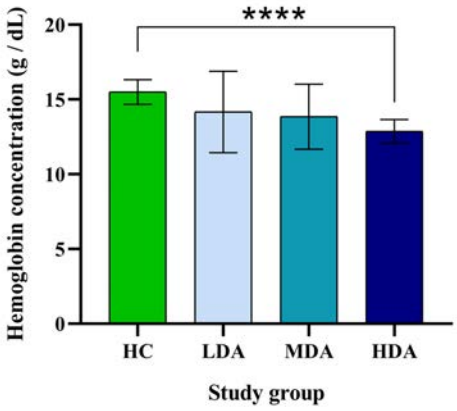


Fig. 5: Concentration of hemoglobin among the groups of study population

(40.75±3.43%), and HDA (38.33±1.56%) when compared to those of HC (47.63±1.07%). However, values of HDA were reduced more significantly (p<0.05) than those of LDA and MDA (Figure 6).

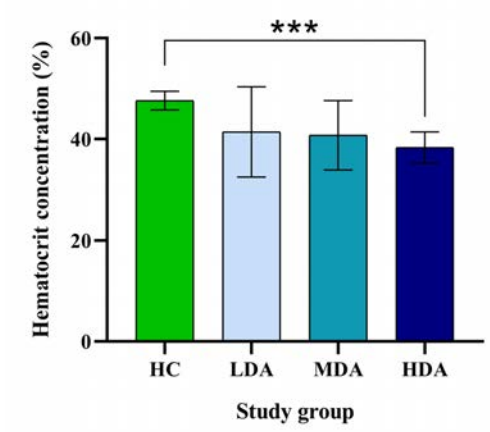


Fig. 6: Levels of hematocrit among the groups of study population

Regarding platelets, the findings of MDA (330±33.55×10$^3$/×L) and HDA (385.75±26.77×10$^3$/×L) groups in rheumatoid arthritis patients were elevated significantly (p<0.0036; 95%CI: 184.9 to 413.1) compared to those of HC (243±14.56×10$^3$/×L) and LDA (237.33±6.17×10$^3$/×L) groups. However, the findings of HDA were significantly higher than those of MDA (Figure 7).

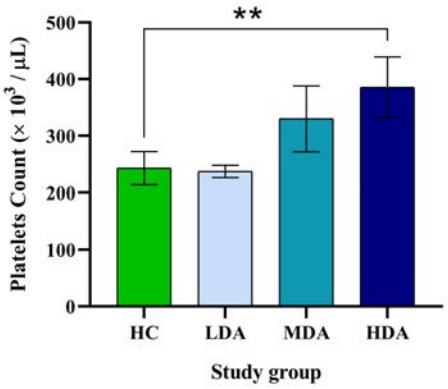


Fig. 7: Levels of platelets count among the groups of study population

**Immunological Findings:** The findings of this study demonstrated that the values of IFN-α were elevated significantly (p<0.0285; 95%CI: 7.860 to 71.25) throughout all levels of diseased-activity patients; LDA (35.54±1.61pg/ml), MDA (40.72±3.19pg/ml), and HDA (65.16±3.33pg/ml) when compared to individuals of HC (16.81±0.38pg/ml). However, significant higher (p<0.05) values were shown in patients of HDA than those of LDA and MDA (Figure 8).

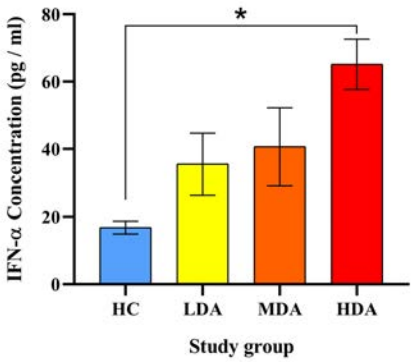


Fig. 8: Concentrations of IFN-α marker among all groups of study population

In comparison to values of HC (22.61±0.89ng/L), findings of IL-6 were elevated significantly (p<0.0285; 95%CI: 7.860 to 71.25) among groups of rheumatoid

arthritis patients; LDA (35.54±1.61ng/L), MDA (40.72±3.19ng/L), and HDA (65.16±3.33ng/L). However, no marked changes (p>0.05) were seen between findings of LDA, MDA, and HDA (Figure 9).

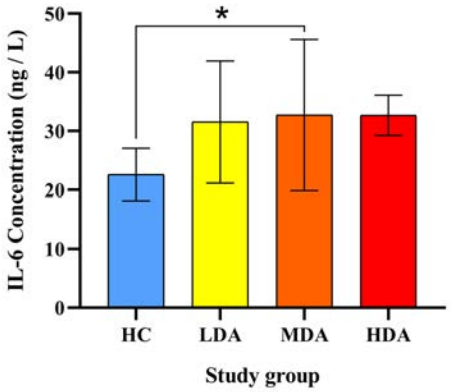


Fig. 9: Concentrations of IL-6 marker among all groups of study population

Significantly (p<0.0096; 95%CI: 53.25 to 176.5), IL-8 was shown an elevation in values of rheumatoid arthritis patients; LDA (129.81±4.82pg/ml), MDA (149.15±5.07pg/ml), and HDA (121±9.2pg/ml) when compared to those of HC (59.52±3.49pg/ml). However, values of MDA were significantly (p<0.05) higher than those recorded in individuals of LDA and HDA (Figure 10).

