

Inflammation-Mediated Dysregulation of Iron Homeostasis and Its Association with Anaemia Severity in Hidradenitis Suppurativa: A Cross-Sectional Study with Mediation Analysis

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Abstract

Objectives

To examine the associations between C-reactive protein (CRP), hepcidin, and haemoglobin in adults with hidradenitis suppurativa (HS), and to formally test the hypothesis that hepcidin mediates the effect of inflammation on anaemia.

Methods

We performed a secondary cross-sectional analysis of a public dataset of 88 HS patients. Anaemia was defined using World Health Organization criteria. We used Spearman's correlation, multivariable regression, and formal mediation analysis with bootstrapping to assess the relationships between CRP, hepcidin, and haemoglobin.

Results

Anaemia was present in 58.0% of patients ($n = 51$). CRP was moderately correlated with hepcidin ($\rho = 0.431$, $p < 0.001$) and inversely with haemoglobin ($\rho = -0.382$, $p < 0.001$). Formal mediation analysis revealed a significant indirect effect of CRP on haemoglobin through hepcidin ($\beta = -0.124$; 95% Bootstrap CI: -0.197 to -0.065), accounting for 66.8% of the total effect. In the multivariable model adjusted for hepcidin, the direct effect of CRP became non-significant ($p = 0.24$).

Conclusions

Our findings provide strong statistical evidence that the association between systemic inflammation and anaemia severity in HS is substantially mediated by hepcidin, supporting its role as a potential therapeutic target.

NOVELTY STATEMENT

What is new? This study is the first to statistically demonstrate and quantify that hepcidin partially mediates the relationship between systemic inflammation and anaemia severity in hidradenitis suppurativa.

What is the central finding? The effect of C-reactive protein on haemoglobin is substantially (66.8%) mediated by hepcidin, providing quantitative evidence for a key pathophysiological mechanism.

What is the clinical significance? These findings support hepcidin as a key therapeutic target for managing anaemia in HS and reinforce the importance of controlling inflammation to mitigate this

common comorbidity.

1. INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, debilitating inflammatory disorder of the pilosebaceous unit characterised by recurrent painful nodules, abscesses, and sinus tracts primarily affecting the axillary, inguinal, and anogenital regions (1, 2). Beyond its dermatological manifestations, HS is increasingly recognised as a systemic inflammatory condition with multiple extracutaneous manifestations, including cardiovascular disease, metabolic syndrome, and anaemia of chronic disease (ACD) (3, 4). The prevalence of anaemia in HS patients ranges from 30% to 60%, significantly higher than in the general population, and is associated with reduced quality of life and increased disease burden (3).

The pathophysiology of ACD involves the dysregulation of hepcidin, the master regulator of systemic iron homeostasis (5). During chronic inflammation, pro-inflammatory cytokines, particularly interleukin-6 (IL-6), stimulate hepatic hepcidin production through STAT3 signalling (6, 7). Elevated hepcidin blocks dietary iron absorption and prevents the recycling of iron from macrophage stores by inducing degradation of ferroportin, the sole cellular iron exporter, leading to reduced iron availability for erythropoiesis and subsequent anaemia (5, 8). This mechanism results in functional iron deficiency despite adequate or elevated total body iron stores, a hallmark of ACD.

While this mechanism is well-established in other chronic inflammatory conditions such as rheumatoid arthritis and chronic kidney disease, its quantitative contribution to anaemia in HS has not been formally demonstrated (9, 10). Previous studies have shown associations between inflammatory markers and anaemia in HS, but none have performed formal mediation analysis to quantify the role of hepcidin as an intermediary. Understanding the magnitude of hepcidin's mediating role is crucial for developing targeted therapeutic strategies.

This study aimed to: (1) quantify the associations between inflammatory markers, hepcidin, and haemoglobin in HS patients; and (2) perform a formal mediation analysis to test the hypothesis that hepcidin mediates the relationship between systemic inflammation (measured by CRP) and anaemia severity.

