Medical Science Journal for Advance Research

Vol. 5, No.2, June 2024
e-ISSN: 2774-4892

Comparison of Some Clinical, Hematological and Serological Parameters According to the Level of Disease Activity in Patients with Rheumatoid Arthritis

Mays Saleh Khamees[1] and Raad Abdulameer Alasady[2]
[1,2] University of Kufa, Faculty of Medicine, Medical Microbiology, Iraq.
E-mail: mays.s.khamees@gmail.com

ABSTRACT

Background: *This study aimed to evaluate the usefulness of some clinical, hematological, and serological parameters in monitoring of RA activity.*
Methods: *This study included 107 RA patients [98 females and 9 males; mean age 46.85 years (range 18–70)]. The patients were classified into four groups based on their disease activity scores. Disease activity scores (DAS-28 ESR and DAS-28 CRP), complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), and anti-citrullinated peptide antibody (ACPA) were measured.*
Results: *Both "DAS-28 ESR and DAS-28 CRP" showed a significant difference among the four disease activity groups regarding family history, disease duration, regularity of treatment intake, response to treatment, and ESR level (P <0.05). Furthermore, DAS-28 CRP revealed a significant difference (P = 0.021) in the CRP levels across the four disease activity groups.*
Conclusion: *The study found an association between some clinical, hematological, and serological factors and the level of disease activity in patients with RA.*
Keywords: Rheumatoid Arthritis (RA), Disease Activity Index, DAS-28 ESR, DAS-28

Article Information
Received: March 18, 2024; Revised: May 29, 2024; Online: June, 2024

INTRODUCTION

"Rheumatoid arthritis (RA) is a common autoimmune disorder characterized by severe inflammation that affects several joints symmetrically" (Feng *et al*., 2019). The prevalence of RA is estimated to be around 1% in the global population (Goma *et al*., 2019). In Iraq, there is an increasing incidence of RA patients, according to studies conducted by Alkazzaz (2013) and Al_Badran *et al*, (2022).The common symptoms of RA include high fever, joint stiffness in the morning, fatigue, swollen and painful joints, and the formation of skin nodules (Bullock *et al.*, 2019). Furthermore, RA have extra-articular manifestations; it can affect the skin, lungs, heart, eyes, and blood vessels (O'Neil & Kaplan, 2019; Smith & Berman, 2022). Because of the progressive nature of RA, untreated or inadequately controlled disease activity causes structural degeneration of the joints and ultimately deformities (Uribe *et al*., 2016; Conti *et al.*, 2020; Wright *et al.*, 2021). Both short-term and long-term physical and functional decline contribute to a reduction in a person's quality of life and increase in mortality and morbidity rates (Uribe *et al*., 2016). When treating RA, the ultimate goal is to arrest the disease's erosive progression and achieve and maintain clinical remission with maintaining the

https://doi.org/10.46966/msjar.v5i2.180

Published by: READ INSTITUTE

patient's mobility and physical function (Bullock *et al*., 2019). In this context, determining the disease activity level, progression, and response to a specific intervention is necessary for assessing the success of treatment goals (Uribe *et al*., 2016). This study aimed to evaluate the usefulness of some clinical, hematolo gical, and serological parameters in monitoring of RA activity by evaluate their association with the disease activity level.

METHODS

A cross-sectional study was conducted on 107 patients with RA who fulfilled the "2010 ACR/EULAR (American College of Rheumatology/European League Against Rheumatism) diagnostic criteria for RA.". In this study, all the involved participants were pioneers of the rheumatology department in Al-Sader Medical City in Al-Najaf City from July 2023 to September 2023. The study involved 98 females and 9 males, ranging in age from 18 to 70 years. Patients who had other autoimmune diseases, recent surgery, acute local wounds or inflammation, central nervous system diseases, chronic infections, cancer, and immunodeficiency diseases were excluded from the study.

Before commencing the study project, the ethical committee of the College of Medicine at the University of Kufa had approved. The Rheumatology Department of Al-Sadr Medical City also granted permission, and the patient's consent was obtained to conduct a questionnaire and collect a blood sample.

Data were collected through a questionnaire that including the patient's name, age, sex, oral contraceptive pill use, body mass index, and the presence of history of RA within the family, as well as any history of chronic diseases such as hypertension, diabetes mellitus, and other related information. Also, the rheumatologist provides a physical examination of the joints to evaluate the condition, based on the number of tender and swollen joints to determine the activity of the disease.