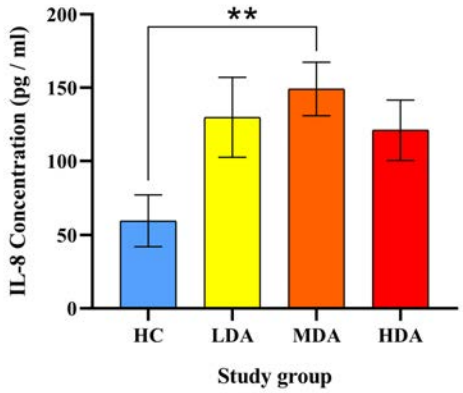


Fig. 10: Concentrations of IL-8 marker among all groups of study population

Concerning IL-10, values of rheumatoid arthritis patients; LDA (49.56±2.47pg/ml), MDA (50.08±4.88pg/ml), and HDA (77.2±2.18pg/ml) were elevated significantly (p<0.0106; 95%CI: 23.24 to 81.62) in comparison with those of HC (32.88±1.8pg/ml). However, significant higher values (p<0.05) were detected in HDA than those of LDA and MDA (Figure 11).

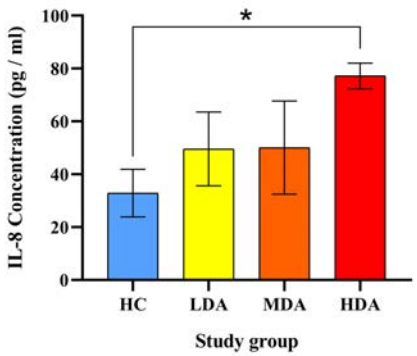


Fig. 11: Concentrations of IL-10 marker among all groups of study population

Significant elevation (p<0.0154; 95%CI: 51.68 to 232.5) in values of TNF-α were identified among all groups of rheumatoid arthritis patients; LDA (149.78±6.88pg/ml), MDA (163.62±6.46pg/ml), and HDA (193.6±7.34pg/ml) comparing to HC (61.4±3.86pg/ml); however, significant higher values (p<0.05) were recorded in HDA more than findings of LDA and MDA (Figure 12).

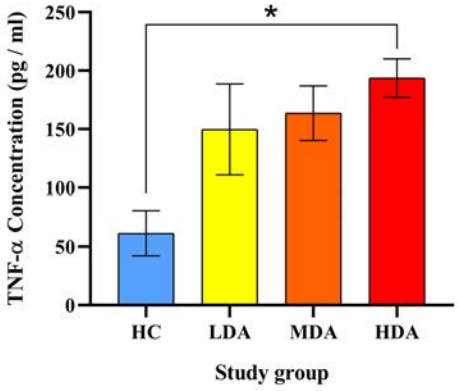


Fig. 12: Concentrations of TNF-a marker among all groups of study population

For TNF-β, the findings of rheumatoid arthritis patients; LDA (44.42±3.87pg/ml), MDA (29.26±3.27pg/ml), and HDA (41.06±8.59pg/ml) were elevated significantly (p<0.0077; 95%CI: 17.15 to 50.95) more than those of HC (21.45±0.62pg/ml). However, values of LDA and HDA were significantly (p<0.05) higher than the results of MDA (Figure 13).

In comparison to HC group, the findings of hematology were shown a significant elevation in values of WBCs and neutrophils among all groups of rheumatoid arthritis patients (LDA, MDA, and HDA) while platelets were increased markedly in MDA and HDA groups; whereas, lymphocytes were decreased markedly in MDA and HDA groups. In contrast, the