2. METHODS

2.1 Study Design and Data Source

We conducted a secondary analysis of a cross-sectional dataset of HS patients, publicly available on Mendeley Data (11). The original study collected demographic, clinical, and laboratory data from adult patients with confirmed HS diagnosis at a tertiary dermatology centre. Of 114 patients in the original dataset, 26 were excluded due to missing laboratory data (12 for CRP, 8 for ferritin, and 6 for ESR, with some patients having multiple missing values). The final analytical sample comprised 88 patients with

complete data for all variables of interest. This study was conducted in accordance with the Declaration of Helsinki.

2.2 Variables and Definitions

Anaemia was defined according to World Health Organization criteria: haemoglobin < 13 g/dL for males and < 12 g/dL for females (12). The primary exposure variable was C-reactive protein (CRP), measured in mg/L using high-sensitivity immunoturbidimetric assay. The hypothesised mediator was serum hepcidin (ng/mL), measured by enzyme-linked immunosorbent assay. Secondary inflammatory markers included erythrocyte sedimentation rate (ESR, mm/hr) and ferritin (ng/mL). Iron status indicators included serum iron ($\mu\text{g/dL}$) and transferrin saturation (TSAT, %). Demographic variables included age (years) and sex.

2.3 Statistical Analysis

Continuous variables were summarised using means $\pm$ standard deviation (SD) for normally distributed data or medians and interquartile ranges (IQR) for skewed distributions. Normality was assessed using the Shapiro-Wilk test. Categorical variables were presented as frequencies and percentages.

Comparisons between anaemic and non-anaemic groups were performed using independent t-tests or Mann-Whitney U tests for continuous variables and chi-square tests for categorical variables.

Bivariate associations were assessed using Spearman's rank correlation coefficients. Multivariable linear regression was used to model haemoglobin concentration, and logistic regression was used to model anaemia status. Models were adjusted for age, sex, and hepcidin to assess the independent effect of CRP after accounting for the hypothesised mediator.

To test our primary hypothesis, we performed a formal mediation analysis using the Baron and Kenny method (13), supplemented with bootstrapping (1000 iterations) to estimate the 95% confidence interval for the indirect effect. The mediation model tested was: CRP (Independent Variable) $\rightarrow$ Hepcidin (Mediator) $\rightarrow$ Haemoglobin (Dependent Variable). The Sobel test was used to assess the significance of the indirect effect. The proportion of the total effect mediated was calculated as the indirect effect divided by the total effect. A p-value < 0.05 was considered statistically significant. All analyses were performed using Python 3.11 with scipy and statsmodels packages.

3. RESULTS

3.1 Cohort Characteristics

The analytical cohort comprised 88 HS patients with a mean age of 33.8 ± 12.3 years. The majority were male (81.8%, $n = 72$), and anaemia was present in 58.0% of patients ($n = 51$). The mean haemoglobin concentration was 12.3 ± 1.8 g/dL. Patients with anaemia had significantly higher CRP (median 4.1 vs 2.1 mg/L, $p < 0.001$) and hepcidin (median 35.1 vs 18.5 ng/mL, $p < 0.001$) compared to non-anaemic patients. Anaemic patients also had significantly lower serum iron (58.2 vs 82.7 $\mu\text{g/dL}$, $p < 0.001$) and

TSAT (18.5% vs 28.3%, $p < 0.001$). Baseline characteristics stratified by anaemia status are presented in Table 1.

