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The Impact of Disease Activity on Hematological Parameters among Rheumatoid Arthritis Patients: A Cross-Sectional Analysis

Hajar khaled Masser[1a],Mostafa Nuhad Al daraji[1b] Rana Talib Mohsen[2c]*,

[1]*Department of, Biology, College of Science, University of Anbar, Al-Anbar, Iraq*
[2]*Department of Biotechnology, College of Science, University of Anbar, Al-Anbar, Iraq*

[a]E-mail haj22s1015@uoanbar.edu.iq , [b]E-mail: sc.mustafa_nt79@uoanbar.edu.iq, [c]*Corresponding author: rana2011@uoanbar.edu.iq
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***Abstract*-Rheumatoid arthritis (RA) is a systemic autoimmune disorder primarily characterized by persistent inflammation of the synovial joints, often with extraarticular involvement affecting multiple organ systems. Despite extensive research on inflammatory and hematological parameters in Iraqi RA patients, a significant gap exists in region-specific data, particularly for Anbar Governorate. This study aimed to assess and compare levels of key inflammatory and immunological markers—erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), anti-cyclic citrullinated peptide (Anti-CCP) antibodies, white blood cell (WBC) count, and interleukins IL-17 and IL-21—between RA patients and healthy controls in Anbar, Iraq.A case-control study included 50 RA patients and 40 healthy controls. Markers (ESR, CRP, RF, Anti-CCP, WBC) were measured via routine lab techniques, while IL-17 and IL-21 used ELISA. Significance was set at $p < 0.05$.RA patients' mean age was 49.58 ± 11.36 years; controls was 33.80 ± 12.20 years. RA group: 80% females (40), 20% males (10); controls: 60% females (24), 40% males (16). Results showed significantly elevated ESR and CRP in patients ($P < 0.001$). RF and Anti-CCP were positive only in patients ($P < 0.001$), underscoring diagnostic value. WBC, IL-17, and IL-21 exhibited no significant differences, though mildly higher in patients.Conclusion: ESR, CRP, RF, and Anti-CCP are effective for differentiating RA. WBC, IL-17, and IL-21 have limited standalone utility. Further research on cytokine profiles in RA subtypes and progression is recommended.**

***Keywords*—Rheumatoid Arthritis (RA); Inflammatory Markers; Hematological Parameters; Anti-CCP; Interleukin17 (IL-17); Interleukin-21 (IL-21); Anbar, Iraq**

I. INTRODUCTION

Rheumatoid arthritis (RA) is a long-term autoimmune disorder mainly targeting the synovial joints, leading to pain, stiffness, and limited joint movement., and may eventually lead to disability [1]. Extra-articular organs (the lungs, the heart, the eyes) Other organ systems may also be affected in RA, which adds complexity to both diagnosis and management [2]. It occurs most often at the age of 30-60, and its prevalence is large among women (3:1), possibly because of hormonal and immune impairment [3][4].RA is observed in 0.5-1 percent of adults on the planet, with regional and genetic variations in cases[5].Pathophysiologically, The disease is characterized by synovial membrane swelling caused by the infiltration of T cells, B cells, and macrophages.[6][7].The secretion of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-17, along with the proliferation of immune cells, contributes to cartilage and bone destruction as well as pannus formation.[8]. RA is clinically characterized by joint aches and pains, morning stiffness, and fatigue, which are symmetrical [9]. ESR and Creactive protein (CRP) are the most common laboratory examinations to measure systemic inflammation [10]. The counts of white blood cells (WBC) and lymphocytes are alsoEase of Use hematological markers that give information on immune function [6]. Recently, the attention has been directed toward such cytokines as IL-17 and IL-21 with regard to their involvement in RA immunopathology [11][12]. These cytokines have been studied in several cases in Iraq, yet none had studied them in patients in Anbar Governorate. Besides, the classical markers of RA Biomarkers such as Rheumatoid Factor (RF), anti-cyclic citrullinated peptide antibodies (AntiCCP), and C-reactive protein (CRP) remain central to the diagnosis and prognosis of RA." [13][14][15]

II. MATERIALS AND METHODS

A. Study Design and Population

This was a case-control study, which occurred in Anbar Governorate between November 2024 and January 2025. The trial used 90 participants, among which 50 were patients with rheumatoid arthritis (RA) and 40 were healthy individuals who became the controls. Patient samples were collected from private rheumatology clinics in Ramadi city, and all cases were diagnosed by board-certified specialists using the 2010 ACR/EULAR classification criteria.

