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Disease Activity in Rheumatoid Arthritis Patients Stratified by Hemoglobin Levels: A Multi-center Study

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ABSTRACT

Objectives: Hemoglobin (Hb) level and its relation to rheumatoid arthritis (RA) is multifactorial. The primary aim of this study was to examine the association between Hb levels and disease activity in patients with RA. ***Methods***: This retrospective study obtained data from adult RA patients with Hb reports from the Kuwait Registry for Rheumatic Diseases. Patients were recruited from four public hospitals in Kuwait between February 2013 and February 2022. The cohort was stratified into two groups: Hb ≤ 110 g/L and Hb > 110 g/L. Demographic, treatment, clinical, and laboratory characteristics were used to compare the two Hb groups. Multivariate and univariate statistical analyses were used to analyze the data. ***Results:*** The total number of patients visited (N_v) was 11 393 and consecutive patients with RA diagnoses and Hb data (N_p) were 1584. Both N_v and N_p were included in the study. Of these, 72.5% (n = 8260) had high Hb levels and 27.5% (n = 3133) had low Hb levels. The average age of the cohort was 55.9 ± 12.5 years. Logistic regression analysis revealed that a greater number of non-Kuwaiti patients had anemia than Kuwaiti patients [adjusted odds ratio (aOR) = 1.34, 95% CI: 1.16–1.56; $p < 0.001$). Patients who received biologic treatment were more likely to be non-anemic [aOR = 1.33, 95% CI: 1.23–1.45; $p < 0.001$). Additionally, the study demonstrated that patients with anemia had greater odds of acquiring Disease Activity Score -28 joint count (DAS-28) ≥ 3.2 versus DAS-28 < 3.2 [aOR = 0.74, 95% CI: 0.61–0.90; $p = 0.002$]. ***Conclusions:*** Lower Hb levels in RA are an independent predictor of disease activity.

Anemia is a multifactorial, pervasive, extra-articular manifestation that is a significant burden in rheumatoid arthritis (RA).[1,2] The most common types of anemia in RA are chronic anemia and iron-deficiency anemia. Several existing studies observed anemia in 24.0–70.6% of patients with RA.[3–12] Low Hb concentrations in patients with RA have been associated with increased mortality, extensive physical disability, and disease activity.[2,3,13] Inversely, replenishing Hb levels in anemia was associated with improved quality of life in RA.[8] Previous studies have classified anemia in RA according to the World Health Organization as Hb < 130 g/L in males and Hb < 120 g/L in females.[3–12,14,15] However, a paucity of studies created a standardized low cut-off Hb value for anemia irrespective of gender. Additionally, there are scant data regarding the prevalence, clinical, and

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laboratory characteristics of patients with anemia and RA in Kuwait. We aimed to stratify patients with RA residing in Kuwait based on low and high Hb values to assess the prevalence and ascertain the association between demographics, treatment characteristics, and disease activity.

METHODS

Patients with RA and Hb reports were analyzed retrospectively using information collected from the Kuwait Registry for Rheumatic Diseases (KRRD). The registry design and methodology were previously delineated in detail.[16] In brief, KRRD is a prospective, national registry for adult patients diagnosed with rheumatic disease in four Kuwaiti government hospitals. Hospitals are established in different governorates to ensure ethnic diversity. Patients with RA are referred to government hospitals to undergo treatment, as medicine is inexpensive for Kuwaitis and expensive for non-Kuwaitis. The study recruitment was conducted from February 2013 to February 2022.

Baseline, demographic, clinical, and laboratory data (i.e., disease activity and treatment) were obtained. Nurses and rheumatologists who were trained to fill standard manuals or electronic forms collected the data. Data storage was secured through a safe digital program which connected the four hospitals. The Ethics Committee of the Ministry of Health in Kuwait (Letter No. VDR/JC/882 dated 10.10.2012) approved the study. Informed written consent was taken from all patients.

