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BIOCHEMICAL AND INFLAMMATORY PROFILES ASSOCIATED WITH ANEMIA IN RHEUMATOID ARTHRITIS: A RETROSPECTIVE LABORATORY STUDY

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ABSTRACT

Introduction: Anemia is a frequent extra-articular finding in rheumatoid arthritis (RA), driven by inflammation, iron deficiency, or both. This study aimed to determine the association between anemia and hematological and biochemical (kidney and liver) markers in rheumatoid factor (RF)-positive RA.

Methodology: In this retrospective cross-sectional analysis, 142 adults with RF-positive RA with complete results were studied. Anemia was defined as hemoglobin below 12 g/dL. Variable groups were compared with Mann-Whitney and Fisher tests; associations were assessed with Spearman correlation, and independent correlates were identified with logistic regression.

Results: Anemia affected 47 patients (33.1%), mostly normocytic (70.2%) but microcytic in 27.7%. Anemic patients had lower albumin (median 34.0 vs 42.0 g/L), higher red cell distribution width (13.7% vs 12.0%), higher neutrophil-to-lymphocyte ratio (3.74 vs 2.12), and higher urea. After adjustment, only albumin (odds ratio 0.17 per 5 g/L; 95% CI 0.09–0.33) and alanine aminotransferase (0.56 per doubling; 0.36–0.88) remained associated with anemia (AUC 0.87).

Conclusions: In RF-positive RA, anemia clustered with low albumin and red cell anisocytosis, suggesting an inflammatory component.

KEYWORDS: albumin, neutrophil-to-lymphocyte ratio, anemia, rheumatoid arthritis, red cell distribution width

1. INTRODUCTION

Rheumatoid arthritis (RA) is estimated to affect about 17.6 million people worldwide, a figure projected to reach 31.7 million by 2050 [1]. It is a systemic inflammatory condition in which cytokine signaling reaches well beyond the synovium [2], and treatment guidance stresses early and sustained control of inflammation [3,4]. Laboratory findings that track the inflammatory burden therefore need to be explored.

Anemia is one of the important inflammatory findings in rheumatoid arthritis. When inflammation persists, hepcidin traps iron in macrophages, while the response to erythropoietin and red cell survival decline, producing the anemia of inflammation [5,6]. True iron deficiency, from blood loss or drug-related gastrointestinal injury, can coexist with it and is hard to separate on a single hemoglobin value [7]. A cross-sectional study of 139 patients with RA in Pakistan reported iron deficiency anemia as the most frequent type (43.2%), followed by anemia of chronic disease (28.8%) [8]. A Romanian study of 88 adults with RA found anemia in 55%, with anemia of chronic disease and iron deficiency accounting for 40.5% and 21.4% of the anemic patients, and anemia was linked to higher disease activity [9].

Most such studies relied on ferritin, iron panels and acute-phase proteins. In routine practice, these are not always ordered together, whereas a blood count and kidney and liver profiles usually are, and the blood count carries more diagnostic information than its screening role suggests [10]. We therefore examined, in RF-positive RA, how common anemia is, how it looks on red cell indices, and which inflammation-related and organ-function markers accompany it.

Anemia of chronic disease and iron deficiency anemia in RA differ in their inflammatory and hematological profiles, and comparisons of interleukin-6, other inflammatory markers, ferritin and blood count parameters between the two show how much they overlap [11]. Indices from the differential count are attractive as inexpensive inflammation markers. A meta-analysis of 13 studies of the neutrophil-to-lymphocyte ratio (NLR) and 8 of the platelet-to-lymphocyte ratio (PLR) tied both ratios to the presence of RA [12]. A later synthesis of 18 studies found higher NLR and PLR in active than inactive disease, with standardized mean differences of 0.37 and 0.48 [13]. Pooled diagnostic accuracy is moderate: area under the curve (AUC) 0.76 for NLR in detecting RA and 0.70 for active disease, and 0.80 for PLR in detecting RA [14]. Red cell distribution width (RDW) has likewise been examined with NLR in RA [15].

