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ORIGINAL ARTICLE

Associations of haemoglobin with C-reactive protein and erythrocyte sedimentation rate in patients with rheumatoid arthritis: a cross-sectional study

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Running title: Tanthonius et al. Haemoglobin and inflammation in RA

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ABSTRACT

Aim: To examine the associations of haemoglobin with C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in patients with rheumatoid arthritis (RA).

Methods: This retrospective cross-sectional study included 168 adults with RA whose medical records for 2022–2024 were reviewed at Murni Teguh Memorial Hospital, Medan, Indonesia. Associations of haemoglobin with CRP and ESR were evaluated using Spearman's rank correlation and multiple linear regression.

Results: Anaemia was present in 69 (41.1%) patients. Mean haemoglobin was 12.18 ± 1.41 g/dL, and median ESR was 39.50 mm/hour (interquartile range 23.00–64.00). Elevated CRP was recorded in 94 (56.0%) patients: 16 (9.5%) had moderate, 57 (33.9%) marked, and 21 (12.5%) severe elevation. Haemoglobin correlated inversely with CRP ($\rho = -0.267$; $p < 0.001$) and ESR ($\rho = -0.415$; $p < 0.001$). In the two-predictor model, ESR remained inversely associated with haemoglobin ($B = -0.022$; $p < 0.001$), whereas ordinal CRP category did not ($B = -0.002$; $p = 0.984$).

Conclusion: Haemoglobin was inversely associated with CRP and ESR, but only ESR remained associated with haemoglobin after mutual adjustment. The cross-sectional design and limited control of confounding preclude causal interpretation.

Keywords: anaemia; C-reactive protein; erythrocyte sedimentation rate; haemoglobin; rheumatoid arthritis

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that can cause progressive joint damage, disability, and reduced quality of life (1). C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are commonly used acute-phase markers, although both are influenced by clinical and biological factors beyond RA activity (2). Anaemia is a frequent extra-articular manifestation and is associated with worse clinical and patient-reported outcomes (3).

Inflammation-associated anaemia in RA is mediated partly by cytokine-driven hepcidin production and iron sequestration (4). Impaired erythropoiesis and reduced erythrocyte survival may also contribute (5). Consequently, haemoglobin concentration may decline as inflammatory burden increases.

CRP and ESR differ biologically. CRP is synthesised by the liver in response to cytokine signalling, whereas ESR is an indirect measure affected by plasma proteins and erythrocyte number, size, and aggregation (2). Because anaemia itself may increase ESR, an inverse association between haemoglobin and ESR may reflect both inflammation and the physical effects of altered erythrocyte characteristics (6).

An inverse association between haemoglobin and inflammatory markers has been reported in patients with RA (7), but the relative associations of CRP and ESR vary across populations and analytical approaches. Evidence from Indonesian clinical populations remains limited.

The aim of this study was to examine the associations of haemoglobin with CRP and ESR in patients with RA. Secondary objectives were to describe the frequency and severity of anaemia and compare haemoglobin concentrations between female and male patients.

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MATERIAL AND METHODS

Subjects and study design

This retrospective cross-sectional study was conducted at Murni Teguh Memorial Hospital, Medan, North Sumatra, Indonesia. Source records covered the period between January 2022 and December 2024; record identification and data extraction were conducted from July to September 2025, after ethics approval had been granted on 30 June 2025 by the Health Research Ethics Committee of Universitas Sumatera Utara (No. 530/KEPK/USU/2025). Eligible records were from patients aged 18 years or older with a recorded diagnosis of RA and first-visit laboratory results for haemoglobin, CRP, and ESR. Records were excluded for severe infection, another active inflammatory or autoimmune disease, cancer, pneumonia, tuberculosis, acute or chronic bleeding, or incomplete data required for the analysis.

Of 264 potentially eligible records, 17 were excluded because of prespecified clinical conditions. Further 79 records lacked a complete set of the three required biomarkers, leaving 168 patients (160 outpatients and 8 inpatients) in the complete-case analytical sample. All descriptive, correlation, group-comparison, and regression analyses reported here used these 168 complete cases.

All records that met the eligibility criteria during the study period were included; no sampling or Slovin-derived minimum was used to select records.

