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Original article

Association between pharmacotherapy and circulating hematological profile in rheumatoid arthritis

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Abstract: *Background* — Hematological indices are useful predictors and prognostic biomarkers in rheumatoid arthritis (RA). Some antirheumatic drugs (ARD) have a negative effect on circulating blood cells and bone marrow and therefore may bias the interpretation of biomarker value.
Objective — Our cross-sectional study aimed to demonstrate the effect of ADR use on peripheral blood indices in RA patients.
Methods — This cross-sectional study was conducted on 103 adult RA patients and 21 healthy subjects at Rizgari Teaching Hospital in collaboration with the Department of Clinical Pharmacy and College of Pharmacy, Hawler Medical University, Erbil, Iraq, from January 2020 through December 2022. Patients were treated with methotrexate (MTX), hydroxychloroquine (HCQ), biologics (BL), MTX+HCQ, MTX+BL, and HCQ+BL. RA activity and complete blood count were obtained from patient records.
Results — Our results implied that HCQ was associated with significantly lower hemoglobin levels, while MTX+BL was accompanied by significantly lower mean corpuscular volume. The mean platelet volume was significantly higher in all treatment groups than in healthy subjects.
Conclusion — We concluded that BL use was statistically significantly associated with changes in hematological indices and ratios in patients with RA. It is important to consider the category of pharmacotherapy when interpreting circulating blood cell indices as predictors or prognostic biomarkers in RA.

Keywords: rheumatoid arthritis, hematological indices, biologics, methotrexate, hydroxychloroquine.

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory and autoimmune disease affecting the joints and other organs of the body, thereby leading to physical disability and systemic complications [1]. Hematological indices have been identified as diagnostic and/or prognostic biomarkers of RA. It has been noted that red blood cell indices are significantly altered in RA. Normocytic normochromic anemia is a hallmark of RA, and patients with higher hemoglobin (Hb) levels exhibit better clinical outcomes [2, 3], since there is a relationship between Hb level and disease activity. Recently, significantly lower Hb level has been observed in active RA compared with inactive status [4]. The use of biologics (BL) or corticosteroids has been found to be associated with a significant increase in Hb [5].

Red blood cell distribution width (RDW) with a cutoff value of 14.85 was significantly associated with the severity of RA [6]. In one cross-sectional study including 134 RA patients treated with antirheumatic drugs (ARD), no significant correlation between RDW value and disease activity was observed; however, a cutoff value of ≥14.2 was found to differentiate between active and inactive RA [7]. There is no doubt that erythrocyte sedimentation rate (ESR) is a useful marker for assessing disease severity. In a retrospective study, RA patients with a Disease Activity Score-28 for Rheumatoid Arthritis with ESR (DAS28-ESR) >3.2 were considered to have a relapse or active phase of the disease [8].

Some authors have investigated leukocyte subtypes and ratios as a prognostic biomarker of disease activity and used them as markers of response to ARD. Neutrophil-to-lymphocyte ratio (NLR) was found to be significantly higher in RA patients vs. healthy controls (median value 1.96 in the former vs. 1.32 in the latter) and significantly correlated with inflammatory markers [9]. Sargin et al. discovered that NLR value was significantly higher in RA patients compared with healthy subjects, and that rituximab significantly decreased NLR value [10]. A significant correlation between DAS28-ESR and NLR value existed regardless of rituximab treatment. Other hematological indices that have been recognized as biomarkers of active RA are platelet-to-lymphocyte ratio (PLR), mean platelet volume (MPV), and plateletcrit (PCT). A significantly higher median PLR value was found in RA patients compared to that in healthy subjects (135.5 vs. 126.2) [9]. A recent systematic review and meta-analysis showed that the mean MPV is not a useful discriminatory marker between RA and healthy subjects [11]. A significantly higher median PCT was found in RA patients with DAS28-ESR≥5.1 than in RA patients with DAS28-ESR<5.1 (0.23 vs. 0.21) [12, 13].