Hypoalbuminemia is now seen less as a nutritional marker and more as a consequence of inflammation, because increased capillary permeability and a shorter albumin half-life lower the circulating concentration even when synthesis rises [16]. Dilution, malnutrition, liver dysfunction, and serous losses also contribute [17]. Kidney function enters by another route, since anemia is a common, multifactorial complication of chronic kidney disease [18]. The current analysis brings these markers together in RF-positive RA. The aim of this study was to determine the association between anemia and hematological, inflammatory, and biochemical (kidney and liver) markers in rheumatoid factor (RF)-positive RA, and to identify the markers independently associated with anemia.

2. METHODOLOGY

2.1 Study Design and Data Source

This was a retrospective cross-sectional analysis of de-identified results from patients with RF-positive RA, drawn from the hospital laboratory information system, Sakaka, Saudi Arabia. Diagnosis and RF positivity were confirmed by the investigators from clinical and laboratory records of 142 adults.

2.2 Eligibility Criteria and Data Handling

The records that were included were those of adults (age 18 years or older) who had documented rheumatoid arthritis, a positive rheumatoid factor test, and a full blood count together with a routine biochemistry panel obtained during the same sampling visit. Records that were duplicates, those containing implausible values, and those missing a hemoglobin result—since this prevented the classification of anemia-were excluded. The data were exported from the laboratory information system and then coded prior to analysis, meaning that the analysts did not have access to any direct identifiers. The values were checked for entry errors, inconsistencies in units, and implausible results, and any doubtful entries were verified against the original record and either corrected or deleted. The results were used exactly as they were reported, including the laboratory's units and reference ranges, and missing values were not estimated; for variables with missing data, the analysis was based on the available observations, and the number of such observations was stated where this differed from the total number of patients in the cohort. Only routine laboratory data were included, and the reporting complied with the STROBE guideline.

2.3 Variables and Definitions

Hematology comprised hemoglobin, hematocrit, red cell count, MCV, MCH, MCHC, RDW-CV, white cell count and differential, platelets and MPV; kidney tests were creatinine, urea and electrolytes; liver tests were ALT, AST, ALP, GGT, bilirubin, albumin and total protein. Absolute lymphocytes were white cell count multiplied by lymphocyte percentage; NLR was neutrophil percentage divided by lymphocyte percentage, and PLR was platelets divided by absolute lymphocytes. Sex and pregnancy status were not in the file, so anemia was defined as hemoglobin below 12 g/dL, the WHO threshold for non-pregnant women [19], for all participants; 13 g/dL was used in sensitivity analysis. Severity was mild (11.0–11.9), moderate (8.0–10.9) or severe (below 8.0 g/dL), and morphology by MCV was microcytic (below 80 fL), normocytic (80–100 fL) or macrocytic (above 100 fL). Albumin below 35 g/L and NLR above 3 served as descriptive cut-offs.

2.4 Statistical Analysis

Most continuous variables were non-normal (Shapiro-Wilk, $p < 0.05$), so data are presented as median and interquartile range (IQR). Groups were compared with the Mann-Whitney U test, and proportions with Fisher's exact test; p-values for the 18 continuous comparisons were adjusted by the Benjamini-Hochberg false discovery rate (q). Spearman correlations of hemoglobin, MCV and RDW with 13 markers (39 tests) were likewise adjusted. Independent correlates of anemia were assessed by logistic regression with six predictors chosen a priori: age, albumin, NLR, creatinine, platelets and ALT. Skewed variables (NLR, creatinine, ALT) were log2-transformed so that odds ratios (OR) describe a doubling. We examined collinearity (variance inflation factors below 1.6), calibration (Hosmer-Lemeshow), discrimination (AUC), and Nagelkerke R^2. Sensitivity analyses used the 13 g/dL threshold and excluded two records with creatinine above 400 µmol/L. Tests were two-sided with $\alpha = 0.05$.

3. RESULTS

3.1 Cohort and Anemia Profile

The 142 patients had a median age of 48.5 years (IQR 30.7–61.6). Anemia was present in 47 (33.1%; 95% CI 25.9–41.2%); with the 13 g/dL threshold, 62 (43.7%; 95% CI 35.8–51.9%). Among anemic patients, 20 (42.6%) had mild, 22 (46.8%) moderate, and 5 (10.6%) severe anemia; morphology was normocytic in 33 (70.2%), microcytic in 13 (27.7%), and macrocytic in 1 (2.1%).