Records were retrieved using International Classification of Diseases, 10th Revision (ICD-10) codes M05 and M06. The diagnoses had been recorded by consultant rheumatologists; the codes were used to identify records and were not the sole diagnostic criterion. M05 identified seropositive RA, whereas M06 included other RA, including seronegative disease. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) results were inconsistently available and were not used to reconfirm eligibility. The 2010 American

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College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria could not be independently reconstructed for all records.

Methods

Haemoglobin was reported in g/dL from routine automated haematology testing. Anaemia was classified using sex-specific thresholds: mild, 11.0–12.9 g/dL in males and 11.0–11.9 g/dL in females; moderate, 8.0–10.9 g/dL; and severe, < 8.0 g/dL (8). CRP was measured using an immunoturbidimetric method, reported in mg/L, and categorised as normal (< 6 mg/L), moderately elevated (6–10 mg/L), markedly elevated (> 10–50 mg/L), or severely elevated (> 50 mg/L). ESR was measured using the Westergren method and reported in mm/hour.

The three measurements were obtained at the same initial clinical encounter and before treatment changes at the study institution. Age and sex were extracted from the medical records.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows (version 22.0, IBM Corp., Armonk, NY, USA). Continuous variables are reported as mean ± standard deviation or as median and interquartile range (IQR), according to distribution, and categorical variables as numbers and percentages. Kolmogorov–Smirnov testing indicated that haemoglobin was approximately normally distributed ($p = 0.200$), whereas ESR was not ($p = 0.001$). Associations among haemoglobin, ordinal CRP category, and ESR were evaluated using Spearman's rank correlation. Haemoglobin was compared between sexes using an independent-samples t-test after assessment of equality of variances. Multiple linear regression examined the mutually adjusted associations of ordinal CRP category (coded 1–4 as a linear trend) and continuous ESR (mm/hour) with haemoglobin (g/dL). Complete-case analysis was used. Tests were two-sided, and $p < 0.05$ was considered statistically significant.

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Regression assumptions were assessed using residual plots and tests of residual distribution. Multicollinearity was assessed using tolerance and the variance inflation factor (VIF); tolerance was 0.597 and VIF was 1.674 for both predictors. The overall model F statistic was verified algebraically from R^2, the analytical sample size, and the number of predictors. Observation-level influence statistics were not available in the retained analytical output and were therefore not reported.

RESULTS

The study included 168 patients with RA. Patients aged 18–44 years accounted for 66 (39.3%), those aged 45–59 years for 61 (36.3%), those aged 60–74 years for 37 (22.0%), and those aged ≥ 75 years for 4 (2.4%). The sample included 157 (93.5%) females and 11 (6.5%) males (Table 1).

Mean haemoglobin was 12.18 ± 1.41 g/dL, and median ESR was 39.50 mm/hour (IQR 23.00–64.00) (Table 1).

Elevated CRP was recorded in 94 (56.0%) patients: 16 (9.5%) had moderate, 57 (33.9%) marked, and 21 (12.5%) severe elevation. CRP was normal in 74 (44.0%) patients. Anaemia was present in 69 (41.1%) patients, including mild anaemia in 43 (25.6%), moderate anaemia in 25 (14.9%), and severe anaemia in 1 (0.6%) (Table 1).

Haemoglobin correlated inversely with CRP ($\rho = -0.267$; $p < 0.001$) and ESR ($\rho = -0.415$; $p < 0.001$). CRP and ESR were positively correlated ($\rho = 0.644$; $p < 0.001$) (Table 2).

Mean haemoglobin was 12.12 ± 1.40 g/dL in females and 13.04 ± 1.23 g/dL in males. The female–male mean difference was −0.92 g/dL (95% CI −1.78 to −0.06; $t = -2.112$; $p = 0.036$); Levene's test indicated equal variances ($p = 0.668$) (Table 3). In the two-predictor model (n = 168), ESR was inversely associated with haemoglobin (B = −0.022; 95% CI −0.032 to −0.012; SE = 0.005; $\beta = -0.404$; $p < 0.001$), whereas ordinal CRP category was not (B = −0.002; 95% CI −0.227 to 0.223; SE = 0.115; $\beta = -0.002$; $p = 0.984$). The model

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explained 16.4% of haemoglobin variability ($R^2 = 0.164$; adjusted $R^2 = 0.154$; $F = 16.18$; $p < 0.001$) (Table 4).

DISCUSSION

In this retrospective cross-sectional study, haemoglobin was inversely associated with both CRP and ESR. The association was stronger for ESR, which remained associated with haemoglobin when both markers were included in the same model. Anaemia affected 41.1% of the sample. These findings describe statistical associations and do not establish that inflammation caused lower haemoglobin.