Several categories of medicines have been used in the treatment of RA to seek symptomatic relief, suppress inflammation, prolong the period of remission and improve quality of life. These medicines are not free from adverse effects on bone marrow and circulating blood cells [1, 14, 15]. Treatment with methotrexate (MTX), leflunomide or azathioprine was associated with higher RDW values (14.5±1.44, 14.7±2.06 and 14.7±1.23, respectively) compared with patients treated with sulfasalazine, hydroxychloroquine (HCQ) or biologics (BL) [16]. Case studies have shown that ARD caused specific changes in platelet counts in terms of thrombocythemia and thrombocytopenia [17, 18].

The rationale for this study is that both ARD and RA pathologies cause changes in hematological indices and ratios. Besides that, ARD showed specificity in targeting blood cells. This cross-sectional study examined the hypothesis that ARD may cause specific changes in hematological indices or ratios that may alter the interpretation of identified values of hematological indices as diagnostic or prognostic markers of RA.

Material and Methods

Design of the study

This retrospective cross-sectional study was conducted by a three-year review of medical records of 103 adult patients with RA at Rizgari Teaching Hospital in collaboration with the Department of Clinical Pharmacy, College of Pharmacy, Hawler Medical University, Erbil, Iraq, from January 2020 through December 2022. This study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice standards and was approved by the Research Ethics Committee of Hawler Medical University (HMU-PH-EC 250623-30). The medical records of patients with active RA were retrieved from the Department of Rheumatology at Rizgari Teaching Hospital from January 2020 through December 2022. Patients met the revised 1987 American Rheumatism Association criteria [19]. Eligible patients were of both genders, aged 18-75 years; they had moderate to severe disease activity, defined as DAS28-ESR>3.2 [20]. The median (interquartile range) DAS28-ESR and ESR values were 5.13 (3.41-6.36) and 30.0 (15-50), respectively, indicating that patients had a disease in the active phase despite treatment. Patients were eligible for the study if they received at least four weeks of monotherapy (MTX, HCQ, or BL such as etanercept, adalimumab, or infliximab) or a combination of these treatments. Patients with concomitant autoimmune diseases, ongoing microbial infections, liver and kidney disease, terminal illness, pregnancy, or treated with corticosteroids were excluded.

Our study included 103 patients (12 male and 91 female) with RA (Group I). Patients were grouped based on their current therapy into the following subgroups: MTX (n=27), HCQ (n=17), BL (n=21), MTX + HCQ (n=14), MTX + BL (n=13), and HCQ + BL (n=11). The control group (Group II) included 21 healthy subjects without RA (3 male and 18 female) who were recruited from the pool of hospital healthcare workers. The following data were extracted from patients' medical records: age, gender, disease duration, DAS28-ESR, ESR, RBC count, Hb, hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), RDW, neutrophil count (%), lymphocyte count (%), monocyte count (%), platelet count, PCT, MPV, and platelet distribution width (PDW). NLR and PLR values were calculated by dividing the neutrophil or platelet count by the lymphocyte count, and DAS28-ESR was calculated using MD CALC (https://www.mdcalc.com/calc/2176/disease-activity-score-28-rheumaoid-arthritis-esr-das28-esr).

Statistical data processing

Results of our study are presented as percentage, median (interquartile range: Q1, Q3), or mean ± SE. Statistical analyses were performed using a two-tailed one-way analysis of variance (ANOVA) with Tukey's Honest Significant Difference post hoc test and Mann-Whitney U test for comparisons of continuous variables. A nominal significance level of 0.05 was applied to all analyses. IBM-SPSS Statistics software for Windows (version 25, IBM Corp., Chicago) was used for all statistical analyses.