Sample Collection Peripheral venous blood (5 mL) was collected from each participant using sterile vacutainer tubes. The blood was centrifuged to separate the serum, which was either used immediately for hematological testing or stored at −80°C in aliquots until cytokine analysis was performed.

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B. Hematological and Immunological Tests

1) •Complete Blood Count (CBC):

Total white blood cell (WBC) counts were assessed using the Nipigon NP-50H automated hematology analyzer (Nipigon Health Ltd., Canada). Whole blood samples were collected in EDTA tubes and analyzed immediately without storage.

2) •Erythrocyte Sedimentation Rate (ESR):

Measured using the traditional Westergren method.

3) Rheumatoid Factor (RF) and C-Reactive Protein (CRP):

Both RF and CRP levels were Both RF and CRP levels were measured using a fully automated immunoassay analyzer (Biosystems S.A., Spain). All procedures were performed using the manufacturer's standardized protocol and dedicated reagents. Serum samples were processed immediately after collection, without freezing.

4) Anti-CCP Antibiose:

Anti-cyclic citrullinated peptide (Anti-CCP) antibodies were detected using a rapid immunochromatographic test provided by Hotgen Biotech Co., Ltd. (China). The test was performed on fresh serum following the manufacturer's instructions, without the use of specialized analytical instruments.

5) Cytokine Quantification

"Serum levels of interleukin-17 (IL-17) and interleukin-21 (IL-21) were quantified employing the sandwich enzyme-linked immunosorbent assay (ELISA) method, following the protocols provided by the manufacturer. The assays utilized commercially available kits supplied by ELK Biotechnology Co., Ltd. (China), and optical density measurements were performed at a wavelength of 450 nm using a microplate reader.

C. Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics software (version 27). Initially, the distribution of the data was assessed using the Shapiro–Wilk test to determine whether the serum variables followed a normal distribution. Continuous variables were presented as mean ± standard error (SE), with 95% confidence intervals reported for each group. The appropriate statistical tests were applied based on the distribution of the data. Parametric or non-parametric tests were used to compare variables between rheumatoid arthritis (RA) patients and healthy controls, depending on the statistical nature of each variable.Categorical variables, such as rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (Anti-CCP), were analyzed using the Pearson Chi-square test.Additionally, Univariate Analysis of Variance (UNIANOVA) was used to evaluate the effects of disease status, gender, and their interaction on selected hematological parameters.A p-value of less than 0.05 was considered statistically significant in all analyses.

III. Result and Discussion

A. ESR Levels in RA Patients and Healthy Controls

The mean ESR level among RA patients (n = 50) was 47.75 ± 21.75 mm/h, while in the control group (n = 40), it was 16.90 ± 5.26 mm/h. This difference was statistically significant (P <0.001).When stratified by gender, female RA patients had a mean ESR of 49.17 ± 8.257 mm/h, and males had 46.33 ± 6.952 mm/h (P = 0.268). In the control group, females showed a mean ESR of 21.20 ± 4.171 mm/h, whereas males had 12.60 ± 5.385 mm/h. The interaction between gender and disease status was not statistically significant (P = 0.576), as illustrated in Table 1

Table 1. Mean ESR levels (mm/h) among RA patients and healthy controls, stratified by gender with 95% Confidence Intervals

				95% Confidence Intervalle	
Status	Gender	Mean	Std. Error	Lower Bound	Upper Bound
C	F	21.200	4.171	12.908	29.492
	M	12.600	5.385	1.895	23.305
p	F	49.171	3.257	42.696	55.646
	M	46.333	6.952	32.513	60.153

The current study demonstrated a clear elevation in erythrocyte sedimentation rate (ESR) levels among rheumatoid arthritis (RA) patients compared to healthy controls. The mean ESR in female RA patients was 49.17 mm/h and 46.33 mm/h in male RA patients, while the values in the control group were substantially lower, at 21.2 mm/h for females and 12.6 mm/h for males. These differences were further supported by the analysis of 95% confidence intervals, which showed no overlap between the two groups, thus reinforcing the presence of statistically significant differences.