3.2 Comparison of Anemic and Non-Anemic Patients

Anemic patients (Table 1) were older, with lower MCV, higher RDW, and higher white cell counts. NLR was higher (3.74 vs 2.12), while albumin (34.0 vs 42.0 g/L) and total protein (64.6 vs 72.0 g/L) were lower. Urea, creatinine, and ALP were higher in the anemic group. Platelets, PLR, ALT, AST, GGT, and bilirubin did not differ after correction. Microcytosis (27.7% vs 4.2%), albumin below 35 g/L (59.6% vs 7.4%), and NLR above 3 (59.6% vs 31.6%) were all more frequent in anemic patients.

Table 1. Characteristics of RF-positive RA patients with and without anemia (hemoglobin < 12 g/dL)

Variable	All (n = 142)	Anemic (n = 47)	Non-anemic (n = 95)	p	q
Age, years	48.45 (30.73–61.60)	54.50 (39.00–71.30)	45.10 (29.35–57.35)	0.004	0.008
Hemoglobin, g/dL	13.21 (11.39–14.61)	10.43 (8.74–11.37)	14.02 (13.21–15.32)	<0.001	<0.001
Hematocrit, %	41.06 (36.85–44.54)	33.91 (28.61–36.74)	43.54 (41.06–46.71)	<0.001	<0.001
MCV, fL	86.03 (82.98–89.28)	82.65 (79.87–88.91)	86.87 (84.48–89.33)	0.002	0.006
RDW-CV, %	12.49 (11.71–13.58)	13.67 (13.25–15.18)	11.99 (11.45–12.80)	<0.001	<0.001
WBC, $\times 10^9$/L	9.03 (6.80–11.84)	10.47 (8.07–13.01)	8.52 (6.50–10.88)	0.013	0.024
Platelets, $\times 10^9$/L	254.20 (212.10–302.57)	251.90 (190.95–304.20)	254.50 (217.00–302.15)	0.739	0.782

Variable	All (n = 142)	Anemic (n = 47)	Non-anemic (n = 95)	p	q
NLR	2.51 (1.45–4.84)	3.74 (1.84–8.92)	2.12 (1.36–3.57)	0.003	0.006
PLR	119.28 (86.18–165.66)	139.74 (103.39–185.86)	114.85 (83.25–159.04)	0.096	0.123
Albumin, g/L	40.14 (35.04–43.33)	33.98 (31.99–37.74)	42.00 (39.66–44.64)	<0.001	<0.001
Total protein, g/L	70.00 (64.39–73.97)	64.62 (57.42–69.64)	72.00 (68.09–74.98)	<0.001	<0.001
Creatinine, µmol/L	84.84 (65.00–108.18)	106.67 (65.53–141.91)	80.70 (65.08–98.34)	0.021	0.035
Urea, mmol/L	4.92 (3.49–7.29)	7.67 (4.58–12.25)	4.25 (3.45–5.73)	<0.001	<0.001
ALT, U/L	15.16 (11.00–27.86)	12.68 (9.16–23.39)	16.40 (11.94–29.27)	0.075	0.105
AST, U/L	18.41 (14.79–29.81)	17.57 (14.00–33.77)	18.43 (15.06–29.12)	0.440	0.528
ALP, U/L	72.85 (57.65–97.17)	79.00 (60.60–111.10)	69.00 (55.64–89.05)	0.029	0.043
GGT, U/L	21.25 (13.41–40.44)	24.71 (12.16–54.16)	20.34 (13.70–35.91)	0.563	0.633
Total bilirubin, µmol/L	9.29 (6.55–13.28)	9.29 (6.00–14.41)	9.28 (6.75–13.14)	0.998	0.998
Microcytosis (MCV < 80 fL), n (%)	17 (12.0)	13 (27.7)	4 (4.2)	<0.001	—
Albumin < 35 g/L, n (%)	35 (24.6)	28 (59.6)	7 (7.4)	<0.001	—
NLR > 3, n (%)	58 (40.8)	28 (59.6)	30 (31.6)	0.002	—

Values are median (IQR) unless stated. p: Mann-Whitney U test (Fisher's exact test for proportions); q: Benjamini-Hochberg adjusted p for the 18 continuous comparisons. Hemoglobin and hematocrit differ by definition. NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; RDW-CV, red cell distribution width.