Two indices of disease activity (DAS28 ESR and DAS28 CRP) were used to measure the level of the RA patient's disease activity score by using the equation below:

"DAS-28= 0.28*√(SJC28) + 0.56*√(TJC28) + 0.70*Ln (ESR or CRP) + 0.014xPGH"

Where:

- SJC: Swollen Joint Count (0-28).
- TJC: Tender Joint Count (0-28).
- ESR: The erythrocyte sedimentation rate (mm/h).
- CRP: C- reactive protein level (mg/l).
- PGH: The patient's global health assessment (from 0 = best to 10 = worst) (Verma, 2013).

Aletaha & Smolen (2005) classify RA patients based on the disease activity using "DAS-28-ESR and DAS-28 CRP to remission (<2.6), low disease activity (2.6–3.2), moderate disease activity (3.2–5.1), and high disease activity (>5.1)."

The collected blood sample of each patient was used for various laboratory tests, including CBC using a hematological analyzer, ESR using the Westergren method, CRP using a particle-enhanced immune-turbidimetry assay from Cobas, Germany, RF using the sandwich immunodetection method from Boditech, Korea, and ACPA using the ELISA from Sunlong, China.

STATISTICAL ANALYSIS

Version 21 of the Statistical Package for the Social Sciences (SPSS) software (San Diego, California, USA) was used to analyze the data. It was shown that categorical variables were represented as frequency and percentage, and continuous variables as means and SD. For categorical variables, the chi-square test was used to determine significance. The correlation between ordinal and nominal scales was assessed using Pearson and Spearman correlations. ANOVA and independent t-tests

were used to evaluate the significant level of various clinical and laboratory data and measure serological parameters across research groups. Median ± IQR was reported when variance was not found. A statistically significant level was defined as P<0.05, and a highly significant level as P<0.01.

RESULTS

This cross-sectional study included 107 patients with RA. The mean age of the RA patients was 46.85 years, with a deviation of ± 10.564. According to sex, there were 98 female patients (91.6%) and 9 male patients (8.4%). Furthermore, 45 (42.06%) of the RA patients had a positive family history of RA, while 62 patients (57.94%) had a negative family history. Regarding the disease duration, 28 patients (26.2%) had duration of less than six months, while 79 patients (73.8%) had a duration of more than six months. Additionally, 67 patients (70.5%) were regularly taking their treatment, while 28 patients (29.5%) were taking it irregularly. Concerning the response to treatment, 57 patients (60.0%) had a good response, while 38 patients (40.0%) had a poor response. These values are shown in Table 1.

Based on the DAS-28 ESR, significant differences existed in the family history, disease duration, regularity of treatment intake, and response to treatment, (P = <0.001, P = <0.001, P = <0.001, and P = <0.001, respectively) among the four activity groups of the RA patients. Based on the DAS-28 CRP, the four disease activity groups of the patients had highly

significant differences in their family history, disease duration, regularity of treatment intake, and response to treatment (P= 0.007, P= <0.001, P= <0.001 and, P= 0.022, respectively), as presented in Table 2.

Table 1: Demographic Characteristics, Family History, Disease Duration, and Features of Treatment History of the RA Patients (N=107)

Characteristic		RA patients
Age, mean (year) ±S.D.		46.85±10.564
Sex [females/males (% of females)]		98/9 (91.6%)
Family history (N=107)	Positive, number (%)	45 (42.06 %)
	Negative, number (%)	62 (57.94 %)
Disease duration (N=107)	Less than 6 months, number (%)	28 (26.2 %)
	More than 6 months, number (%)	79 (73.8%)
Regularity of treatment intake (N=95)	Regular, number (%)	67 (70.5 %)
	Irregular, number (%)	28 (29.5 %)
Response to treatment (N=95)	Good, number (%)	57 (60.0 %)
	Poor, number (%)	38 (40.0 %)

Table 2: Comparison of the Family History, Disease Duration and Features of Treatment History of the Patients with RA among Different Disease Activity Groups Using the DAS-28 ESR and DAS-28 CRP (N=107)