Table 1. Comparison of hematological indices between Groups I and II

Hematological index	*Group I (n=103)*	*Group II (n=21)*	*P-value*
Red blood cell (RBC) count, $\times10^6$/ mm^3	4.640 (4.320-5.060)	4.710 (4.505-4.925)	0.575
Hemoglobin (Hb), g/dL	12.2 (11.3-12.9)	13.4 (12.4-13.95)	0.013
Mean corpuscular hemoglobin (MCH), pg	26.8 (24.8-29.00)	28.7 (26.95-29.40)	0.006
Mean corpuscular hemoglobin concentration (MCHC), g/dL	33.2 (32.0-34.2)	31.8 (31.45-32.60)	0.001
Mean corpuscular volume (MCV), fL	81.0 (77.0-85.0)	88.8 (83.55-91.85)	0.002
White blood cell (WBC) count, $\times10^3$/ mm^3	7.14 (5.70-8.55)	7.54 (6.335-9.360)	0.632
Neutrophils, %	65.0 (55.7-71.0)	63.95(57.41-66.54)	0.632
Lymphocytes, %	27.0 (21.0-35.2)	28.06 (25.37-31.65)	0.871
Monocytes, %	6.0(4.0-7.0)	5.90 (4.60-7.63)	0.397
Platelet count, $\times10^3$/ mm^3	264.0(217.0-315.0)	259.0 (239.0-293.5)	0.632

The results are presented as median (interquartile range); P-values were calculated using Mann-Whitney U test; Group I: patients with rheumatoid arthritis; Group II: healthy subjects.

Table 2. Evaluation of hematological indices and ratios used as inflammatory biomarkers in rheumatoid arthritis

Hematological index/ratio	*Group I (n=103)*	*Group II (n=21)*	*P-value*
Plateletcrit (PCT), %	0.25 (0.21-0.30)	0.200 (0.170-0.215)	0.004
Red blood cell distribution width (RDW), %	13.3 (12.7-14.3)	12.4 (12.0-13.4)	0.031
Neutrophil-to-lymphocyte ratio (NLR)	2.407(1.60-3.453)	2.319 (1.819-2.650)	0.935
Platelet-to-lymphocyte ratio (PLR)	140.4 (103.2-191.3)	122.8 (104.9-148.5)	0.151
Mean platelet volume (MPV), fL	9.39 (8.7-10.1)	7.30 (6.35-8.80)	0.031

The results are presented as median (interquartile range); P-values were calculated using Mann-Whitney U test; Group I: patients with rheumatoid arthritis; Group II: healthy subjects.

Table 3. Comparison of hematological indices and ratios based on the category of pharmacotherapy

Hematological index/ratio	*Healthy subjects (n=21)*	*MTX (n=27)*	*HCQ (n=17)*	*BL (n=21)*	*MTX+HCQ (n=14)*	*MTX+ BL (n=13)*	*HCQ+ BL (n=11)*
RBC count, $\times10^6$/mm^3	4.715±0.075	4.839±0.111	4.802±0.159	4.587±0.150	4.744±0.182	4.691±0.170	4.465±0.140
Hb, g/dL	13.2±0.3	12.4±0.3	11.8±0.3*p=0.030	12.0±0.2	12.4±0.3	12.2±0.5	12.2±0.5
MCH, pg	28.1±0.5	26.9±0.6	25.1±0.9	26.4±0.7	26.7±0.9	25.6±0.8	27.5±0.7
MCHC, g/dL	32.2±0.3	32.7±0.3	32.6±0.4	33.7±0.4* p=0.034	32.7±0.6	32.7±0.4	34.0±0.2* p=0.041
MCV, fL	87.2±1.4	81.9±1.6	77.0±2.0* p<0.001	78.4±1.6* p=0.002	83.8±1.1	79.3±1.8* p=0.033	80.8±1.7
WBC count, $\times10^6$/mm^3	7.659±0.425	8.1±0.6	7.2±0.4	6.8±0.6	7.8±0.6	8.2±0.8	6.6±0.6
Neutrophils, %	62.4±1.3	59.7±2.4	65.2±1.9	62.2±2.3	63.8±2.3	65.8±3.8	72.0±3.5
Lymphocytes, %	28.9±1.0	30.8±2.3	26.8±1.9	29.9±1.9	26.8±2.4	27.9±3.6	21.0±3.0
Monocytes, %	5.9±0.4	6.8±0.6	5.9±0.4	6.0±0.6	6.2±0.5	4.0±0.5	5.5±0.8
Platelet count, $\times10^6$/mm^3	264.3±8.8	290.7±20.1	302.5±18.5	267.6±18.7	265.0±14.5	282.5±34.0	224.7±18.0
PCT, %	0.203±0.016	0.263±0.020	0.280±0.017	0.253±0.182	0.248±0.018	0.278±0.025	0.221±0.017
RDW, %	13.2±0.4	14.0±0.3	13.8±0.3	13.6±0.3	13.0±0.1	13.9±0.5	14.0±0.6
NLR	2.238±0.114	2.534±0.387	2.773±0.338	2.491±0.349	2.817±0.411	3.585±0.907	4.239±0.597
PLR	127.1±6.7	139.8±11.8	175.7±20.9	156.9±18.8	146.6±15.2	162.6±27.6	202.9±28.1
MPV, fL	7.40±0.46	9.02±0.16* p=0.005	9.33±0.22*p=002	9.85±0.34* p<0.001	9.0±0.47* p=0.034	10.1±0.33* p<0.001	10.0±0.51* p<0.001