Table 1
Baseline Characteristics of the Study Population (n = 88)

Characteristic	Overall (n = 88)	Anaemic (n = 51)	Non-Anaemic (n = 37)	p-value
Age, years (mean $\pm$ SD)	33.8 $\pm$ 12.3	35.1 $\pm$ 11.9	32.0 $\pm$ 12.8	0.25
Male Sex, n (%)	72 (81.8)	40 (78.4)	32 (86.5)	0.31
Haemoglobin, g/dL (mean $\pm$ SD)	12.3 $\pm$ 1.8	11.1 $\pm$ 1.4	14.0 $\pm$ 0.8	< 0.001***
CRP, mg/L (median, IQR)	3.2 (1.8–5.8)	4.1 (2.5–6.9)	2.1 (1.5–3.5)	< 0.001***
Hepcidin, ng/mL (median, IQR)	26.3 (15.2–48.7)	35.1 (18.9–55.2)	18.5 (12.1–29.8)	< 0.001***
Ferritin, ng/mL (median, IQR)	120 (75–210)	145 (88–250)	98 (65–155)	0.002**
Serum Iron, μ g/dL (mean $\pm$ SD)	68.5 $\pm$ 28.3	58.2 $\pm$ 24.1	82.7 $\pm$ 28.5	< 0.001***
CRP: C-reactive protein; IQR: interquartile range; SD: standard deviation.				
p < 0.01; *p < 0.001				

3.2 Bivariate Correlation Analysis

As shown in Fig. 1, CRP demonstrated moderate positive correlations with hepcidin ($\rho = 0.431$, $p < 0.001$) and ESR ($\rho = 0.623$, $p < 0.001$), and moderate inverse correlations with serum iron ($\rho = -0.613$, $p < 0.001$), TSAT ($\rho = -0.491$, $p < 0.001$), and haemoglobin ($\rho = -0.382$, $p < 0.001$). Hepcidin showed a strong positive correlation with ferritin ($\rho = 0.715$, $p < 0.001$) and moderate inverse correlations with serum iron ($\rho = -0.521$, $p < 0.001$), TSAT ($\rho = -0.467$, $p < 0.001$), and haemoglobin ($\rho = -0.408$, $p < 0.001$). The scatter plots illustrating these key relationships are presented in Fig. 3.

3.3 Dose-Response Relationship

A dose-response relationship was observed between CRP levels and anaemia parameters (Fig. 2). Patients with CRP ≥ 5 mg/L (n = 9) had significantly lower mean haemoglobin (10.2 vs 12.6 g/dL, $p < 0.001$), higher median hepcidin (52.8 vs 22.5 ng/mL, $p = 0.005$), and higher anaemia prevalence (100% vs 54.4%, $p = 0.023$) compared to patients with CRP < 5 mg/L (n = 79). This gradient effect supports a biological relationship between inflammation severity and anaemia.

3.4 Multivariable Regression Analysis

In the multivariable linear regression model adjusted for age, sex, and hepcidin, hepcidin was a highly significant independent predictor of haemoglobin ($\beta=-0.035$, 95% CI: -0.050 to -0.019 , $p < 0.001$), while the direct effect of CRP became non-significant ($\beta=-0.062$, 95% CI: -0.164 to 0.041 , $p = 0.24$). The model explained 54.2% of the variance in haemoglobin (Adjusted $R^2=0.542$). In the logistic regression model for anaemia, hepcidin remained a significant predictor (OR = 1.04 per ng/mL, 95% CI: 1.02–1.07, $p = 0.001$), while CRP was no longer significant after adjustment. Results are presented in Table 2.

Table 2
Multivariable Linear Regression Model Predicting Haemoglobin Concentration

Variable	β Coefficient	95% CI	p-value
CRP (mg/L)	-0.062	-0.164 to 0.041	0.24
Hepcidin (ng/mL)	-0.035	-0.050 to - 0.019	< 0.001***
Age (years)	-0.010	-0.032 to 0.012	0.36
Sex (Male)	0.92	-0.12 to 1.96	0.08
Model Adjusted $R^2 = 0.542$			
CI: confidence interval; CRP: C-reactive protein.			
*** $p < 0.001$			