RA was defined and classified according to the American College of Rheumatology criteria.[17] Our study defined adults with anemia as low Hb (≤ 110 g/L) and adults without anemia as high Hb (> 110 g/L). We defined Disease Activity Score-28 (DAS-28) ≥ 3.2 as moderate/severe disease activity, and DAS-28 < 3.2 as low disease activity/remission; the values were calculated using a DAS calculator.[18]

The measurement of serological data was standardized across laboratories in the participating hospitals. Immunoglobulin (Ig) M rheumatoid factor (RF) measurement was obtained quantitatively by nephelometry, and a count of > 20 was positive. Anti-nuclear antibodies (ANAs) were evaluated by indirect immunofluorescence using the Hep-2 cell line, and a titre > 1:40 was positive. Anti-cyclic citrullinated peptide antibodies were assessed by enzyme-linked immunosorbent assay, and values ≥ 20 U/mL were considered positive. Although tofacitinib is a targeted synthetic disease-modifying antirheumatic drugs (DMARDs), it is included here under biologics, given its high efficacy in treating RA, similar to biologics.[19] The work has been reported in line with the STROCSS criteria.[20]

We stratified our cohort into two groups according to their Hb scores: high Hb (non-anemic) and low Hb (anemic). Skewed continuous variables, medians, and IQR were performed using the Mann-Whitney U test. Categorical variables were expressed as frequencies and percentages and compared using the chi-square (χ^2) test. Finally, logistic regression analysis was applied to examine the association between Hb groups and the following covariates: sex, nationality, age at RA onset, white blood cell count, creatinine level, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), DAS-28 groups (DAS-28 ≥ 3.2 and DAS-28 < 3.2), treatment (biologics and DMARDs), patient global assessment, physician global assessment, and tender and swollen joints. Statistical significance was set at $p < 0.05$. The dataset was analyzed using JAMOVI (Version 2.3.18) and SPSS (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp).

RESULTS

The total number of patients visited (N_v) was 11 393 and the number of consecutive patients with RA diagnoses and Hb data (N_p) was 1584. Both N_v and N_p were included in the study. Table 1 summarizes the demographic characteristics of patients with RA stratified by Hb levels. The average age of the patients was 55.9 ± 12.5 years and 63.4% were female. The analysis revealed significant differences in the mean age of the patients in the high (56.4 ± 12.6) and low (54.9 ± 12.1 years) Hb groups. The average age at RA onset in the low Hb group was significantly less (10.3 ± 6.2 years) compared to patients with high Hb (11.3 ± 7.0 years). Among those with high Hb, the majority were Kuwaitis (51.7%), whereas in the low Hb group, the prevalence was non-Kuwaitis (54.2%). Moreover, the analysis revealed no significant differences among the Hb groups in terms of body mass index, sex, and smoking status.

Table 2 outlines the association between Hb levels and the baseline medical characteristics. Notably, in

Table 1: Demographic characteristics of rheumatoid arthritis (RA) cohort stratified by Hb levels.

Characteristics	Total (N_p = 1584) n (%)	Hb >10 (N_p = 1053) n (%)	Hb <10 (N_p = 531) n (%)	*p*-value
Age, mean ± SD, years	55.9 ± 12.5	56.4 ± 12.6	54.9 ± 12.1	0.019[1]
Duration of RA, mean ± SD, years	11.0 ± 6.8	11.3 ± 7.0	10.3 ± 6.2	0.007[1]
Sex: female	1004 (63.4)	665 (63.2)	339 (63.8)	0.788[2]
BMI, mean ± SD, kg/m²	30.0 ± 12.5	30.0 ± 13.0	30.1 ± 11.1	0.849[1]
Nationality				0.027[2]
Kuwaitis	787 (49.7)	544 (51.7)	243 (45.8)	
Non-Kuwaitis	797 (50.3)	509 (48.3)	288 (54.2)	
Smoker	112 (7.1)	82 (7.8)	30 (5.6)	0.162[2]

Hb: hemoglobin; N_p: total number of patient.; BMI: body mass index.; [1]Linear model ANOVA; [2]Pearson's chi-squared test.

the high Hb group, 25.2% (N_p = 265) of the patients had positive ANA, while the patients with low Hb had markedly less positive ANA (19.0%, N_p = 101). The other baseline medical characteristics showed no significant differences between the two Hb groups.

Table 3 highlights the results of the DMARDs among the Hb groups. The low Hb group was prescribed leflunomide (17.6% vs. 13.0%; $p < 0.001$), hydroxychloroquine (30.4% vs. 27.5%; $p = 0.002$), and cyclophosphamide (0.3% vs. 0.0%; $p < 0.001$). In contrast, patients with high Hb levels were more commonly prescribed methotrexate (65.2% vs. 61.9%; $p < 0.001$).