3.3 Correlation Structure

In Figure 1, hemoglobin correlated positively with albumin (ρ = 0.59), total protein (ρ = 0.43) and ALT (ρ = 0.28), and negatively with NLR (ρ = −0.25) and urea (ρ = −0.25); all remained significant after correction. RDW moved oppositely, correlating inversely with albumin (ρ = −0.38) and positively with NLR (ρ = 0.36), white cell count (ρ = 0.30), urea (ρ = 0.26), and ALP (ρ = 0.21). MCV was unrelated to inflammatory markers but correlated negatively with platelets (ρ = −0.27).

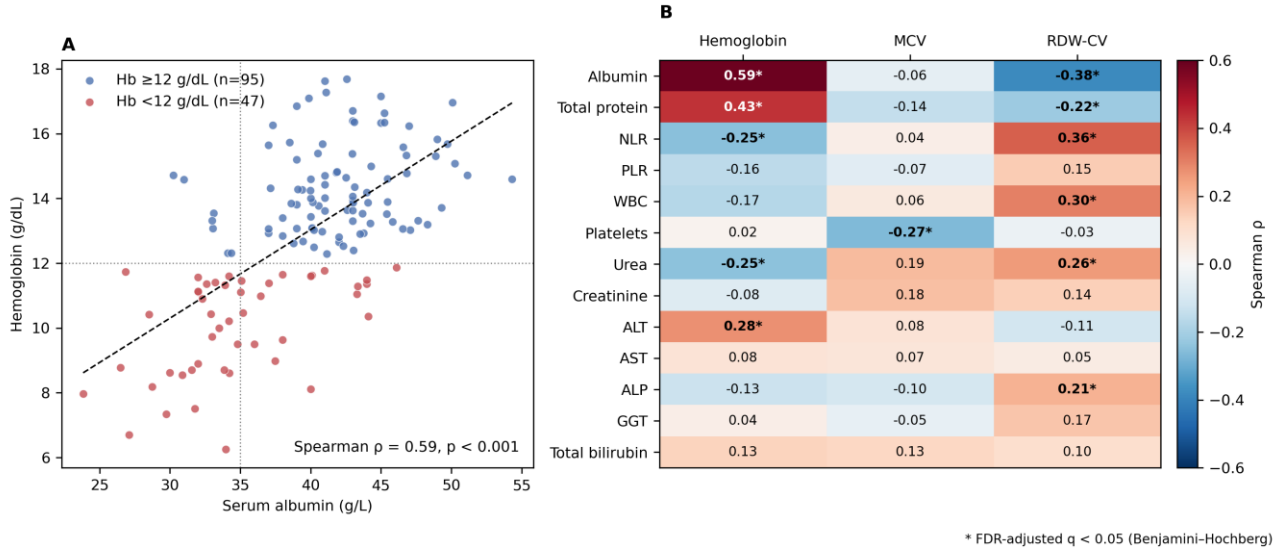


Figure 1. (A) Hemoglobin plotted against serum albumin; dotted lines mark 12 g/dL and 35 g/L, and the dashed line is the linear fit. (B) Spearman correlation coefficients of hemoglobin, MCV, and RDW-CV with inflammatory, kidney, and liver markers; asterisks denote q < 0.05.

3.4 Multivariable Analysis

Unadjusted (Table 2), older age, higher NLR, and higher creatinine were associated with anemia, and higher albumin was protective. After adjustment, only albumin (OR 0.17 per 5 g/L, 95% CI 0.09–0.33) and ALT (OR 0.56 per doubling, 95% CI 0.36–0.88) remained independent. The model had an AUC of 0.87, Nagelkerke R^2 of 0.54, and acceptable calibration (Hosmer-Lemeshow p = 0.35). With the 13 g/dL definition, albumin (OR 0.21, 0.11–0.38) and ALT (OR 0.58, 0.38–0.87) again stood out. Excluding the two extreme creatinine records (n = 140) left albumin unchanged (OR 0.17, 0.09–0.33) and ALT borderline (OR 0.63, 0.40–0.99).