Characteristic			Remission	Low activity	Moderate activity	High activity	P-Value
Family history	DAS-28 ESR	Positive, number (%)	0 (0.0%)	1 (50.0%)	12 (36.4%)	32 (45.7%)	<0.001**
		Negative, number (%)	2 (100.0%)	1 (50.0%)	21 (63.6%)	38 (54.3%)	
	DAS-28 CRP	Positive, number (%)	2 (33.3%)	3 (50.0%)	22 (36.1%)	18 (52.9%)	0.007**
		Negative, number (%)	4 (66.7%)	3 (50.0%)	39 (63.9%)	16 (47.1%)	
Disease duration	DAS-28 ESR	Less than 6 months, number (%)	0 (0.0%)	0 (0.0%)	9 (27.27%)	19 (27.14%)	<0.001**
		More than 6 months, number (%)	2 (100.0%)	2 (100.0%)	24 (72.72%)	51 (72.86%)	
	DAS-28 CRP	Less than 6 months, number (%)	0 (0.0%)	1 (16.67%)	19 (31.15%)	8 (23.53%)	<0.001**
		More than 6 months, number (%)	6 (100%)	5 (83.33%)	42 (68.85%)	26 (76.47%)	
Regularity of treatment intake	DAS-28 ESR	Regular, number (%)	2 (100.0%)	0 (0.0%)	23 (69.69%)	42 (60%)	<0.001**
		Irregular, number (%)	0 (0.0%)	2 (100.0%)	5 (15.15%)	21 (30%)	
	DAS-28 CRP	Regular, number (%)	3 (50%)	5 (83.33%)	39 (63.93%)	20 (58.82%)	<0.001**
		Irregular, number (%)	3 (50%)	1 (16.67%)	13 (21.31%)	11 (32.35%)	
Response to treatment	DAS-28 ESR	Good, number (%)	2 (100.0%)	0 (0.0%)	21 (63.64%)	34 (48.57%)	<0.001**
		Poor, number (%)	0 (0.0%)	2 (100.0%)	7 (21.21%)	29 (51.43%)	
	DAS-28 CRP	Good, number (%)	4 (66.67%)	4 (66.67%)	34 (55.74%)	15 (44.12%)	0.022*
		Poor, number (%)	2 (33.33%)	2 (33.33%)	18 (29.51%)	16 (47.06%)	

**: highly significant difference

There were no significant variations in hemoglobin level, WBC count, or platelet count (P = 0.554, P = 0.120, and P = 0.397, respectively) across the four disease activity patient groups based on the DAS-28 ESR. Similarly, the study findings indicated that no significant difference was observed in hemoglobin level, WBC count, or platelet count (P = 0.596, P = 0.197, and P = 0.067, respectively) among the four disease activity groups regarding the DAS-28 CRP, as shown in Table 3.

The DAS-28 ESR revealed a highly significant difference (P = 0.004) in the ESR level between the four disease activity groups. However, no significant difference existed in CRP, RF, and ACPA levels (P = 0.630, P = 0.568, and P = 0.344, respectively) among the four patient groups. The DAS-28 CRP revealed a significant difference in the ESR and CRP levels (P = 0.008, and P = 0.021, respectively) across the four disease activity groups. However, no significant difference existed in RF and ACPA levels (P = 0.300, and P = 0.928, respectively) among the four patient groups, as shown in Table 4.

Table 3: Comparison of the Haematological Parameters of the Patients with RA among Different Disease Activity Groups Using the DAS-28 ESR and DAS-28 CRP (N=107)

Characteristic		Remission	Low activity	Moderate activity	High activity	P-Value
Haemoglobin level (mg/dl), mean ±S.D.	DAS-28 ESR	12.20± 1.697	12.55± 0.778	11.45± 1.629	11.81± 1.456	0.554
	DAS-28 CRP	12.12± 0.948	11.97± 0.826	11.81± 1.540	11.45± 1.605	0.596
WBC count (x 10^9/liter), mean ±S.D.	DAS-28 ESR	11.07± 3.578	6.78± 1.583	7.06± 2.111	7.57± 2.488	0.120
	DAS-28 CRP	8.18± 2.956	5.93± 1.427	7.29± 2.061	7.93± 2.855	0.197
Platelets count (x10^9/liter), mean ±S.D.	DAS-28 ESR	257.50± 3.535	220.50± 111.016	240.76± 67.136	273.67± 107.878	0.397
	DAS-28 CRP	235.83± 56.012	189.00± 66.206	256.18± 95.845	290.65± 100.401	0.067