3.5 Formal Mediation Analysis

The formal mediation analysis confirmed that hepcidin significantly mediated the relationship between CRP and haemoglobin (Table 3). The total effect of CRP on haemoglobin was significant ($c = -0.185$, 95% CI: -0.279 to -0.092 , $p < 0.001$). Path a (CRP $\rightarrow$ Hepcidin) was significant ($\beta = 3.59$, 95% CI: 2.44 to 4.74, $p < 0.001$), indicating that higher CRP was associated with higher hepcidin. Path b (Hepcidin $\rightarrow$ Haemoglobin, controlling for CRP) was also significant ($\beta = -0.035$, 95% CI: -0.050 to -0.019 , $p < 0.001$), indicating that higher hepcidin was associated with lower haemoglobin.

Table 3
Formal Mediation Analysis: CRP → Hepcidin → Haemoglobin

Path	Coefficient	95% CI	p-value
Total Effect (c)	-0.185	-0.279 to - 0.092	< 0.001***
Path a (CRP → Hepcidin)	3.59	2.44 to 4.74	< 0.001***
Path b (Hepcidin → Hb)	-0.035	-0.050 to - 0.019	< 0.001***
Direct Effect (c')	-0.062	-0.164 to 0.041	0.24
Indirect Effect (a×b)	-0.124	-0.197 to - 0.065†	< 0.001***
†Bootstrap 95% CI (1000 iterations)			
Sobel Test: Z = - 3.52, p < 0.001			
Proportion of total effect mediated: 66.8%			
CI: confidence interval; CRP: C-reactive protein; Hb: haemoglobin.			
***p < 0.001			

The indirect effect of CRP on haemoglobin via hepcidin was - 0.124, and the 95% bootstrap confidence interval did not contain zero (- 0.197 to - 0.065), confirming statistical significance. The Sobel test also confirmed significance (Z = - 3.52, p < 0.001). This indirect effect accounted for 66.8% of the total effect of CRP on haemoglobin. The direct effect (c') became non-significant when hepcidin was included in the model (β = -0.062, p = 0.24), consistent with substantial mediation. The mediation model is illustrated in Supplementary Figure S1.

4. DISCUSSION

This study provides the first quantitative evidence, to our knowledge, that the effect of systemic inflammation on anaemia in HS is substantially mediated by hepcidin. Our findings confirm the central role of the IL-6/hepcidin axis in the pathophysiology of anaemia of chronic disease in this patient population and have important implications for clinical management.

4.1 Principal Findings

We found that nearly 67% of the total effect of CRP on haemoglobin concentration was explained by the indirect pathway through hepcidin. When hepcidin was included in the regression model, the direct association between CRP and haemoglobin was no longer significant, reinforcing hepcidin's role as a powerful mediator. This finding has important mechanistic and therapeutic implications, suggesting that interventions targeting hepcidin or its upstream regulators may be effective in managing anaemia in HS patients.

4.2 Pathophysiological Interpretation

The observed associations are consistent with well-established conceptual frameworks of anaemia of chronic disease (5, 14). Chronic systemic inflammation in HS leads to sustained activation of inflammatory signalling pathways, clinically captured by elevated CRP concentrations (1, 15). This inflammatory milieu promotes hepatic hepcidin synthesis, primarily through IL-6-mediated STAT3 activation (6, 7, 16). Elevated hepcidin concentrations result in ferroportin downregulation on the surface of enterocytes and macrophages, leading to reduced intestinal iron absorption and impaired iron recycling from reticuloendothelial stores (5, 8, 17). Consequently, iron becomes sequestered despite adequate or increased total body iron stores, limiting its availability for erythropoiesis and resulting in reduced haemoglobin synthesis.

The strong correlation between hepcidin and ferritin ($p = 0.715$) observed in our study is consistent with the dual role of ferritin as both an iron storage protein and an acute-phase reactant. In inflammatory states, ferritin levels may be elevated despite functional iron deficiency, making it an unreliable marker of iron stores in HS patients (18). This underscores the importance of measuring hepcidin directly when assessing iron status in inflammatory conditions.