Table 4 presents the results of the biological regimen between the Hb groups. A higher proportion of patients with low Hb levels were prescribed adalimumab (7.2% vs. 5.8%; $p = 0.005$), infliximab (5.2% vs. 3.9%; $p = 0.003$), tofacitinib (1.7% vs. 0.9%; p <0.001), certolizumab (2.3% vs. 1.1%; $p < 0.001$), and golimumab (1.0% vs. 0.3%; $p < 0.001$). A higher proportion of patients with high Hb levels were prescribed rituximab (12.5% vs. 9.3%; $p < 0.001$), tofacitinib tocilizumab (20.1% vs. 10.3%; $p < 0.001$), and abataceptdalimumab (7.5% vs. 5.8%; $p = 0.002$). Overall, a higher proportion of the high Hb group received biologics than low HB group (57.2% vs. 50.0%; $p < 0.001$) and a higher proportion of the low Hb group received DMARDs than high Hb group (50.0% vs. 42.8%; $p < 0.001$).

The results of the laboratory tests in the cohort are summarized in Table 5. The analysis revealed higher values in the low Hb group for ESR, CRP, and platelet count ($p < 0.001$). Conversely, higher values were found in the high Hb group for aspartate aminotransferase, alanine transaminase, alkaline phosphatase, total cholesterol, low-density cholesterol, and uric acid ($p < 0.001$).

Logistic regression analysis examined clinical and demographic variables [Table 6]. Data demonstrated a significant association between Hb levels and nationality [OR = 0.745, 95% CI: 0.643–0.862; $p < 0.001$), age at RA diagnosis [OR = 0.974, 95% CI: 0.965–0.984; $p < 0.001$), ESR [OR = 1.006, 95% CI: 1.003–1.009; $p < 0.001$), DAS-28 levels [OR = 0.738, 95% CI: 0.607–0.896; $p = 0.002$], DMARDS and biologics treatment [OR = 1.171, 95% CI: 1.011–1.355; $p = 0.035$], patient global assessment [OR = 0.926, 95% CI: 0.880–0.975;

Table 2: Baseline medical characteristics of rheumatoid arthritis cohort stratified by Hb levels.

Characteristics	Total (N_p = 1584) n (%)	Hb >10 (N = 1053) n (%)	Hb <10 (N = 531) n (%)	*p*-value
Secondary Sjogren's	247 (15.6)	175 (16.6)	72 (13.6)	0.218[1]
Rheumatoid Nodules	33 (2.1)	20 (1.9)	13 (2.4)	0.408[1]
Positive RF	1118 (70.6)	745 (70.8)	373 (70.2)	0.572[1]
Anti-CCP positive	819 (51.7)	538 (51.1)	281 (52.9)	0.628[1]
ANA positive	366 (3.1)	265 (25.2)	101 (19.0)	0.005[1]

Hb: hemoglobin; N_p: total number of patients; RF: rheumatoid factor; Anti-CCP: anti–cyclic citrullinated peptide; ANA: antinuclear antibodies; [1]Pearson's chi-squared test.

Table 3: DMARDs regimen among rheumatoid arthritis cohort stratified by Hb levels.

Characteristics	Total (N_v = 11393) n (%)	Hb > 10 (N_v = 8260) n (%)	Hb < 10 (N_v = 3133) n (%)	*p*-value
MTX	7322 (64.3)	5384 (65.2)	1938 (61.9)	< 0.001[1]
SSZ	1501 (13.2)	107 (13.0)	424 (13.5)	0.486[1]
LEF	1623 (14.2)	1070 (13.0)	551 (17.6)	< 0.001[1]
HCQ	3222 (28.3)	227 (27.5)	952 (30.4)	0.002[1]
IMUR	208 (1.8)	138 (1.7)	70 (2.2)	0.045[1]
CYC	9 (0.1)	1 (0.0)	8 (0.3)	< 0.001[1]

DMARDs: disease-modifying antirheumatic drugs; Hb: hemoglobin; N_v: total number of patients visit; MTX: methotrexate; SSZ: sulfasalazine; LEF: leflunomide; HCQ: hydroxychloroquine; IMUR: azathioprine; CYC: cyclophosphamide; [1]Pearson's chi-squared test.