Table 2. Unadjusted and adjusted odds ratios for anemia (hemoglobin < 12 g/dL)

Predictor	Crude OR (95% CI)	p	Adjusted OR (95% CI)	p
Age	1.33 (1.10–1.61)	0.003	0.86 (0.64–1.16)	0.330
Albumin	0.21 (0.12–0.35)	<0.001	0.17 (0.09–0.33)	<0.001
NLR	1.43 (1.10–1.86)	0.007	1.08 (0.72–1.61)	0.722
Creatinine	2.22 (1.28–3.86)	0.005	1.50 (0.71–3.18)	0.293
Platelets (per 100 ×10⁹/L)	1.07 (0.71–1.61)	0.735	1.55 (0.84–2.87)	0.160
Serum ALT	0.74 (0.52–1.04)	0.082	0.56 (0.36–0.88)	0.012

n = 142. Adjusted model includes all six predictors: AUC 0.873; Nagelkerke R^2 0.535; Hosmer-Lemeshow p = 0.349. OR, odds ratio; CI, confidence interval.

4. DISCUSSION

The present study examined the association between anemia and hematological and biochemical markers. In rheumatoid arthritis (RA) patients, one-third of cases were anemic. The degree of anemia was linked with reduced serum albumin, wider red cell size variation, and a higher neutrophil-to-lymphocyte ratio (NLR). Serum albumin was independently associated with hemoglobin and other red cell variables. The prevalence is lower than the 55% reported in another RA population [9], but this study did not compare sex-specific thresholds and kept only patients with complete panels.

The current study found that serum albumin was consistent with its inflammatory role. The mechanism of capillary leak and reduced albumin survival reflects inflammation due to hypoalbuminemia [16]. Similarly, hepcidin-mediated iron limitation through inflammatory cytokines develops anemia of inflammation [5,6]. Two findings support the role of albumin as a marker of inflammatory burden. In anemic patients, NLR was found to be higher, but its association was not observed with serum albumin levels. Platelet-to-lymphocyte ratio (PLR) and NLR were found to be linked to RA presence and activity [12–14]; thus far, discrimination is reasonable [14], and PLR did not diverge. On the other hand, liver functions including AST and bilirubin were similar between anemic and non-anemic groups, contrary to low hepatic synthesis of albumin. However, other contributing effects including dilution, malnutrition, and protein loss cannot be excluded [17].

The present study showed consistent variability in red cell indices. In anemic RA patients, RDW was found to be highest, followed by NLR, white cell count, and albumin, suggesting that anisocytosis may reflect inflammatory burden [15]. In inflammation-related anemia, normocytic morphology is the most prevalent red cell pattern [5,6]. Although 27.7% of anemic patients were microcytic, compared with 4.2% of non-anemic patients, suggesting an iron-deficiency component or a hemoglobinopathy trait in a subset [7]. Also, a negative association was observed between MCV and platelets compatible with iron deficiency, though platelet counts were higher. Biochemical parameters, including ferritin and transferrin saturation are considered standard biomarkers. In previous studies, a mixed picture aligns with RA studies in which iron deficiency and chronic disease anemia coincide in variable magnitudes [8,9,11].

Also, renal function tests were higher in anemic patients, while the creatinine association was lost after adjustment, consistent with the multifactorial nature of anemia in renal impairment [18]. Age may also influence this association. Because sex-specific creatinine and eGFR analyses could not be performed, so residual confounding is possible. The same gap may explain the unexpected inverse ALT association: men usually have both higher ALT and higher hemoglobin, so lower ALT among anemic patients may reflect an excess of women; reduced muscle mass or poor nutrition are other possibilities. We would not treat this finding as biological until sex is controlled.

Because RA guidance centers on controlling inflammation [3,4], separating inflammation-driven from iron-deficient anemia matters for treatment. Our data suggest that albumin and red cell width add information about the inflammatory side of anemia whenever a blood count is available, but typing the anemia still requires iron indices and CRP, and relating it to DAS28 was not possible here. The study's limitations include the absence of gender, medications, disease duration, DAS28, iron indices, CRP, ESR, vitamin B12, and folate, so anemia could not be typed or linked to disease activity. Only RF-positive patients were included, without a comparison group, so findings may not extend to seronegative RA.

5. CONCLUSION

In RF-positive RA patients with routine hematology, kidney and liver results, anemia was common and was characterized by low albumin, higher RDW and a raised NLR, with albumin the only strong independent correlate. These patterns are consistent with an inflammatory contribution but cannot substitute for iron indices and CRP. Future work should add sex, treatment, disease activity, iron studies, acute-phase markers, and a seronegative comparison group so that these signals can be tested properly.

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