4.3 Clinical Significance

C-reactive protein proved to be particularly informative in this cohort as a marker of inflammation-associated anaemia risk. As a widely available, routinely measured, and inexpensive biomarker, CRP provides practical clinical utility for reflecting systemic inflammatory burden in HS patients. The dose-response relationship observed between CRP categories and anaemia parameters suggests that CRP may serve as a useful clinical tool for risk stratification and therapeutic monitoring. Clinicians should consider screening for anaemia in HS patients with elevated CRP levels.

Our findings also support the rationale for anti-inflammatory therapies in managing anaemia in HS. Biologic agents such as adalimumab, which is approved for HS treatment, have been shown to reduce inflammatory markers and may consequently improve anaemia outcomes (15). Future studies should evaluate the effect of anti-inflammatory therapies on hepcidin levels and anaemia in HS patients.

4.4 Comparison with Prior Literature

The findings of this study extend and complement prior investigations of anaemia in chronic inflammatory conditions. In rheumatoid arthritis, elevated hepcidin has been associated with anaemia severity, and anti-inflammatory therapy has been shown to improve anaemia outcomes (9, 19). Similarly, in chronic kidney disease, hepcidin dysregulation contributes to anaemia of chronic disease, and recent therapeutic strategies targeting hepcidin regulation have shown promise (10, 20). The current findings suggest that analogous mechanisms operate in hidradenitis suppurativa, supporting the therapeutic rationale for anti-inflammatory interventions to mitigate anaemia-related morbidity.

4.5 Limitations

Several important limitations warrant consideration when interpreting these findings. First, the cross-sectional design precludes assessment of temporal relationships and definitive causal inference

regarding the relationship between inflammation, hepcidin regulation, and anaemia development. Prospective longitudinal studies are required to establish causality. Second, the use of complete-case analysis may introduce selection bias if data missingness is related to unmeasured variables. Third, the overall sample size ($n = 88$) is modest, and the number of patients with markedly elevated CRP is particularly small ($n = 9$ with $\text{CRP} \geq 5 \text{ mg/L}$), limiting the statistical power to detect associations in high-inflammation subgroups.

Fourth, the cohort is predominantly male (81.8%), which is atypical for HS and may limit the generalisability of findings to female HS patients, who represent the majority of the HS population. Fifth, the dataset lacked several important variables that could provide additional mechanistic insights or allow adjustment for additional confounders, including disease duration and severity (Hurley staging), current medications, vitamin B12 and folate concentrations, renal and hepatic function markers, and direct cytokine measurements (IL-6, TNF- α). Finally, the mediation analysis assumes no unmeasured confounders of the mediator-outcome relationship, which cannot be verified in observational data.

4.6 Future Directions

Future research should address the limitations of the current study and extend our understanding of inflammation-driven anaemia in hidradenitis suppurativa. Prospective longitudinal studies incorporating repeated measurements of inflammatory markers, hepcidin, iron parameters, and haemoglobin would help establish temporal relationships. Comprehensive cytokine profiling including IL-6, TNF- α , and other pro-inflammatory cytokines would provide mechanistic insights. Interventional studies evaluating the impact of targeted anti-inflammatory therapies on iron homeostasis and anaemia outcomes are needed. Finally, population-based studies in diverse geographic and ethnic populations would improve generalisability.

5. CONCLUSION

In patients with hidradenitis suppurativa, C-reactive protein is a moderate and independent correlate of anaemia severity, demonstrating a dose-dependent relationship with both hepcidin concentrations and haemoglobin levels. Our formal mediation analysis provides strong statistical evidence that hepcidin mediates approximately two-thirds of the effect of CRP on haemoglobin, consistent with the established pathophysiology of anaemia of chronic disease. These findings highlight the clinical relevance of systemic inflammation in HS and support the importance of inflammation control as an integral component of comprehensive disease management to mitigate associated systemic complications, including anaemia. Future prospective studies are warranted to establish causality and to evaluate whether targeted anti-inflammatory interventions improve anaemia outcomes in this patient population.