The results are presented as mean ± SE; P-values were calculated using two-tailed one-way ANOVA with Tukey's Honest Significant Difference post hoc test; MTX: methotrexate; HCQ, hydroxychloroquine; BL, biologics; *statistically significant difference from healthy subjects; for explanation of RBC, Hb, MCH, MCHC, MCV, WBC, PCT, RDW, NLR, PLR and MPV see Tables 1 and 2.

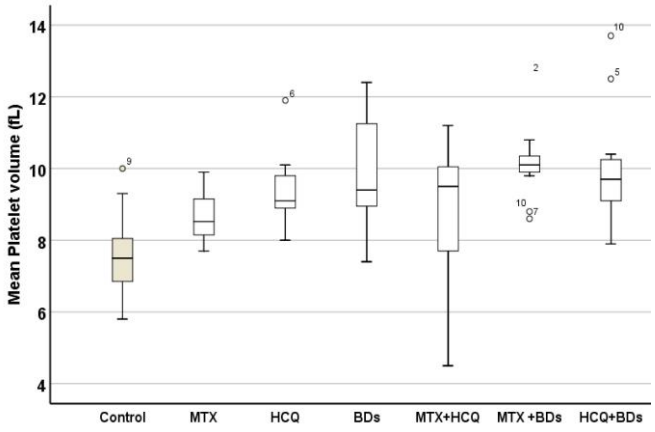

Figure 1. The mean platelet volume (fL) in rheumatoid arthritis treated with different medicines compared with that in healthy subjects. MTX: methotrexate; HCQ, hydroxychloroquine; BL, biologics.

Results

A total of 103 patients (12 men and 91 women) and 21 healthy subjects (3 men and 18 women) were included in our study. The median and interquartile ranges of baseline patient characteristics were 50.0 (42-60) years of age, 8.0 (2-15) years of disease duration, and 5.13 (3.41-6.36) for DAS28-ESR. Median (interquartile range) ESR values (mm/h) were significantly (p=0.017) higher in Group I vs. Group II: 30 (15-50) vs. 20 (7.5-27.5). *Table 1* shows the comparison between healthy subjects and RA patients in terms of hematological indices. Group II patients had significantly lower values of red blood cell indices than in Group I. The median values of Hb, MCH, MCHC and MCV decreased by 9%, 3.4%, 4.2% and 10.7%, respectively. The indices related to leukocytes and platelets did not differ significantly from the corresponding values in healthy subjects.

Table 2 demonstrates significantly higher median (interquartile range) values of hematological indices used as inflammatory biomarkers of RA. PCT, RDW and MPV increased by 25%, 6.8%, 12.5% and 22.3%, respectively. The median values of NLR and PLR were not significantly different from the corresponding median values in Group II.