The sample was predominantly female, consistent with the greater occurrence of RA among women (9). Age represented age at the recorded clinical encounter rather than age at disease onset.

Male patients had higher mean haemoglobin than female patients, but this comparison should be interpreted cautiously because only 11 males were included. Sex-related biological differences in arthritis and haemoglobin are well established (10). Unmeasured factors such as menstruation, iron status, renal function, and treatment could also have contributed to the difference (11).

The observed frequency of anaemia was within the range reported in other RA cohorts (12). Inflammation-associated anaemia may involve hepcidin-mediated iron restriction, impaired erythropoiesis, shortened erythrocyte survival, and an inadequate erythropoietin response (4). The inverse correlations of haemoglobin with CRP and ESR are consistent with previous observational findings (7). However, the stronger correlation with ESR does not establish that ESR is a superior inflammatory marker for anaemia. ESR is influenced by plasma proteins and erythrocyte characteristics; therefore, reduced erythrocyte concentration and altered aggregation can increase sedimentation and create a potentially bidirectional association (6).

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The regression model explained 16.4% of haemoglobin variability. Although ESR remained associated with haemoglobin after mutual adjustment for CRP, the model did not account for major potential confounders, including age, sex, disease duration and activity, iron indices, renal function, nutritional status, bleeding, comorbidities, or treatment. ESR should therefore be described as an associated variable rather than an independent predictor or causal determinant.

This study is limited by its retrospective cross-sectional and single-centre design, possible selection and information bias, the complete-case analysis, markedly unequal sex groups, and the absence of key clinical and laboratory covariates. The analyser manufacturer and model, ESR equipment, specimen type, detailed calibration and quality-control records, and observation-level influence statistics were unavailable in the retained dataset or analytical output. The 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria could not be independently reconstructed for all records. The use of ordinal CRP category as a linear predictor may also have obscured non-linear associations. Future studies should use prespecified diagnostic criteria, concurrent laboratory measurements, comprehensive anaemia phenotyping, disease-activity measures, and clinically justified multivariable models.

CONCLUSION

Haemoglobin was inversely associated with CRP and ESR in patients with RA, but only ESR remained associated with haemoglobin in a model containing both inflammatory markers. Because ESR is influenced by erythrocyte characteristics and major confounders were unavailable, the finding should not be interpreted causally. Prospective studies incorporating disease activity, iron status, renal function, and treatment are required.

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FUNDING

No specific funding was received for this study.

CONFLICTS OF INTEREST

None to declare.

AUTHOR CONTRIBUTIONS (CRediT)

Conceptualisation: WAT, RAS; methodology: WAT, RAS; formal analysis: WAT; investigation: WAT; data curation: WAT; software: WAT; visualisation: WAT; writing—original draft: WAT; writing—review and editing: WAT, RAS; validation: RAS; supervision: RAS; project administration: RAS. Authors approved the final version of the manuscript.

ETHICS STATEMENT

The study protocol was approved by the Health Research Ethics Committee of Universitas Sumatera Utara on 30 June 2025 (No. 530/KEPK/USU/2025), before data access, and the study was conducted in accordance with the Declaration of Helsinki.

DATA AVAILABILITY STATEMENT

The de-identified dataset and analysis files, containing study codes but no direct patient identifiers, are available from the corresponding author upon reasonable request, subject to institutional and ethics approval.