Declarations

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CONFLICT OF INTEREST

The authors declare no conflicts of interest relevant to this work.

AUTHOR CONTRIBUTIONS

MA: Conceptualization, Funding acquisition, Writing – original draft. MBA: Methodology, Data analysis, Writing – review & editing. EB: Methodology, Writing – review & editing. AA: Data interpretation, Writing – review & editing. OAA: Writing – review & editing. NAQ: Clinical expertise, Writing – review & editing. SA: Writing – review & editing. MAS: Writing – review & editing. AAA: Writing – review & editing. All authors approved the final manuscript.

CLINICAL TRIAL NUMBER

Clinical trial number: not applicable.

ETHICS APPROVAL STATEMENT

This study was a secondary analysis of an anonymised, publicly available dataset previously published and approved by the original investigators. Formal institutional review board approval and informed consent were not required for this secondary analysis, as all data were de-identified and publicly available.

PATIENT CONSENT STATEMENT

Not applicable. This study involved secondary analysis of de-identified public data.

DATA AVAILABILITY STATEMENT

The dataset analysed in this study is publicly available in the Mendeley Data repository at doi:10.17632/9x4n84cxxw.2 and is freely accessible to researchers.

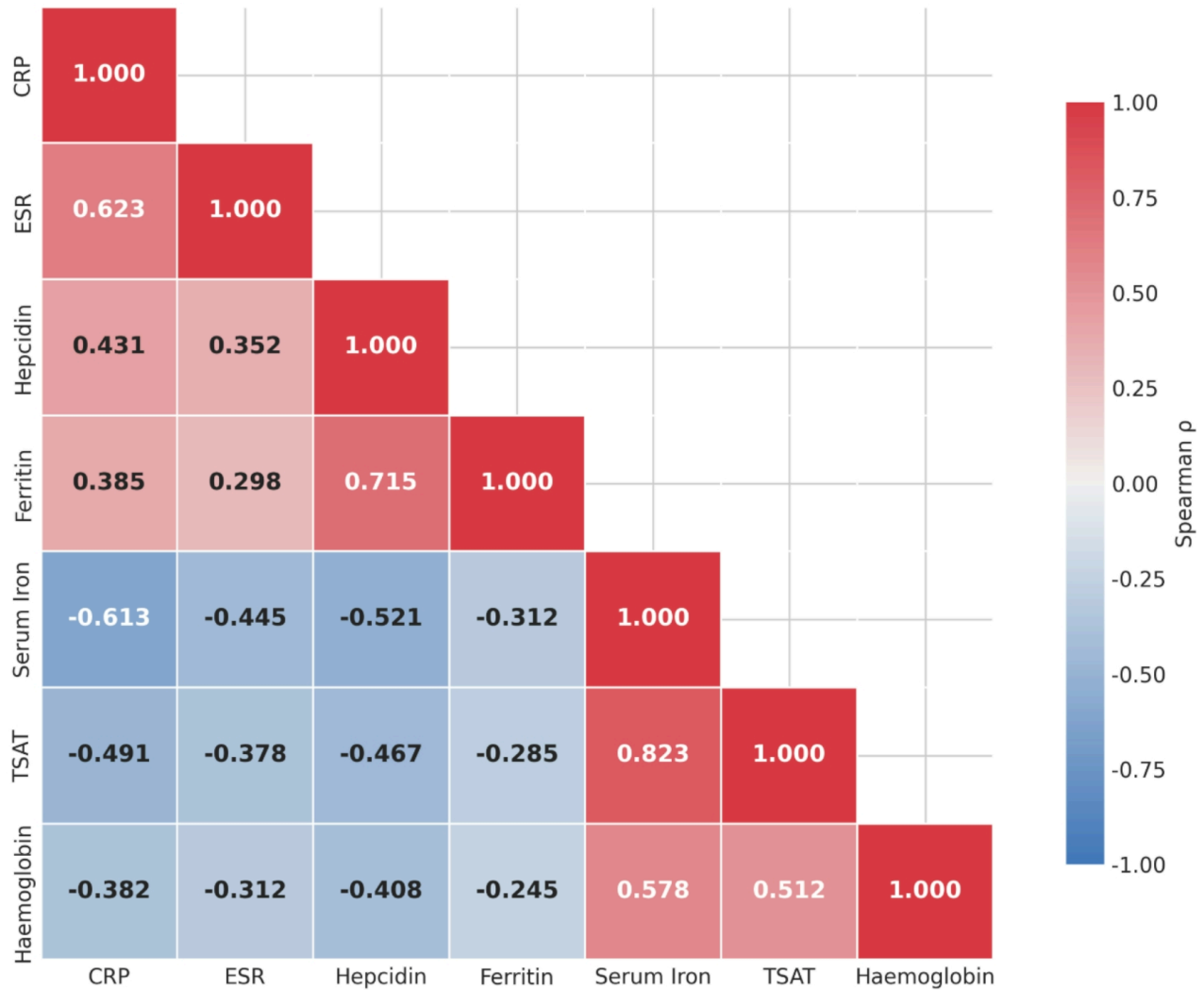
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Figures