To illustrate these findings visually, a boxplot was used, which highlighted the overall distribution of ESR values in each group. The plot clearly indicated that RA patients had a wider distribution in the values of ESR and this means that some of the patients had a very high level of ESR whereas others were comparatively lower. Conversely, the values of the control group were densely and tightly packed in a smaller interval. Such a great difference (or dispersion) between patients is regarded as one of the natural effects of the heterogeneity of RA, i.e., that the extent of inflammatory activity varies greatly across patients. There will be some people who have a mild inflammation and some people who have this severe disease activity which leads to a wide range of variation in the inflammatory markers, like ESR. Thus, the dispersion is a realistic representation of clinical diversity in the disease activity, rather than a statistical wimp.These results are concordant with a number of recent studies performed in Iraq which recorded significant lowering of ESR rates in normal ones relative to RA patients. To give an example, [16].freported a significant increase in ESR in patients diagnosed with RA in the province of Wasit. On the same note, [17] showed a meaningful difference among the parameters of

inflammations, such as ESR, in Iraqi RA patients. [18] also proved that RA patients had increased levels of ESR. Moreover, the same results were observed in an investigation by [19] in Misan Province as well as by [20] in their study of the immunological and biological presentation of RA. All together, they make the current findings even more credible and assure the clinical usefulness of ESR as a stable indicator of the inflammatory state in RA patients.

B. ESR Levels According to CRP Status

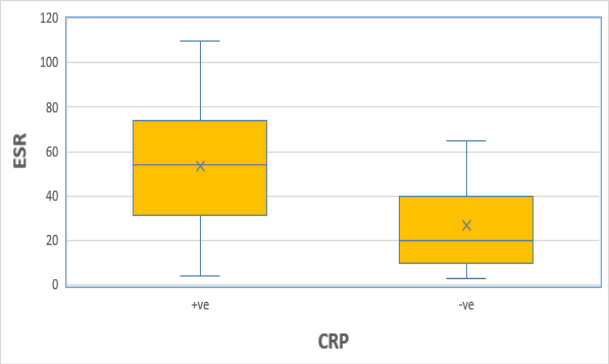

Figure 1 . Boxplot showing ESR distribution in CRP-positive and CRP-negative individuals

Comparison of ESR on the basis of CRP status showed that the CRP +ve value had an increase in ESR value as compared to the CRP -ve value. These results were visually confirmed by the boxplot in Figure 2 in which a greater range of interquartile and higher median were recorded in the CRP-positive. This pattern implies that a consistent increase of ESR could occur in response to high levels of active inflammatory markers, which are indicated by CRP status.

The results of the present study confirm the proposed role of CRP as an efficient indicator of systemic inflammation since the average C-reactive protein (CRP) level in RA patients was significantly higher than in healthy individuals. This level is elevated and its level of values amongst patients is varied implying that the activity levels of disease vary between individuals. The inflammatory process in RA is heterogeneous which is represented by the high value of the standard deviation.

In alignment with our findings, [19] pointed out that CRP and ESR are complementary predictive markers to use in checking RA activity with outcomes indicating that the two indicators are highly related to clinical manifestations of the disease.

In addition, [23]found that there are great increases in CRP and ESR in RA patients and showed a readable connection between the mentioned factors and changes in the lipid pathway. This demonstrates the interaction between inflammatory disorders in the body and metabolic problems in RA.

Also, [20] have found that there is positively significant correlation between CRP, ESR in patients with RA, and the disease activity score (DAS-28), which means that CRP is a constituent of inflammatory process within RA.

These findings as a whole justify the clinical significance of CRP as a measure of RA on its own account or in combination with ESR, inflammation in various parts of the body.