Table 4: Biologics regimen among rheumatoid arthritis cohort stratified by Hb levels.

Characteristics	Total (N_v = 11393) n (%)	Hb > 10 (N_v = 8260) n (%)	Hb < 10 (N_v = 3133) n (%)	*p*-value
Medications				
RIT	1319 (11.6)	1029 (12.5)	290 (9.3)	< 0.001[1]
ADA	707 (6.2)	480 (5.8)	227 (7.2)	0.005[1]
TOC	1983 (17.4)	1660 (20.1)	323 (10.3)	< 0.001[1]
ETA	515 (4.5)	355 (4.3)	160 (5.1)	0.063[1]
ABA	802 (7.0)	619 (7.5)	183 (5.8)	0.002[1]
INF	486 (4.3)	324 (3.9)	162 (5.2)	0.003[1]
TOF	124 (1.1)	71 (0.9)	53 (1.7)	< 0.001[1]
CER	161 (1.4)	88 (1.1)	73 (2.3)	< 0.001[1]
GOL	54 (0.5)	24 (0.3)	30 (1.0)	< 0.001[1]
Treatment				< 0.001[1]
Biologics	6125 (55.3)	4629 (57.2)	1496 (50.0)	
DMARDs	4959 (44.7)	3465 (42.8)	1494 (50.0)	

Hb: hemoglobin; N_v: total number of patients visit; RIT: rituximab; ADA: adalimumab; TOC: tocilizumab; ETA: etanercept; ABA: abatacept; INF: infliximab; TOF: tofacitinib; CER: certolizumab pegol; GOL: golimumab; DMARDs: disease-modifying antirheumatic drugs; [1]Pearson's chi-squared test.

$p = 0.004$), physician global assessment [OR = 1.073, 95% CI: 1.007–1.143; $p = 0.029$], tender joints [OR = 0.968, 95% CI: 0.950–0.987; $p < 0.001$], and swollen joints [OR = 1.107, 95% CI: 1.075–1.139; $p < 0.001$).

Table 7 shows the relationship between demographic and clinical parameters stratified by Hb levels using univariate and multivariate analyses. Univariate analysis revealed that sex, nationality, age at RA diagnosis, creatinine, ESR, CRP, DAS-28 levels, treatment, patient global assessment, physician global assessment, tender joints, and swollen joints were significantly associated with Hb levels. Multivariate logistic regression analysis confirmed the association of nationality, age at diagnosis, ESR, CRP, DAS-28 levels, treatment, patient global assessment, physician global assessment, tender joints, and swollen joints with Hb. Figure 1 illustrates how the adjusted odds ratio (aOR) corresponds to the demographic and clinical parameters for the dependent variable Hb. A larger number of non-Kuwaiti patients had lower Hb levels than their Kuwaiti counterparts [aOR = 1.34, 95% CI:1.16–1.56; $p < 0.001$]. Patients who received biologics were more likely to have high Hb levels [aOR = 1.33, 95% CI:1.23–1.45; $p < 0.001$). Additionally, patients with DAS-28 ≥ 3.2 were more likely to have low Hb levels than patients with DAS-28 < 3.2 [aOR = 0.74, 95% CI: 0.61–0.90; $p = 0.002$).

DISCUSSION

We examined the clinical impact of RA stratified by Hb levels in the KRRD cohort. The average age in the cohort was 55.9 ± 12.5 years, 63.4% were females, and 50.3% were non-Kuwaiti. The median

Table 5: Findings of laboratory test in rheumatoid arthritis cohort stratified by Hb levels.

