Original Article

Hepcidin as a Central Mediator of Anemia in Malaria: Interaction with IL-6, TNF-α, and Iron Stores

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Abstract

Background: Hemolysis, inflammatory activation, and poor iron control all contribute to anaemia, a frequent complication of malaria. Hepcidin is the main hormone that regulates iron in the body, and its extreme importance to the body is underscored by its response to cytokine signals and its regulation of the amount of available iron for red blood cell formation. This understanding can help explain why anemia worsens in some patients. Hypotheses: To investigate hepcidin's function in malaria-induced anaemia and its correlation with pro-inflammatory cytokines in circulation, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha), as well as markers of vital iron metabolism. **Material and Methods:** This was a cross-sectional study wherein 160 cases of laboratory-confirmed malaria were identified. Haemoglobin and erythrocyte indices were measured with the help of an automated analyser. Measures of hepcidin serum, IL-6, TNF-alpha, and IL-10 were measured using ELISA. Biochemical parameters to be examined included an analysis of iron in the bloodstream, using standard biochemical techniques, including monthly serum iron, ferritin, ferritin saturation, and total iron-binding capacity. We also observed the C-reactive protein and erythrocyte sedimentation rate. Correlation and group-comparison methods were used in the statistical analysis. **Results:** The mean Hb among participants was 8.9 g/dL ± 1.5, and a quarter of the cases met the criteria for severe anaemia. The hepcidin levels were also high, with a mean of 79.22 ± 20.6, compared with 92.52 ± 17.8 in severe anaemia ($p < 0.001$). Good positive correlations between IL-6 (69.4 ± 18.7 pg/mL) and TNF-69.447 pg/mL and hepcidin ($r = 0.73$ and 0.67, respectively; $p < 0.001$). There were significant reductions in serum iron (36.1 pmol/dl) and transferrin saturation (11.2 pmol/dmol/per cent), and no decrease in ferritin (548 pmol/dl). The increase in parasitemia is associated with decreased haemoglobin ($r = -0.55$, $p < 0.001$) and increased IL-6 ($r = 0.60$, $p < 0.001$). **Conclusion:** The findings reveal that hepcidin plays a role in the pathogenesis of malarial anaemia by reducing iron supply due to cytokine-mediated effects. The addition of hepcidin and inflammatory markers to routine analysis could improve the early diagnosis of individuals at risk of severe anaemia and guide clinical care.

Keywords: Hepcidin, Malarial anaemia, Iron metabolism, inflammatory cytokines, TNF- alpha Functional iron deficiency.

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Introduction

Malaria remains one of the leading health problems worldwide, particularly in regions where it propagates rapidly, and individuals are not able to access medical treatment easily. Malaria is a major concern for physicians, and anaemia is among the most common and serious side effects of the illness, even if fewer people are dying from it now than there were 20 years ago.[1] Malarial anemia is caused by intricate mechanisms that go beyond the breakdown of parasitised red blood cells. The reduction in haemoglobin levels is exacerbated by the spleen's early destruction of non-parasitised red blood cells, erythropoiesis, acute infection, and inflammatory processes that alter the body's iron distribution.[2,3] Hepcidin has recently attracted attention as a molecule linking inflammation, iron metabolism, and infection. Together with ferroportin, the primary iron-exporting protein on enterocytes and macrophages, hepcidin, a peptidoglycan hormone produced by the liver, controls blood iron levels. This facilitates the absorption and dissection of iron.[4] This measure reduces intestinal iron absorption and stores iron. The action defends against infections by reducing the amount of available iron for attackers. However, excessive hepcidin may induce or aggravate anaemia by preventing the utilisation of iron in the manufacture of red cells.[5]

The inflammatory response to malaria strongly influences hepcidin synthesis. A major expression controller of hepcidin production during infection is interleukin-6 (IL-6), which acts through the JAK-STAT3 pathway to potentiate hepatic hepcidin transcription.[6] Higher levels of IL-6 have been repeatedly reported in acute malaria. They are associated with decreased

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serum iron, defective erythropoiesis, and low transferrin saturation, features of functional iron deficiency rather than iron depletion.[7] Tumor necrosis factor-alpha (TNF-α), another crucial inflammatory mediator released during acute malaria, alone induces ineffective erythropoiesis, decreased red blood cell survival, and dysserythropoiesis in the bone marrow.[8] These cytokine-mediated mechanisms explain why mild parasitemia can be associated with severe anaemia. Ferritin, transferrin saturation, serum iron, and total iron-binding capacity are key indicators of iron status during malaria; however, because ferritin is an acute-phase reactant, it rises during inflammation independently of iron stores, complicating the interpretation of its response.[9] As a result, elevated ferritin, decreased serum iron, and low transferrin saturation are often due to sequestration of iron by inflammation, rather than deficiency. In the formation of this biochemical pattern, Hepcidin plays a very important role. The pathways of interaction between hepcidin and inflammatory cytokines can, in some ways, inform us about the aetiology of malarial anaemia and help us identify individuals likely to deteriorate. Further, it has been demonstrated that elevated hepcidin levels in malaria are associated with worse hemoglobin rescue and a delay in normal erythropoiesis, even after parasite clearance, in both children and adults.[10] This observation explains the clinical importance of explicating hepcidin-mediated pathways. Due to the global concern with the reduction of morbidity of malaria and its related complications, the discovery of reliable biomarkers capable of predicting the intensity of anaemia is an urgent clinical imperative. Measuring hepcidin along with IL-6, TNF-alpha, ferritin, and transferrin saturation can help improve the detection of the disease at a very early stage and inform patient management decision pathways. The paper aims to test the relationships between hepcidin and major inflammatory cytokines and indicators of iron metabolism in humans with acute malaria, and to understand the extent to which cytokine-induced increases in hepcidin affect both the onset and severity of malarial anaemia.