C. White Blood Cell (WBC) Counts in RA Patients and Controls

White blood cell (WBC) counts varied slightly across gender and disease status groups. Among healthy controls (n = 40), females had a mean WBC count of 8.48 $\times 10^3/\mu L$ (95% CI: 7.517–9.459), while males had a slightly higher mean of 8.94 $\times 10^3/\mu L$ (95% CI: 7.686–10.194).In rheumatoid arthritis (RA) patients (n = 50), the mean WBC count was 7.57 $\times 10^3/\mu L$ in females (95% CI: 6.802–8.338) and 8.056 $\times 10^3/\mu L$ in males (95% CI: 6.437–9.674). Although these values show some variation, the differences were not statistically significant with respect to disease status (P = 0.138), gender (P = 0.438), or their interaction (P = 0.978), according to UNIANOVA results (Table -3).

Table 2. Mean White Blood Cell (WBC) Counts Among RA Patients and Healthy Controls, Stratified by Gender with 95% Confidence Intervals

				95% Confidence Interval	
Status	Gender	Mean	Std. Error	Lower Bound	Upper Bound
C	F	8.488	0.489	7.517	9.459
	M	8.940	0.631	7.686	10.194
p	F	7.570	0.386	6.802	8.338
	M	8.056	0.814	6.437	9.674

Table 3. P-values obtained from UNIANOVA test comparing disease status, gender, and their interaction in relation to WBC counts.

Comparison	Groups Compared	P-value
Disease Status	RA patients vs. Healthy controls	0.138
Gender	Females vs. Males	0.438
Disease Gender	Interaction between disease status and gender	0.978

The current study revealed slight variations in white blood cell (WBC) counts across different gender and disease status groups. Among healthy controls, females had a mean WBC of 8.488 (95% CI: 7.517–9.459), while males had a slightly higher mean of 8.94 (95% CI: 7.686–10.194). In contrast, rheumatoid arthritis (RA) patients showed lower mean WBC counts: 7.57 for females (95% CI: 6.802–8.338) and 8.06 for males (95% CI: 6.437–9.674).Despite these differences, the Results of UNIANOVA test showed that WBC changes were not statistically significant in relationship to disease status (p = 0.138), gender (p = 0.438) and interaction (p = 0.978). It indicates that WBC is not a good discriminator between RA patients and healthy people in this sample when used in isolation. It is noted that the results of the current study correspond to the results of the study performed by [21], which also found the mean of WBC slightly higher in RA patients (7.34 2 0.25) than in

healthy people (6.73 2 0.19) though it was not statistically significant. On the same note, [22].did not find any significant difference in the WBC counts between RA patients and controls. Such uniformities of independent researches support the idea of low diagnostic value of WBC in RA assessment. These differences could indicate the differences in the characteristics of the studied population, treatment and activity of the disease. It is important to note that the current study makes a contribution to the literature, as few of the studies conduct the UNIANOVA test on the interaction between gender and disease status, which shows no significant interaction ($p = 0.978$). This is usually an ignored aspect in previous research hence the need to look at the demographics of the patients when assessing the inflammatory markers.

D. Anti-CCP and RF Status Among Study Groups

Anti-cyclic citrullinated peptide (Anti-CCP) antibodies were detected in 14 out of 50 RA patients (28%), while all 40 healthy controls tested negative for Anti-CCP. This difference was statistically significant, as shown by the Chi-square test ($\chi^2 = 104.411$, $df = 4$, $P < 0.001$), indicating a strong association between Anti-CCP positivity and disease status (Table 4).Regarding Rheumatoid Factor (RF), 27 out of 50 RA patients (54%) were RF-positive, whereas all 40 healthy controls were RF-negative. This difference also showed a highly significant association with disease status ($\chi^2 = 122.200$, $df = 4$, $P < 0.001$), as summarized in Table 4.