Table 4: Comparison of the Routine Biomarkers of the Patients with RA among Different Disease Activity Groups Using the DAS-28 ESR and DAS-28 CRP (N=107)

Characteristic		Remission	Low activity	Moderate activity	High activity	P-Value
ESR level (mm/hr), mean ±S.D.	DAS-28 ESR	17.50 ± 17.678	16.50 ± 9.192	31.97 ± 18.487	48.69 ± 27.816	0.004**
	DAS-28 CRP	26.50 (35.00)	27.50 (18.75)	35.00 (25.00)	45.50 (50.00)	0.008**
CRP level (mg/L), mean ±S.D.	DAS-28 ESR	4.88 ± 6.639	2.295± 2.439	7.195 ± 13.487	14.74 35.632	0.630
	DAS-28 CRP	3.94 (8.45)	1.44 (1.61)	5.21 (5.22)	10.54 (18.47)	0.021*
RF level (IU/mL), median (IQR)	DAS-28 ESR	114 (.)	8.5 (.)	19 (31.5)	18 (33.5)	0.568
	DAS-28 CRP	14.50 (93.75)	36.50 (75.50)	18.00 (18.50)	18.00 (53.25)	0.300
ACPA level (U/ml), mean ±S.D.	DAS-28 ESR	19.16± 2.471	8.07± 5.523	13.24± 5.270	13.71± 6.587	0.344
	DAS-28 CRP	12.93± 5.794	13.80± 2.723	13.29± 5.236	14.12± 8.128	0.928

*: significant difference, **: highly significant difference

DISCUSSION

Based on the disease activity indices (DAS-28 ESR and DAS-28 CRP), the RA patients with family history had a significant association with DAS-28 and were more susceptible to having an active form of RA arthritis. This result agrees with Cawley *et al.* (2023) and Buckman *et al.* (2024). As well, Cawley *et al.* (2023) found RA patients with a family history had a considerably increased possibility of complications than those without a family history. The family history is significant risk factors for RA development, with a three- to five-fold increase which considered an indication of environmental and genetic risk factors. There is evidence that RA patients with RA HLA-DRB1 risk allele have worse disease activity, radiographic damage, mortality, and outcomes in general (Murata *et al.*, 2019). The results of the current study contradicts with the results of Frisell *et al.* (2016), Murata *et al.* (2019), Ghali Alanazi (2021), and EL-Kasmi *et al.* (2023), who revealed a non-significant association between the disease activity and the family history of RA. The disease duration of patients with RA showed a significant association with disease activity indices based on both DAS-28 ESR and DAS-28 CRP. Moreover, the results of this study showed that RA patients with disease durations more than six months were more susceptible to higher disease activity compared to those with disease durations less than six months, which aligns with Jung *et al.* (2018) and Buckman *et al.* (2024). The possible explanation of this result is that persistent RA disease for a long time results in erosion and joint destruction, as well as the RA patients being more likely to have comorbid conditions, that ultimately lead to increase the disease activity (Groth Madsen *et al.*, 2016).

Both disease activity indices of RA (DAS-28 ESR and DAS-28 CRP) demonstrated a significant association with regularity of treatment intake. Surprisingly, the results showed that RA patients with regular treatment intakes had a higher disease activity than those with irregular treatment intake. This finding may attributed to the few numbers of RA patients in the remission and low activity groups. This indicate that a real association between the disease activity and the regularity of treatment intake was not shown. Another possible explanation of this result is the most of the RA patients who went to the hospital in this study had moderate to high disease activities. This study showed a significant association between the treatment response in patients with RA and both disease activity indices. Therefore, RA patients with poor response to treatment had higher disease activity compared to those with good response to treatment. This findings consistent with Son *et al*. (2017). The current research suggests that ineffective treatment of RA may lead to joint damage and increase the disease activity.The levels of the hematological parameters (hemoglobin, WBC, and platelet) showed a non-significant difference among the four RA disease activity groups according to both DAS-28 ESR and DAS-28 CRP. This results aligns with Gaballah *et al*. (2022). Moreover, van Riel (2014) found a non-significant differences between hemoglobin and disease activity and Ming Yang *et al*. (2018) found a non-significant difference between WBC and DAS-28 ESR, while platelets showed significant differences with DAS-28 ESR.