Table 3 presents further analysis of the data according to the current status of pharmacotherapy. Patients treated with MTX had significantly higher mean MPV (21.9%) and ESR (135.5%) values than the corresponding values in healthy subjects. Significantly lower mean Hb (10.6%) and MCV (11.6%) values and significantly higher mean MPV (26.1%) were observed in Group I patients treated with HCQ. As for hematological indices in patients treated with BL, significantly lower MCHC (1.4%) and MCV (11.2%) and higher MPV (26.1%) values were observed. The combination therapy of MTX and HCQ yielded a significantly higher MPV value (21.6), while the combination therapy of MTX and BL resulted in a significantly lower MCV value (9.1%) and higher MPV value (36.5%). The combination of HCQ and BL produced significantly higher mean MCHC (5.6%) and MPV (35.1%) values. *Figure 1* demonstrates that regardless of pharmacotherapy category, the MPV box plot values were significantly higher in RA (Group I) than in healthy participants (Group II).

Discussion

The results of our study confirmed that the changes in values of hematological indices in RA patients were partly attributed to ARD. The lower median values that were recorded in RA patients were not within reference ranges of healthy subjects, indicating that these indices were not affected by the intake of ARD. All patients had significantly higher MPV values, which means that this index is not a useful prognostic biomarker for the efficacy of specific medicines. RA is known to cause microcytic hypochromic anemia, and our study has revealed significantly lower median Hb and MCV values in RA patients vs. healthy controls [18]. There were minor changes in white blood cell (WBC) and platelet counts, while other studies have demonstrated significant changes in peripheral blood mononuclear cells and platelets [21, 22]. These discrepancies are attributed to ARD, which counteract inflammation and thereby normalize WBC and platelet counts [23, 24].

Table 2 shows that hematological indices, which served as inflammatory biomarkers, exhibited significantly higher values in treated RA patients vs. healthy participants, implying that ARD

helped reduce inflammation. According to the evidence, the median (interquartile range) values of DAS28-ESR and ESR at the time of recruitment were 5.13 (3.41-6.36) and 30.0 (15-50), respectively, suggesting that the patients had active phase of the disease despite treatment. Our findings are consistent with previous studies that discovered that PCT, MPV, NLR, PLR, and RDW had higher values in active phase of the RA [6, 12, 25].

Table 3 showed that MTX therapy had a positive effect on hematological counts, indices and ratios except MPV. These findings indicate that MTX is a safe medicine at least for blood cells [26]. Patients treated with HCQ exhibited significantly lower mean Hb values and higher MPV value. These results may be attributed to adverse response of the body to HCQ or its ineffectiveness against RA associated with anemia [27]. We observed a positive effect of BL on blood cell elements except MPV, indicating the safety and efficacy of these medicines in RA [28]. The mean MPV value was significantly higher in all treated RA patients than in healthy subjects (*Figure* 1), suggesting that MPV is not a useful predictor of ARD, since higher MPV values were observed in all treated patients regardless of pharmacotherapy category. Moreover, patients treated with MTX and HCQ had larger variations in MPV, implying that this combination reduces MPV in some patients. Our study is consistent with other studies that have shown little difference in DAS28-ESR scores in RA patients whose MPV was less than or greater than 11.25 fL [6].

Limitations

Limitations of the study included a small sample size and some laboratory tests to diagnose the type of anemia that were omitted. Baseline values of hematological indices before the start of pharmacotherapy were not considered because the patients had a long disease duration and were taking many medicines, which may have affected the results.

Conclusion

We conclude that it is necessary to consider the category of pharmacotherapy when interpreting the values of circulating blood cell indices as predictors or prognostic biomarkers in RA. Regardless of whether ARD were given as monotherapy or in combination, the median value of the MPV in patients with RA was significantly greater than that in healthy individuals.

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Ethical approval

Ethical approval and consent to participate: the institutional Ethics Committee at Hawler Medical University, Erbil, Iraq, has approved this study (Code: HMU-PH-EC 250623-30).

Informed consent

Not available since the data on the patients with active RA were obtained from the Department of Rheumatology in Rizgary Teaching Hospital.

Conflicts of interest

The authors declare no conflicts of interest pertaining to this study.

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