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REFERENCES

1. Taylor PC. Update on the diagnosis and management of early rheumatoid arthritis. Clin Med (Lond) 2020;20:561-4. doi: 10.7861/clinmed.2020-0727.
2. Shapiro SC. Biomarkers in rheumatoid arthritis. Cureus 2021;13:e15063. doi: 10.7759/cureus.15063.
3. Rubbert-Roth A, Furst DE, Fiore S, Praestgaard A, Bykerk V, Bingham CO 3rd, et al. Association between low haemoglobin, clinical measures, and patient-reported outcomes in patients with rheumatoid arthritis: post hoc analyses of three phase III trials of sarilumab. Arthritis Res Ther 2022;24:207. doi: 10.1186/s13075-022-02891-x.
4. Nita E, Bairaktari E, Kolios G, Migkos MP, Somarakis GP, Markatseli T, et al. Role of hepcidin in anaemia of chronic disease in rheumatoid arthritis. J Lab Physicians 2021;13:317-22. doi: 10.1055/s-0041-1732827.
5. Marques O, Weiss G, Muckenthaler MU. The role of iron in chronic inflammatory diseases: from mechanisms to treatment options in anaemia of inflammation. Blood 2022;140:2011-23. doi: 10.1182/blood.2021013472.
6. Siemons L, Ten Klooster PM, Vonkeman HE, van Riel PLCM, Glas CAW, van de Laar MAFJ. How age and sex affect the erythrocyte sedimentation rate and C-reactive protein in early rheumatoid arthritis. BMC Musculoskelet Disord 2014;15:368. doi: 10.1186/1471-2474-15-368.
7. Liu D, Yan J, Luo T, Yang L. Association between C-reactive protein and haemoglobin in US rheumatoid arthritis patients with rheumatoid arthritis based on NHANES data. Sci Rep 2025;15:8905. doi: 10.1038/s41598-025-93720-z.
8. World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity [Internet]. Geneva: World Health Organization; 2011

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[cited 2026 Aug 16]. Available from: https://www.who.int/publications/i/item/WHO-NMH-NHD-MNM-11.1. doi: not available.

9. Misra DP. Clinical manifestations of rheumatoid arthritis, including comorbidities, complications, and long-term follow-up. Best Pract Res Clin Rheumatol 2025;39:102020. doi: 10.1016/j.berh.2024.102020.
10. Kim J, Kim HA. Molecular mechanisms of sex-related differences in arthritis and associated pain. Int J Mol Sci 2020;21:7938. doi: 10.3390/ijms21217938.
11. Su F, Cao L, Ren X, Hu J, Tavengana G, Wu H, et al. Age and sex trend in hemoglobin levels in China: a cross-sectional study. BMC Endocr Disord 2023;23:8. doi: 10.1186/s12902-022-01218-w.
12. Shah J, Farooq A, Zadran S, Kakar ZH, Zarrar M, Bhatti HMHS Prevalence of anaemia in patients with rheumatoid arthritis presenting at tertiary care hospitals. Cureus 2024;16:e72418. doi: 10.7759/cureus.72418.

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TABLES AND FIGURES

Table 1. Demographic and laboratory characteristics of patients with rheumatoid arthritis

Variable	Value*
Age group, years	
18–44	66 (39.3)
45–59	61 (36.3)
60–74	37 (22.0)
≥75	4 (2.4)
Sex	
Female	157 (93.5)
Male	11 (6.5)
Haemoglobin, g/dL	
Mean ± SD	12.18±1.41
ESR, mm/hour	
Median (IQR)	39.50 (23.00–64.00)
CRP category, mg/L	
Normal	74 (44.0)
Moderately elevated	16 (9.5)
Markedly elevated	57 (33.9)
Severely elevated	21 (12.5)
Anaemia	
None	99 (58.9)
Mild	43 (25.6)
Moderate	25 (14.9)
Severe	1 (0.6)

*Values are n (%) unless otherwise indicated.
CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range; SD, standard deviation

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Table 2. Correlations among haemoglobin and inflammatory markers

Variable pair	ρ	p
Haemoglobin–CRP	−0.267	< 0.001
Haemoglobin–ESR	−0.415	< 0.001
CRP–ESR	0.644	< 0.001

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ρ, Spearman correlation coefficient

Table 3. Haemoglobin concentration by sex

Sex	n	Haemoglobin, mean ± SD (g/dL)
Female	157	12.12 ± 1.40
Male	11	13.04 ± 1.23

Female–male mean difference = −0.92 g/dL (95% CI −1.78 to −0.06; t = −2.112; p = 0.036); Levene's test p = 0.668
CI, confidence interval; SD, standard deviation

Table 4. Multiple linear regression of haemoglobin on inflammatory markers

Predictor	B (95% CI)	SE	β	p
CRP category (1–4)	−0.002 (−0.227 to 0.223)	0.115	−0.002	0.984
ESR (mm/hour)	−0.022 (−0.032 to −0.012)	0.005	−0.404	<0.001

Dependent variable: haemoglobin (g/dL). CRP was coded 1–4. $R^2 = 0.164$; adjusted $R^2 = 0.154$; $F = 16.18$; $p < 0.001$; standard error of the estimate = 1.2955
B, unstandardised coefficient; β, standardised coefficient; CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SE, standard error

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