Regarding the routine biomarkers, the current study found that ESR mean of RA patients in high disease activity group was significantly higher than those in the other groups of the disease activity. This result aligns with Ateş *et al*. (2007), Choe *et al*. (2013), Uslu *et al*. (2015), Mercan *et al*. (2016), Helal *et al*. (2019), Gaballah *et al*. (2022), and Hassan *et al*. (2022), who found a significant association between ESR and DAS-28. Moreover, the RA patients in high disease activity group had higher CRP levels compared to those in the other disease activity groups. While the lowest levels of CRP were in the remission and low disease activity groups. This result was statistically significant for DAS-28-CRP, which aligns with Ateş *et al*. (2007), Helal *et al*. (2019), and Gaballah *et al*. (2022), while not significant for DAS-28 ESR, which aligns with Serdaroğlu *et al*. (2008) and van Riel (2014).A possible explanation for these results is that both ESR and CRP are biomarkers commonly used to assess RA activity because they are acute phase reactants that increase in response to the release of inflammatory cytokines produced during tissue injury. The liver cells produce these reactants due to the high protein synthesis initiated by the cytokines. When there is an inflammatory state, such as in active RA, it leads to an escalation of joint inflammation, causing a rise in both ESR and CRP levels (Farheen & Agarwal, 2011).

According to the disease activity indices (DAS-28 ESR and DAS-28 CRP), RF level exhibited a non-significant association with the four disease activity groups. This finding aligns with previous studies by del del Val del Amo *et al*. (2006), Abdel-Nasser *et al*. (2008), and Hamad *et al*. (2013), despite the documented link between RF and erosive disease (Manfredsdottir *et al*., 2006). However, other studies by Nell *et al*. (2005) and Ibn Yacoub *et al*. (2012) reported a significant association between RF and DAS-28. Similarly, according to both DAS-28 ESR and DAS-28 CRP, this study revealed no significant difference between the levels of ACPA in RA patients and the disease activity groups. This result aligns with Correa *et al*. (2004), Nell *et al*. (2005), Abdel-Nasser *et al*. (2008), Serdaroğlu *et al*. (2008), Choe *et al*. (2013), and Hamad *et al*. (2013), which found a non-significant association between ACPA and DAS-28 score. Furthermore, Sulaiman *et al*. (2019) found a

non-significant association between ACCP and DAS-28 ESR. However, other studies by Kastbom *et al*. (2004), del Val del Amo *et al*. (2006), Ibn Yacoub *et al*. (2012), and Alwan & Ghali (2021) reported a significant association between ACPA and the DAS-28. Choe *et al*. (2013) suggest that a large-scale, prospective, population-based study is necessary to confirm the correlation between ACPA and disease activity due to this discrepancy.

CONCLUSION

The research found an association between some clinical, hematological, and serological parameters and the disease activity level in RA patients. As well, they could be useful in monitoring RA activity.