Characteristics	Total (N_v = 11393) Median (IQR)	Hb > 10 (N_v = 8260) Median (IQR)	Hb < 10 (N_v = 3133) Median (IQR)	*p*-value
ESR, mm/hr	23.0 (10.0–40.0)	22.0 (10.0–38.0)	26.0 (11.0–48.0)	< 0.001[1]
CRP, mg/L	4.7 (2.0–8.9)	4.3 (2.0–8.2)	5.0 (2.0–9.0)	< 0.001[1]
WBC, × 10^9/L	6.9 (5.4–8.6)	6.9 (5.4–8.6)	6.9 (5.4–8.6)	0.793[1]
Hb, g/L	123.0 (107.0– 134.0)	129.0 (121.0– 138.0)	14.5 (12.2–101.0)	< 0.001[1]
PLT, × 10^9/L	264.0 (216.0–321.0)	261.0 (214.0–316.0)	273.0 (220.0–338.0)	< 0.001[1]
Creatinine, µmol/L	59.0 (51.0–70.0)	60.0 (51.0–70.0)	59.0 (50.0–71.0)	0.192[1]
FBS, mmol/L	5.5 (5.0–6.3)	5.5 (5.0–6.3)	5.4 (5.0–6.4)	0.120[1]
AST, U/L	20.0 (17.0–26.0)	21.0 (17.0–26.0)	20.0 (16.0–24.0)	< 0.001[1]
ALT, U/L	19.0 (14.0–26.0)	19.0 (15.0–26.0)	19.0 (14.0–24.0)	< 0.001[1]
ALP, U/L	64.0 (50.0–80.0)	65.0 (51.0–81.0)	58.0 (45.0–76.8)	< 0.001[1]
TC, mmol/L	4.8 (4.2–5.5)	4.9 (4.2–5.6)	4.7 (4.0–5.4)	< 0.001[1]
LDL, mmol/L	2.8 (2.3–3.4)	2.9 (2.3–3.5)	2.7 (2.0–3.3)	< 0.001[1]
UA, µmol/L	261.0 (206.0–319.0)	275.0 (227.0–330.0)	220.0 (193.0–293.0)	< 0.001[1]

Hb: hemoglobin; N_v: total number of patients visit; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: white blood cells; PLT: platelet (thrombocyte) count; FBS: fasting blood glucose; AST: aspartate aminotransferase; ALT: alanine transaminase; ALP: alkaline phosphatase; TC: total cholesterol; LDL: low-density cholesterol; UA: uric acid; [1]Mann–Whitney–Wilcoxon test.

Table 6: Multiple logistic regression analysis of factors associated with DAS-28 in rheumatoid arthritis cohort.

	Model coefficients – Hb levels						
						95% CI	
Predictor	Estimate[+]	SE	Z	*p*-value	Odds ratio	Lower	Upper
Intercept	-0.570	0.163	-3.503	< 0.001*	0.566	0.411	0.778
Gender	-0.033	0.061	-0.538	0.591	0.968	0.859	1.090
Nationality	-0.295	0.075	-3.937	< 0.001*	0.745	0.643	0.862
Duration of RA, years	-0.026	0.005	-5.221	< 0.001*	0.974	0.965	0.984
WBC, × 10^9/L	0.000	0.000	0.719	0.472	1.000	1.000	1.000
Creatinine, µmol/L	0.001	0.001	0.982	0.326	1.001	0.999	1.003
ESR, mm/hr	0.006	0.002	3.852	< 0.001*	1.006	1.003	1.009
CRP, mg/L	0.003	0.006	0.474	0.635	1.003	0.991	1.015
DAS-28 < 3.2 and DAS-28 ≥ 3.2	-0.304	0.099	-3.068	0.002*	0.738	0.607	0.896
DMARDS and biologics	0.158	0.075	2.111	0.035*	1.171	1.011	1.355
Patient global assessment	-0.076	0.026	-2.918	0.004*	0.926	0.880	0.975
Physician global assessment	0.070	0.032	2.185	0.029*	1.073	1.007	1.143
Number of tender joints	-0.033	0.010	-3.330	< 0.001*	0.968	0.950	0.987
Number of swollen joints	0.101	0.015	6.875	< 0.001*	1.107	1.075	1.139