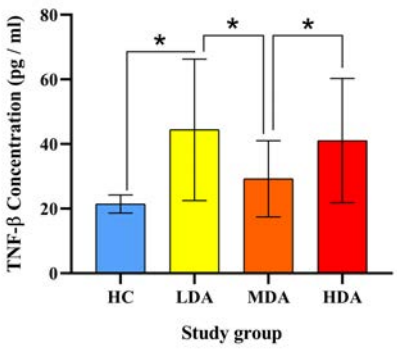


Fig. 13: Concentrations of TNF-β marker among all groups of study population

findings of RBCs, hemoglobin and hematocrit were reduced significantly among all groups of study patients. However, these changes might be attributed to the inflammatory nature of rheumatoid arthritis and infiltration of leukocytes into the synovial compartment which leading to chronic inflammatory states[31,32]. In this regard[33] mentioned that the easily available and affordable indicators such as the parameters of peripheral blood cells could reflect systemic inflammatory load and disease activity in rheumatoid arthritis patients. In fact, it has been documented that the total WBCs, specifically neutrophils, is consistently increased in the active rheumatoid arthritis patients, and the study indicated that the count of WBCs and neutrophils correlates positively with the disease activity scores[34-36]. Also, the increased inflammation associated with rising of WBCs and platelets, is related to releasing of different pro-inflammatory cytokines, proteins, angiogenic factors, and chemokines, which are also involved in the pathogenesis of rheumatoid arthritis[37]. In agreement with several researchers who have demonstrated that the hallmark of rheumatoid arthritis pathogenesis is the dysregulation of the immune system particularly alterations in the circulating lymphocyte populations, which play a critical role in orchestrating the inflammatory response[38,39,6,40]. Although, alterations in lymphocyte profiles are not static as therapeutic interventions can further modify the frequencies of these cell types, sometimes restoring a more balanced immune state, Immunological imbalance underscores the complex interplay of various lymphocyte subsets in perpetuating the autoimmune cascade characteristic of disease[41-43]. Also, this systemic inflammation often leads to anemia, acommon comorbidity in rheumatoid arthritis patients, which attributed primarily to dysregulation of iron metabolism, suppressed erythropoiesis and reduced RBCs lifespan[44,45]. Subsequently, other inflammatory mediators could contribute to increasing of eryptosis of bone marrow erythroid cells[46]. Furthermore, anemia in rheumatoid arthritis, often characterized as anemia of chronic disease, is a predictor of radiographic progression and an indicator of active clinical or subclinical inflammatory states, exacerbating secondary manifestations like fatigue, reduced mobility, and cardiovascular complications[47,48]. Indeed, studies have shown a positive correlation between distribution width of RBCs and inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate in rheumatoid arthritis patients[49,33,50,51].

For immunology, the findings of IFN-a, IL-6, IL-8, IL-10, TNF-α and TNF-β in the current study were elevated significantly among all groups of study patients; however, elevation in values of IFN-α, IL-10, and TNF-α was more significance in HDA than others; while IL-8 in MDA, and TNF-β in LDA and HDA. These findings indicate that aberrant activation in both innate and adaptive immune cells and the subsequent production of various pro-inflammatory cytokines and autoantibodies could be initiated during rheumatoid arthritis. Among these, IFN-α in addition to various interleukins could play pivotal roles in modulating the inflammatory cascade and contributing to the pathogenesis of rheumatoid arthritis[52-54]. Recent research highlights the increasing interest in IFNs across autoimmune rheumatoid diseases, with a growing understanding of their potential contribution to pathology of the disease[55-57]. However, the precise mechanisms by which IFNs exert their effects in rheumatoid arthritis are still under active investigation with studies indicating complex interactions with other cytokines and cellular pathways[58,59]. Beyond IFN, the intricate network of cytokines in rheumatoid arthritis also prominently features ILs which are crucial mediators for immune cell activation, inflammation and tissue damage[60]. Key pro-inflammatory interleukins such as IL-1, IL-6, and IL-8 are extensively implicated in the inflammatory cascade within rheumatoid arthritis, contributing significantly to joint destruction and systemic manifestations[53]. These ILs are frequently elevated in the synovium, synovial fluid, serum, or peripheral blood of the rheumatoid arthritis patients, often correlating with disease activity and seropositivity for rheumatoid factor and anti-cyclic citrullinated peptides[20]. The dysregulation of these ILs contributes to the chronic inflammatory state, driving processes such as synovial hyperplasia, cartilage degradation and bone erosion through complex signaling pathways[61]. Additionally, TNF has been

extensively studied and identified due to its role in driving the inflammatory process during rheumatoid arthritis[62,63]. In last years, emerging evidences suggested that TNF-β is a homologue of TNF-α, and plays a significant albeit less understood role in initiation and progression of rheumatoid arthritis[64]. Also, TNF-β can induce TNF-α production, indicating a possible regulatory feedback loop, and its expression in chondrocytes is significantly increased suggesting a broader involvement in inflammatory processes beyond what was previously acknowledged[64,65].

## CONCLUSION

This study demonstrates a significant association between the hematological and immune markers with the severity of disease suggesting that these markers can serve as valuable, independent biomarkers. However, multifaceted nature of disease necessitates comprehensive understanding the pathophysiology of disease to develop effective therapeutic strategies that target both articular and extra-articular manifestations. Therefore, moreover attempts to explain causal links and mechanism of interaction between different parameters and the risk of rheumatoid arthritis may result in development of potential interventions to prevent the disease. Furthermore, the utility of traditional hematological indices in monitoring disease activity undergoing disease-modifying anti-rheumatic drug therapy has been established, even when acute-phase reactants may appear normal ().

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**Conflict of Interest:** No.

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