REFERENCES

1. Abdel-Nasser, A. M., Mahmoud, M. H., El Mansoury, T. M., & Osman, A. M. (2008). Anti-CCP2 is an adjunct to, not a surrogate for, rheumatoid factor in the diagnosis of rheumatoid arthritis: diagnostic utility of anti-CCP2 antibodies in Egyptian patients with rheumatoid arthritis. *Scandinavian Journal of Rheumatology*, *37*(5), 329–336. https://doi.org/10.1080/03009740802116208
2. Aletaha, D., & Smolen, J. (2005). The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): A review of their usefulness and validity in rheumatoid arthritis. *Clinical and Experimental Rheumatology*, *23*(5), S100.
3. Alkazzaz, A. (2013). Incidence of Rheumatoid Arthritis [2001 to 2011]. *The Iraqi Postgraduate Medical Journal*, *12*(4), 568–572.
4. Alqazzaz, A., Al_Badran, A. K., Algabri, H., & Al Saeedi, K. H. (2022). Incidence of rheumatoid arthritis at Marjan Teaching Hospital in Babylon, Iraq (2014–2019). *Medical Journal of Babylon*, 19(3), 358. https://doi.org/10.4103/mjbl.mjbl_32_22
5. Alwan, I. T., & Ghali, K. H. (2021). The correlation between accp with developing, progression and activity of rheumatoid arthritis. *Annals of the Romanian Society for Cell Biology*, 408-418.
6. Ateş, A., Kinikli, G., Turgay, M., Akay, G., & Tokgöz, G. (2006). Effects of rheumatoid factor isotypes on disease activity and severity in patients with rheumatoid arthritis: a comparative study. *Clinical Rheumatology*, *26*(4), 538–545. https://doi.org/10.1007/s10067-006-0343-x
7. Buckman, T. A., Sakyi, S. A., Yeboah-Mensah, K., Antwi, M. H., Darban, I., Owusu-Brenya, L., *et al.* (2024). Demographic, Clinical Profile of Rheumatoid Arthritis Patients and Their Association with Disease Severity in Ghana. *International Journal of Rheumatology*, *2024*, 1–9. https://doi.org/10.1155/2024/6639079
8. Bullock, J., Rizvi, S., Saleh, A., Ahmed, S., Do, D., Ansari, R., *et al.* (2018). Rheumatoid Arthritis: A Brief Overview of the Treatment. *Medical Principles and Practice*, *27*(6), 501–507. https://doi.org/10.1159/000493390
9. Cawley, A., Bhalla, S., Floresca, R., Alvarado, L., & Dihowm, F. (2023). Disease profile of rheumatoid arthritis and its complications in hispanic population. *The American Journal of the Medical Sciences*, *365*(4), 337–344. https://doi.org/10.1016/j.amjms.2022.12.029
10. Choe, J. Y., Bae, J., Lee, H., Bae, S. C., & Kim, S. K. (2013). Relation of rheumatoid factor and anti-cyclic citrullinated peptide antibody with disease activity in rheumatoid arthritis: cross-sectional study. *Rheumatology International*, *33*(9), 2373–2379. https://doi.org/10.1007/s00296-013-2734-z
11. Conti, V., Corbi, G., Costantino, M., De Bellis, E., Manzo, V., Sellitto, C., *et al.*

(2020). Biomarkers to Personalize the Treatment of Rheumatoid Arthritis: Focus on Autoantibodies and Pharmacogenetics. *Biomolecules*, *10*(12), 1672. https://doi.org/10.3390/biom10121672

12. Correa, P. A., Tobón, G. J., Citera, G., Cadena, J., Schneeberger, E., Camargo, J. F., *et al.* (2004). Anti-cyclic citrullinated peptide antibodies in rheumatoid arthritis: relation with clinical features, cytokines and HLA-DRB1. *Biomédica*, *24*(2), 140. https://doi.org/10.7705/biomedica.v24i2.1260
13. del Val del Amo, N., Ibanez Bosch, R., Fito Manteca, C., Gutierrez Polo, R., & Loza Cortina, E. (2006). Anti-cyclic citrullinated peptide antibody in rheumatoid arthritis: relation with disease aggressiveness. *Clinical and experimental rheumatology*, *24*(3), 281–286.
14. EL-Kasmi, H., Akasbi, N., El Mezouar, I., Omari, M., & Harzy, T. (2023). AB0266 The Influence of Heredity on Rheumatoid Arthritis: Examining the Distinct Characteristics in Patients with a Family History. *Scientific Abstracts*. https://doi.org/10.1136/annrheumdis-2023-eular.4860
15. Farheen, K., & Agarwal, S. K. (2011). Assessment of disease activity and treatment outcomes in rheumatoid arthritis. *Journal of Managed Care Pharmacy*, *17*(9 Supp B), S09-S13.
16. Feng, X., Xu, X., Shi, Y., Liu, X., Liu, H., Hou, H., *et al.* (2019). Body Mass Index and the Risk of Rheumatoid Arthritis: An Updated Dose-Response Meta-Analysis. *BioMed Research International*. https://doi.org/10.1155/2019/3579081
17. Frisell, T., Saevarsdottir, S., & Askling, J. (2015). Does a family history of RA influence the clinical presentation and treatment response in RA? *Annals of the Rheumatic Diseases*, *75*(6), 1120–1125. https://doi.org/10.1136/annrheumdis-2015-207670
18. Gaballah, A. E. A., Elsawy, N. A., El Gendy, W. M., Afifi, A. H., & Hanafi, M. S. M. (2022). Hematological markers and ultrasound 7-joint inflammation score as add-on tools in the assessment of inflammation in rheumatoid arthritis patients. *Egyptian Rheumatology and Rehabilitation*, *49*(1). https://doi.org/10.1186/s43166-022-00126-0
19. Ghali Alanazi, F. (2021). Association of Family history with clinical presentation of rheumatoid arthritis patients in Saudi Arabia: A cross sectional study. *P J M H S*, *15*(1), 685.
20. Goma, S. H., Razek, M. R. A., & Abdelbary, N. M. (2019, October). Impact of rheumatoid arthritis on the quality of life and its relation to disease activity. *Egyptian Rheumatology and Rehabilitation*, *46*(4), 304–312. https://doi.org/10.4103/err.err_39_19
21. Hamad, M. B., Marzouk, S., Kaddour, N., Masmoudi, H., Fakhfakh, F., Rebai, A., *et al.* (2013). Anticyclic Citrullinated Peptide Antibody and Rheumatoid Factor in South Tunisian Patients with Rheumatoid Arthritis: Association with Disease Activity and Severity. *Journal of Clinical Laboratory Analysis*, *28*(1), 21–26. https://doi.org/10.1002/jcla.21638
22. Hassan, S. B., Abdullah, H. N., & Zakair, K. Y. (2022). The Role of IL-37 as an Anti-Inflammatory Biomarker in some Iraqi Rheumatoid Arthritis Patients and Its Correlation with DAS28. *Journal of Techniques*, *4*(33), 123–127. https://doi.org/10.51173/jt.v4i33.708
23. Helal, R. M., El-Naggar, M. H., Zahra, M. K., & El-Nasr, N. M. A. (2019). Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio as Marker of Disease Activity in Rheumatoid Arthritis. *The*