Table 4. Distribution of Anti-CCP and Rheumatoid Factor (RF) Status Among RA Patients and Healthy Controls with Chi-square Test Results

Group	Anti-CCP Negative	Anti-CCP Positive	Total
Control	40	0	40
Patients	36	14	50
Total	76	14	90
Pearson Chi-Square 104.411 a			
Group	**RF Negative**	**RF Positive**	**Total**
Control	40	0	40
Patients	23	27	50
Total	63	27	90
Pearson Chi-Square 122.200 a			

The current study revealed a highly significant difference in Anti-Cyclic Citrullinated Peptide (Anti-CCP) positivity between rheumatoid arthritis (RA) patients and healthy controls. Chi-square analysis demonstrated a strong association between disease status and Anti-CCP positivity ($\chi^2 = 104.411$, $P < 0.001$), with 28% of the patients testing positive for Anti-CCP, whereas none of the healthy individuals were positive. These findings are consistent with the results of [16], who reported that the mean Anti-CCP level among RA patients was 90.0 ± 53.2 U/mL, compared to 5.0 ± 2.2 U/mL in healthy controls, with a highly significant statistical difference ($P < 0.001$). Similarly, [24] found Anti-CCP positivity in 86.67% of untreated patients, 70% in those treated with methotrexate, and 53.33% in patients receiving etanercept, while none of the controls tested positive ($P < 0.01$).In line with these findings, [25]showed that 94% of RA patients treated with infliximab were Anti-CCP positive, whereas the control group had a 0% positivity rate, with a statistically significant difference ($P < 0.001$). This alignment of findings across multiple Iraqi studies strengthens the current results and confirms the value of Anti-CCP as a highly specific serological biomarker in distinguishing RA patients from healthy individuals. On the other hand[26] found no statistically significant association between Anti-CCP levels and disease activity among RA patients ($P = 0.981$). Although this contrasts with the diagnostic aspect explored in the present study, it does not contradict our findings, as our focus was on comparing patients to healthy controls rather than analyzing disease severity within patient subgroups.

The current study demonstrated a strong and statistically significant association between disease status and the presence of Rheumatoid Factor (RF). Among rheumatoid arthritis (RA) patients, 54% (27 out of 50) tested positive for RF, while none of the healthy controls ($n = 40$) exhibited RF positivity. Chi-square analysis revealed a highly significant difference ($\chi^2 = 122.200$, $df = 4$, $p < .001$), indicating a clear relationship between RA diagnosis and the presence of RF. These findings are consistent with several regional and local studies that have emphasized the diagnostic utility of RF in differentiating RA patients from healthy individuals. For instance, [27] reported 100% RF positivity among RA patients ($n = 60$), in contrast to 0% positivity in the control group, with a highly significant difference ($p < .001$). Likewise, (Gahli & Mohammed, 2024) revealed that the average RF concentration in patients with RA was 51.3 +/- 21.6 IU / mL, which is higher by 5 and a half times, compared to the healthy population (3.7 +/- 1.1 IU / mL) with a high level of $p < .001$, again, providing further evidence on RF as a trusted diagnostic indicator.[23]also record even higher levels of RF in their RA All these findings indicate how RF has a persistent level of value as a tool of diagnosis, especially in the local Iraqi clinical settings.

Occurrence of lack of anti-cyclic citrullinated peptide (Anti-CCP) antibodies, rheumatoid factor (RF) presence among patients with rheumatoid arthritis (RA) can be explained by several overlapping factors. It could be possible that some of the patients are in the initial stages of the disease where the development of the immune response is still not occurring and there are still no antibodies present in their body to cross the threshold necessary to detect anti-Anti-CCP). Also, particular immunosuppressive therapy protocols can decrease the level of these antibodies or change their serological behavior. The other cause of concern is sensitivity of the diagnostic instruments; the rapid tests could be less sensitive when picking low levels of antibodies, thus not as sensitive as ELISA-based tests though they are convenient, high speed, and have operational benefit. The inter-ethnic and inter-genetic differences between populations can also influence differences in immune responses as autoantibody production can also vary. Lastly, there are patients who are members of the clinically accepted subtype characterized by the absence of autoantibodies despite the classical manifestations of the disease which is referred to as the seronegative RA.