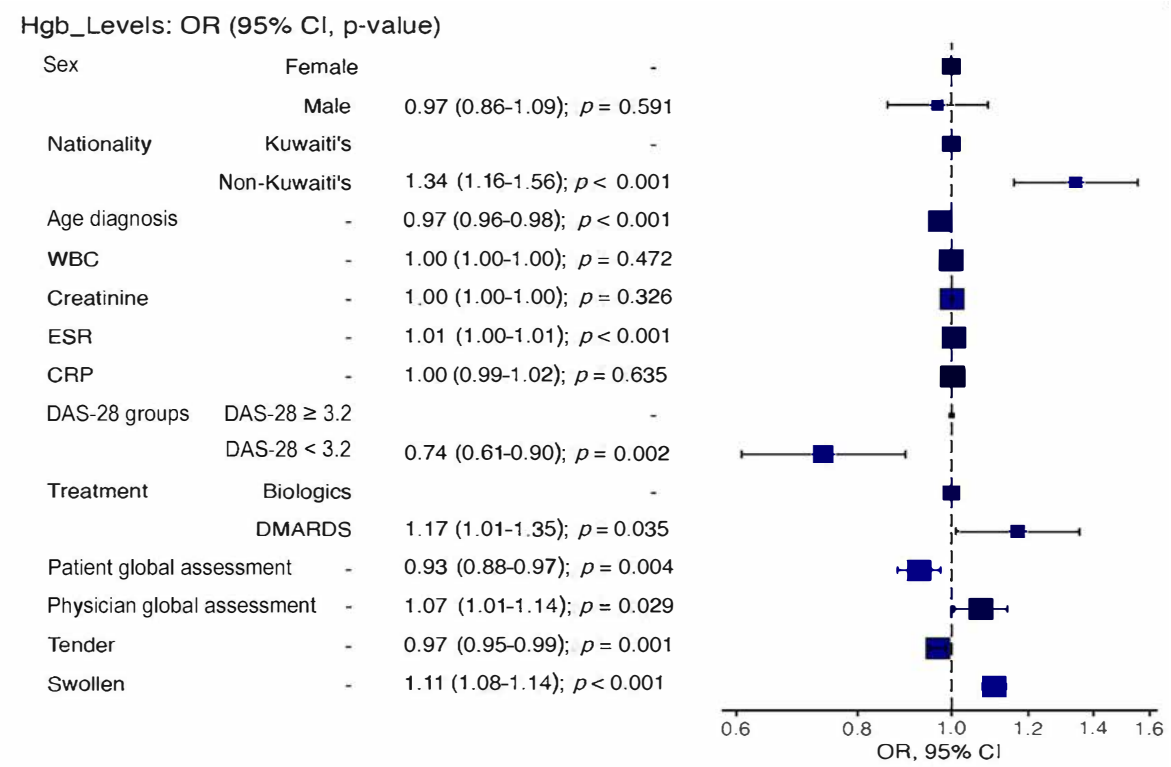
*DAS-28: Hb: hemoglobin; RA: rheumatoid factor; WBC: white blood cells ; DMARDS: disease-modifying antirheumatic drugs; SE: standard error; Z: z-value; DMARD: disease-modifying antirheumatic drugs; [+]Estimate represents the log odds of low Hb (Hb ≤ 110 g/L) vs. high Hb (Hb > 110 g/L); *p-value is significant.*

Hb levels in the groups without anemia and with anemia were 129.0 g/L and 14.5 g/L, respectively. Most patients with positive ANA results were non-anemic (25.2% vs. 19.0%). Regarding treatment, a higher proportion of non-anemic patients received biologics (57.2% vs. 50.0%), unlike anemic patients who were prescribed more DMARDs (42.8% vs. 50.0%). Non-Kuwaitis had 1.34 increased odds of

Table 7: Univariable and multivariable logistic regression analysis of factors associated with DAS-28 in the rheumatoid arthritis cohort (version 2).