Figure 1. Spearman Correlation Matrix of Inflammatory Markers, Hepcidin, Iron Status Indicators, and Haematological Parameters (n=88)



*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$
CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; TSAT: Transferrin saturation

Figure 1

Spearman Correlation Matrix of Inflammatory Markers, Hepcidin, Iron Status Indicators, and Haematological Parameters (n=88). The heatmap displays Spearman correlation coefficients (ρ) between variables. Positive correlations are shown in red, negative correlations in blue. CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; TSAT: transferrin saturation. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

Figure 2. Dose-Response Relationship Between C-Reactive Protein and Anaemia Parameters

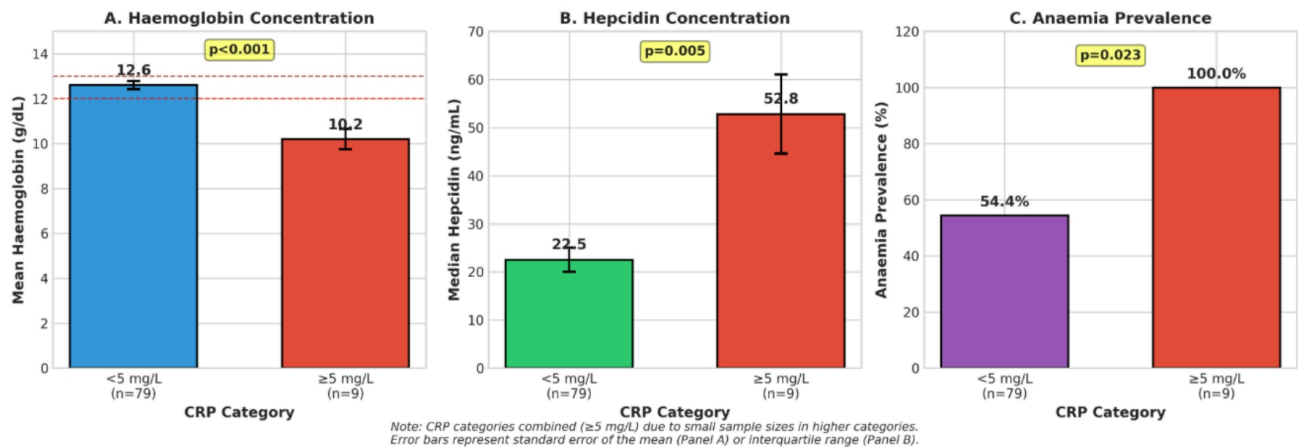


Figure 2

Dose-Response Relationship Between C-Reactive Protein Category and Anaemia Parameters. Panel A shows mean haemoglobin concentration, Panel B shows median hepcidin concentration, and Panel C shows anaemia prevalence across CRP categories (<5 mg/L vs ≥ 5 mg/L). Error bars represent standard error of the mean (Panel A) or interquartile range (Panel B). Dashed horizontal lines in Panel A indicate WHO anaemia thresholds (red: male <13 g/dL; orange: female <12 g/dL). Note: CRP categories were combined (≥ 5 mg/L) due to small sample sizes in higher categories.

Figure 3. Scatter Plots Demonstrating Relationships Between Inflammatory Markers, Hepcidin, and Haemoglobin in Hidradenitis Suppurativa Patients (n=88)

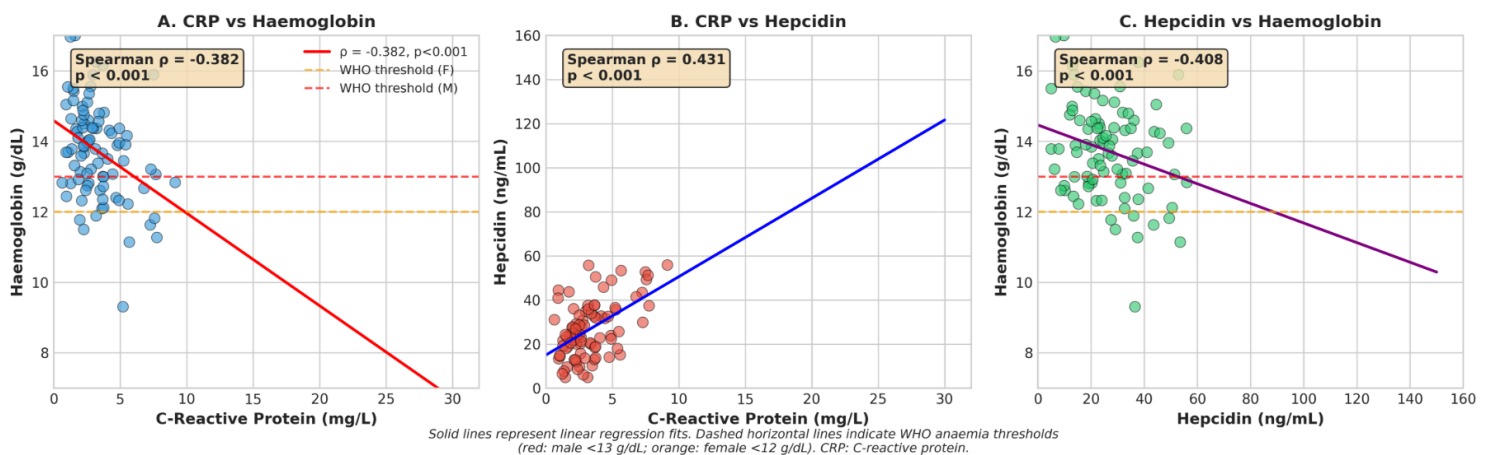


Figure 3

Scatter Plots Demonstrating Relationships Between Inflammatory Markers, Hepcidin, and Haemoglobin in Hidradenitis Suppurativa Patients (n=88). Panel A: CRP vs Haemoglobin ($\rho = -0.382$, $p < 0.001$). Panel B: CRP vs Hepcidin ($\rho = 0.431$, $p < 0.001$). Panel C: Hepcidin vs Haemoglobin ($\rho = -0.408$, $p < 0.001$). Solid lines

represent linear regression fits. Dashed horizontal lines indicate WHO anaemia thresholds (red: male <13 g/dL; orange: female <12 g/dL). CRP: C-reactive protein.

Supplementary Files

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