Medical Journal of Cairo University, *87*(March), 139–145. https://doi.org/10.21608/mjcu.2019.52333

24. Ibn Yacoub, Y., Amine, B., Laatiris, A., & Hajjaj-Hassouni, N. (2011). Rheumatoid factor and antibodies against citrullinated peptides in Moroccan patients with rheumatoid arthritis: association with disease parameters and quality of life. *Clinical Rheumatology*, *31*(2), 329–334. https://doi.org/10.1007/s10067-011-1820-4
25. Jung, S. M., Kwok, S. K., Ju, J. H., Lee, S. W., Song, J. J., Yoon, C. H., *et al.* (2018). Risk factors associated with inadequate control of disease activity in elderly patients with rheumatoid arthritis: Results from a nationwide KOrean College of Rheumatology BIOlogics (KOBIO) registry. *PLOS ONE*, *13*(10), e0205651. https://doi.org/10.1371/journal.pone.0205651
26. Kastbom, A. (2004). Anti-CCP antibody test predicts the disease course during 3 years in early rheumatoid arthritis (the Swedish TIRA project). *Annals of the Rheumatic Diseases*, *63*(9), 1085–1089. https://doi.org/10.1136/ard.2003.016808
27. Madsen, S. G., Danneskiold-Samsøe, B., Stockmarr, A., & Bartels, E. (2015). Correlations between fatigue and disease duration, disease activity, and pain in patients with rheumatoid arthritis: a systematic review. *Scandinavian Journal of Rheumatology*, *45*(4), 255–261. https://doi.org/10.3109/03009742.2015.1095943
28. Manfredsdottir, V. F., Vikingsdottir, T., Jonsson, T., Geirsson, A. J., Kjartansson, O., Heimisdottir, M., *et al.* (2006). The effects of tobacco smoking and rheumatoid factor seropositivity on disease activity and joint damage in early rheumatoid arthritis. *Rheumatology*, *45*(6), 734–740. https://doi.org/10.1093/rheumatology/kei240
29. Mercan, R., Bitik, B., Tufan, A., Bozbulut, U. B., Atas, N., Ozturk, M. A., Haznedaroglu, S., *et al.* (2015). The Association Between Neutrophil/Lymphocyte Ratio and Disease Activity in Rheumatoid Arthritis and Ankylosing Spondylitis. *Journal of Clinical Laboratory Analysis*, *30*(5), 597–601. https://doi.org/10.1002/jcla.21908
30. Murata, K., Hashimoto, M., Yamamoto, W., Son, Y., Amuro, H., Nagai, K., *et al.* (2019). The family history of rheumatoid arthritis in anti-cyclic citrullinated peptide antibody-positive patient is not a predictor of poor clinical presentation and treatment response with modern classification criteria and treatment strategy: the ANSWER cohort study. *Rheumatology International*, *40*(2), 217–225. https://doi.org/10.1007/s00296-019-04464-9
31. Nell, V. P. K. (2005). Autoantibody profiling as early diagnostic and prognostic tool for rheumatoid arthritis. *Annals of the Rheumatic Diseases*, *64*(12), 1731–1736. https://doi.org/10.1136/ard.2005.035691
32. O'Neil, L. J., & Kaplan, M. J. (2019). Neutrophils in Rheumatoid Arthritis: Breaking Immune Tolerance and Fueling Disease. *Trends in Molecular Medicine*, *25*(3), 215–227. https://doi.org/10.1016/j.molmed.2018.12.008
33. Serdaroğlu, M., Çakırbay, H., Değer, O., Cengiz, S., & Kul, S. (2008). The association of anti-CCP antibodies with disease activity in rheumatoid arthritis. *Rheumatology International*. *28*(10), 965–970. https://doi.org/10.1007/s00296-008-0570-3
34. Smith, M. H., & Berman, J. R. (2022, March 22). What Is Rheumatoid Arthritis? *JAMA*, *327*(12), 1194. https://doi.org/10.1001/jama.2022.0786
35. Son, K. M., Lee, S. Y., Seo, Y. I., Choi, J. E., & Kim, H. A. (2017). Contribution of