Characteristics	Hb > 10 n (%)	Hb < 10 n (%)	aOR, *p*-value (univariable)	aOR, *p*-value (multivariable)
Sex, male	3103 (73.7)	1106 (26.3)	0.91 (0.83–0.99); $p = 0.025$*	0.97 (0.86–1.09); $p = 0.591$
Nationality, non-Kuwaiti	3099 (68.0)	1456 (32.0)	1.45 (1.33–1.57); $p < 0.001$*	1.34 (1.16–1.56); $p < 0.001$*
Age at RA onset, years, mean ± SD	11.9 ± 6.8	10.6 ± 6.6	0.97 (0.96–0.98); $p < 0.001$*	0.97 (0.96–0.98); $p < 0.001$
WBC, mean ± SD	33.3 ± 431.4	59.3 ± 1273.7	1.00 (1.00–1.00); $p = 0.166$	1.00 (1.00–1.00); $p = 0.472$
Creatinine, mean ± SD	62.1 ± 24.6	64.1 ± 35.8	1.00 (1.00–1.00); $p = 0.001$*	1.00 (1.00–1.00); $p = 0.326$
ESR, mean ± SD	26.4 ± 20.7	32.6 ± 26.6	1.01 (1.01–1.01); $p < 0.001$*	1.01 (1.00–1.01); $p < 0.001$*
CRP, mean ± SD	5.8 ± 4.9	6.3 ± 5.1	1.02 (1.01–1.03); $p < 0.001$*	1.00 (0.99–1.02); $p = 0.635$
DAS-28 groups				
DAS-28 ≥ 3.2	2212 (65.9)	1145 (34.1)		Reference
DAS-28 < 3.2	6045 (75.3)	1988 (24.7)	0.64 (0.58–0.69); $p < 0.001$*	0.74 (0.61–0.90); $p = 0.002$*
Treatment				
Biologics	4629 (75.6)	1496 (24.4)		Reference
DMARDS	3465 (69.9)	1494 (30.1)	1.33 (1.23–1.45); $p < 0.001$*	1.17 (1.01–1.35); $p = 0.035$*
Patient global assessment, mean ± SD	1.6 ± 2.3	1.8 ± 2.4	1.03 (1.02–1.05); $p < 0.001$*	0.93 (0.88–0.97); $p = 0.004$*
Physician global assessment, mean ± SD	1.0 ± 1.7	1.2 ± 1.9	1.08 (1.06–1.11); $p < 0.001$*	1.07 (1.01–1.14); $p = 0.029$*
Tender joints, mean ± SD	2.7 ± 5.4	3.4 ± 6.0	1.02 (1.01–1.03); $p < 0.001$*	0.97 (0.95–0.99); $p = 0.001$*
Swollen joints, mean ± SD	0.5 ± 2.0	1.2 ± 3.0	1.11 (1.09–1.13); $p < 0.001$*	1.11 (1.08–1.14); $p < 0.001$*

*DAS-28: Disease Activity Score-28; Hb: hemoglobin; aOR: adjusted odds ratio; aP-value: adjusted p-value; *adjusted p-value is significant; RA: rheumatoid factor; WBC: white blood cells; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DMARD: disease-modifying antirheumatic drugs.*



DAS-28: Disease Activity Score-28; WBC: white blood cells; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Figure 1: Odds ratio (OR) plot of dependent and independent variables.

having anemia compared to Kuwaitis. Patients who received biologics had 1.17 increased odds of having normal Hb levels. In addition, patients with DAS-28 ≥ 3.2 had 0.74 increased odds of having anemia in comparison to patients with DAS-28 < 3.2. Non-Kuwaiti patients may have used fewer biologics; hence, they may have a higher DAS-28.[19]

The anemic syndrome has been previously reported as a marker of high activity and severity in patients with RA.[3,21] Table 8 compares our KRRD cohort with other international studies to evaluate the severity of the disease.[6–12] All studies included lower Hb level thresholds for females. The AMU study had the lowest cut-off Hb values (< 110 g/L in females and < 120 g/L in males).[11] Most studies adhered to the Hb concentrations proposed by the World Health Organization.[6,8–10,12] Our study is the sole study to exclude sex and use a generalized low cut-off score. International data have reported that 24.0–70.6% of patients with RA have anemia [Table 8]. The prevalence of anemia in our study was 27.5%, approximately fourfold lower than that reported by Agrawal et al,[7] (70.6%), Goyal et al,[10] (67.8%), and Ganna (64.0%).[9] This was akin to the Swiss Clinical Quality Management study (24.0%) and the Moroccan QUEST-RA study (28.8%).[6,8] All the studies agreed that anemic patients had higher DAS-28 scores and a larger number of tender and swollen joints. These studies reported a negative correlation between Hb concentration and DAS-28 and the number of swollen/tender joints. Similarly, in our study, more anemic patients had a DAS-28 ≥ 3.2 than non-anemic patients (36.5% vs. 26.8). Furthermore, patients with anemia had a higher prevalence of swollen (1.2 ± 3.0 vs. 0.5 ± 2.0) and tender joints (3.4 ± 6.0 vs. 2.7 ± 5.4). Our study had lower averages for swollen and tender joints than other international studies.[7,9–12]

Patients with anemia tend to have elevated inflammatory acute-phase reactants compared to their non-anemic counterparts. A previous analysis of 2120 patients with RA demonstrated CRP and ESR to be predictors of anemia.[22] In our study, anemic patients were associated with 1.01 increased odds of elevated ESR, but CRP was not significant. The treatment of disease activity and inflammation is believed to improve Hb levels.[23] However, long-term DMARDs therapy is associated with abnormal absorption of iron and vitamin B12 as a consequence of gastrointestinal mucosal damage or ulcers.[11,24]

Table 8: Comparison of KRDD and other international studies.