E. IL-17 and IL-21 Serum Levels in RA Patients and Controls

Table 5 presents the comparison of serum concentrations of IL-17 and IL-21 between rheumatoid arthritis (RA) patients and healthy controls, along with their corresponding standard errors and 95% confidence intervals. For IL-17, the mean serum level in healthy controls was 37.388 pg/mL with a standard error of 4.134, and a 95% confidence interval ranging from 29.169 to 45.607 pg/mL. In contrast, RA patients exhibited a slightly higher mean concentration of 39.770 pg/mL with a standard error of 4.660, and a 95% confidence interval of 30.506 to 49.033 pg/mL.For IL-21, the mean serum level in the control group was 10.633 pg/mL, standard error 2.424, and the 95% confidence interval ranged from 5.814 to 15.453 pg/mL. Among RA patients, the mean was 6.830 pg/mL, with a standard error of 2.732, and a 95% confidence interval between 1.398 and 12.262 pg/mL.

Statistical analysis showed that the differences in IL-17 and IL-21 concentrations between patients and controls were not statistically significant ($P > 0.05$).

Table 5. Comparison of IL-17 and IL-21 Serum Concentrations Between RA Patients and Healthy Controls with 95% Confidence Intervals

	Group	Mean	Std. Error	Lower Bound	Upper Bound
IL-17	Control	37.388	4.134	29.169	45.607
	Patients	39.77	4.66	30.506	49.033
IL -21	Control	10.633	2.424	5.814	15.453
	Patients	6.83	2.732	1.398	12.262

This research revealed a relative increase in the levels of IL-17 in the serum of RA victims against healthy cases (39.770 pg/mL against 37.388 pg/mL) but low levels of IL-21 in RA patients (6.830 pg/mL compared to 10.633 pg/mL). Inspite of these differences, statistical analysis denoted no drastic difference in groups ($P > 0.05$). This statistical insignificance is possibly due to other reasons which include a relatively small sample size, a variation in terms of disease stages of the individuals and the possibility of the treatment influencing the expression of the cytokines. Indeed, the study by [28] indicates remarkably high levels of IL-17 in the blood of RA patients ($p = 3.1 \times 10\text{-}6$). In the same fashion, the investigation by [29] swore that IL-17A is directly involved in the process of inflaming the synovium and the destruction of joints through the influence of fibroblasts and macrophages in the synovium. Nevertheless, they also observed inter-individual variability to respond to IL-17-bias therapies, which could be considered as the reason behind the disparity in the levels of cytokines between different studies. In the instance of IL-21, we have observed a reverse in IL-21 levels as compared to studies done by [30], showing that IL-21 plays a critical importance in augmenting Th17 cell differentiation and encourages inflammation by overexpressing TNF-alpha and IL-6. These differences may be brought about by difference in the sensitivity of the assays, duration of the disease, therapies or genetic makeup of the populations the studies are conducted.Generally, despite the views on the role of IL-17 and IL-21 as significant cytokines in the pathogenesis of RA, their serum levels might not necessarily be always involved in reflecting the presence or activity in the disease. More studies are therefore justified to determine its diagnostic value when used together with the clinical indicators and genetic risk factors.

IV. Conclusion

This research study has shown considerable variations in rheumatoid arthritis (RA) patients and healthy subjects with regard to main immunological and hematological indicators in the Anbar Province. It is worth noting that, only Anti-CCP and RF were measured in RA patients and strongly statistically related to disease status, which contributes to their appreciation as diagnostic tests. ESR and CRP levels were also significantly elevated among patients, further supporting their role as indicators of systemic inflammation in RA. Conversely, IL-17, IL-21, and WBC did not show statistically significant differences, which may be related to early disease stages, treatment effects, or population-specific immune variations. These findings underscore the diagnostic importance of traditional serological markers, particularly Anti-CCP and RF, while highlighting the need for further research into the role of cytokines in RA pathogenesis. The study contributes novel data from a geographically underrepresented region and reinforces the clinical relevance of integrating serological, inflammatory, and hematological markers in RA evaluation. Further studies with larger cohorts and stratified disease activity levels are recommended to enhance diagnostic accuracy and improve disease management strategies.

Ethics Approval and Consent to Participate

This study was approved by the Ethical Approval Committee at the University of Anbar, Iraq, under approval number 149, dated February 11, 2024. All procedures involving human participants were conducted in accordance with institutional ethical standards, and verbal informed consent was obtained from all participants prior to sample collection.

Conflict of Interest

The authors have declared that no conflict of interest exists.

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