subjective Disease Activity Score 28 (DAS28) components to the response to treatment of rheumatoid arthritis. *Clinical Rheumatology*, *36*(6), 1221–1227. https://doi.org/10.1007/s10067-017-3628-3

36. Sulaiman, F. N., Wong, K. K., Ahmad, W. A. W., & Ghazali, W. S. W. (2019). Anti-cyclic citrullinated peptide antibody is highly associated with rheumatoid factor and radiological defects in rheumatoid arthritis patients. *Medicine*, *98*(12), e14945. https://doi.org/10.1097/md.0000000000014945
37. Uribe, L., Cerón, C., Amariles, P., Llano, J. F., Restrepo, M., Montoya, N., *et al.* (2016). Correlation between clinical activity measured by DAS-28 and ultrasound in patients with rheumatoid arthritis. *Revista Colombiana De Reumatología (English Edition)*, *23*(3), 159–169. https://doi.org/10.1016/j.rcreue.2016.12.002
38. Uslu, A. U., Küçük, A., Şahin, A., Ugan, Y., Yılmaz, R., Güngör, T., *et al.* (2015). Two new inflammatory markers associated with Disease Activity Score-28 in patients with rheumatoid arthritis: neutrophil-lymphocyte ratio and platelet-lymphocyte ratio. *International Journal of Rheumatic Diseases*, *18*(7), 731–735. https://doi.org/10.1111/1756-185x.12582
39. Uslu, A. U., Küçük, A., Şahin, A., Ugan, Y., Yılmaz, R., Güngör, T., *et al.* (2015). Two new inflammatory markers associated with Disease Activity Score-28 in patients with rheumatoid arthritis: neutrophil-lymphocyte ratio and platelet-lymphocyte ratio. *International Journal of Rheumatic Diseases*, *18*(7), 731–735. https://doi.org/10.1111/1756-185x.12582
40. van Riel, P. L. C. M. (2014). The development of the disease activity score (DAS) and the disease activity score using 28 joint counts (DAS28). *Clinical and Experimental Rheumatology*. *32*(7), S65–S74.
41. Verma, P. K. (2013). Study of autoantibodies DRand#946;1 gene Epstein Barr Virus and Parvovirus B19 in Rheumatoid Arthritis and their correlations with clinical features [Banaras Hindu University]. http://hdl.handle.net/10603/275424
42. Wright, H. L., Lyon, M., Chapman, E. A., Moots, R. J., & Edwards, S. W. (2021). Rheumatoid Arthritis Synovial Fluid Neutrophils Drive Inflammation Through Production of Chemokines, Reactive Oxygen Species, and Neutrophil Extracellular Traps. *Frontiers in Immunology*, *11*. https://doi.org/10.3389/fimmu.2020.584116