Study, country	Study period, year	RA	Anemia n (%)	Hb level cut-off for anemia, g/L	DAS-28 anemic vs. non-anemic	Swollen joint anemic vs. non-anemic	Tender joint anemic vs. non-anemic
SCQM,[6] Switzerland	1996–2007	4377	1054 (24.0)	F < 120; M < 130	5.2 ± 1.5 vs. 4.2 ± 1.4	-	-
Agrawal et al,[7] India	2003	214	151 (70.6)	F ≤ 110; M ≤ 120	5.19 ± 1.50 vs. 3.82 ± 1.36	8.81 ± 8.08 vs. 3.82 ± 5.77	5.37 ± 6.32 vs. 2.23 ± 4.27
Moroccan QUEST-RA,[8] Morocco	2008–2010	1032	297 (28.8)	F < 120; M < 130	5.45 ± 1.55 vs. 4.7 ± 1.69	-	-
Ganna,[9] Ukraine	2014	89	57 (64.0)	F < 120	5.2 ± 1.3 vs. 2.8 ± 1.1	28.67 ± 9.01 vs. 16.53 ± 8.27	31.42 ± 10.07 vs. 18.52 ± 11.28
Goyal et al,[10] India	2012–2013	59	40 (67.80)	F < 120; M < 130	3.2-5.1 = 20.0% vs. 80.0% > 5.1 = 92.0% vs. 8.0%	9.17 ± 3.82 vs. 2.35 ± 0.93	12.98 ± 4.21 vs. 5.82 ± 2.10
AMU,[11] China	2015–2018	890	418 (47.05)	F < 110; M < 120	5.80 ± 1.09 vs. 4.80 ± 1.32	8 (4–12) vs. 5 (2–10)	12 (7–20) vs. 8 (4–15)
RIMS,[12] India	2018– 2020	236	139 (58.9%)	F < 120; M < 130	4.71 ± 1.25 vs. 1.14 ± 1.15	6.17 ± 4.27 vs. 2.91 ± 2.52	3.71 ± 3.21 vs. 0.123 ± 0.1
KRDD, Kuwait	2013–2022	N_y = 11393 N_p = 1584	N = 3133 (27.5%)	M and F ≤ 110	*Hb < 10 = 26.8% vs. 73.2% *Hb > 10 = 36.5% vs. 63.5%	1.2 ± 3.0 vs. 0.5 ± 2.0	3.4 ± 6.0 vs. 2.7 ± 5.4

RA: rheumatoid arthritis; Hb: hemoglobin; DAS-28: Disease Activity Score-28; SCQM: Swiss clinical quality management; QUEST-RA: Quantitative Standard Monitoring Patients with RA; AMU: Anhui Medical University; RIMS: Regional Institute of Medical Sciences; KRDD: Kuwait Registry for Rheumatic Diseases; M: male; F: female; Ny: total number of patients visit; Np: total number of patients.

Emerging data reports tumor necrosis factor is significantly higher in anemic patients with RA.[25] Correspondingly, biologics, such as tocilizumab and adalimumab, have been associated with significant improvements in anemia.[26,27] We did not study Hb concentration before drug administration; thus, we could not ascertain any improvements due to biologic use. However, there is an association between biologics and normal Hb levels in patients.

As this was a retrospective study, bias could be introduced through confounding variables that were unaccounted for, such as history of nonsteroidal anti-inflammatory and glucocorticoid drug use. Moreover, the etiology and hematological features of anemia were not identified. In our study, stratification was done according to Hb levels and not as per the definition of anemia. Furthermore, we did not delineate the changes in Hb concentration before and after treatment. Further studies are required to overcome these limitations.

CONCLUSION

The results establish an interrelation between inflammation and anemia, expressed by the significant association between low Hb levels, higher DAS-28 scores, and ESR. Taken together, these results suggest that low Hb levels is a predictor of worse outcomes in patients with RA.

Disclosure

The authors declared no conflicts of interest. No funding was received for this study.

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