Materials and Methods

Study Design and Setting: The study was designed as a cross-sectional observational study aimed at establishing the relationship between hepcidin, inflammatory cytokines, and iron metabolism in individuals diagnosed with malaria. This was carried out at the Department of Biochemistry of Kakatiya Medical College, as well as with clinical departments of Pathology, general medicine, and Microbiology of MGM Hospital, Warangal, and the Pathology Department of Government Medical College, Kamareddy, Telangana. The institutions provide a significant source of referrals to the region, which helps to encourage the year-round admission of malaria patients. The period covered between 2023 and 2024 includes the high and low seasons of transmission to ensure that the sample reflects the clinical diversity of malaria cases encountered in routine practice.

Population and Eligibility of Study.

A sample of 160 patients with laboratory-confirmed malaria was used. Johns tested adult females of 18 years and above who reported the presence of febrile illness with signs of malaria and who took their peripheral blood smears and rapid antigen diagnostic tests. Individuals who tested positive with Plasmodium falciparum, Plasmodium vivax, or co-infections were considered qualified. Patients who had disorders known to affect iron metabolism or inflammatory markers, such as chronic liver disease, chronic kidney disease, a congenital hemoglobinopathy, or autoimmune disease, were not included. To eliminate confounding variables, participants were also not allowed to take part if they had a recent blood transfusion in the past 3 months, were pregnant, were taking iron supplementation or erythropoietin therapy, or had dengue or typhoid conditions. This choice allowed conducting a study on changes that were specific to malaria itself.

Client Check and Helminthic Examination.

All participants underwent a thorough clinical examination that included detailed history of the duration of fever, prior malaria episodes, past antimalarial use, dietary habits, and comorbidities. Physical exam findings, including pallor, jaundice, hepatosplenomegaly, hydration status, and vital signs, were recorded. Trained microbiologic personnel examined thick and thin Giemsa-stained blood films to determine the type and number of parasites present. To determine the density of parasites, we first multiplied the number of parasites in 200 leukocytes by 200 and 1 million, respectively. We then assign the levels of parasitemia to low, moderate, or high.

Collection and Processing of Samples.

Sample venous blood was collected with aseptic methods at the time of diagnosis of malaria, before the initiation of antimalarial therapy, to exclude the effects of treatment on the biochemicals. One hundred grams of blood were collected from each participant. Samples obtained in EDTA tubes were stored for haematological analysis, and those in plain vacutainers were used to obtain serum. Serum was spun at 3000 rpm for 10 minutes, followed by storage in sterile cryovials at -20O C until it is again testable. This was done at all steps, ensuring the right cold-chain conditions to safeguard the samples' safety.

Hematological Measurements

Complete blood counts were performed on an automated haematology analyser calibrated daily and periodically checked for quality control. The performed measurements were haemoglobin concentration, red cell count, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, red cell distribution width, total leukocyte count, differential leukocyte count, and platelet count. The World Health Organization (WHO) used its own criteria to classify anaemia into three severity levels: mild, moderate, and severe.

Iron Metabolism and Biochemical Parameters.

An automated chemical analyser with verified reagent kits was used for iron-related studies. Serum iron was measured using the ferrozine-colourimetric method, and the standardised colorimetric method was used to determine the total iron-binding capacity. The transferrin saturation was determined using serum iron and total iron-binding capacity. Serum ferritin was measured by immunoturbidimetric assay. Biochemical parameters were also analysed alongside the inflammatory

parameters, bearing in mind that ferritin is an acute-phase protein that typically rises in cases of infection.

Cytokine Assays and hepididin.

The levels of hepcidin, IL-6, TNF-α, and interleukin-10 in serum were measured using commercially available ELISA kits according to the manufacturer's instructions. Each sample, standard, and control was processed twice to ensure they were as close to true as possible. Microplates were incubated for the recommended time, then thoroughly washed in an automatic washer, and the optical densities were measured at 450 nm. Calibration curves for each analyte were prepared to determine serum levels. The differences among assays were maintained at acceptable levels.

Markers of inflammation: Inflammatory lab values.

Our high-sensitivity immunoturbidimetric technique measured C-reactive protein, and the rate of erythrocyte sedimentation was calculated using the Westergren technique. The indicators were added to better understand ferritin and hepcidin, as both are strongly influenced by systemic inflammation.

Ethical Considerations

The study received ethical approval from the Institutional Ethics Committee of Kakatiya Medical College, Warangal. All participants in the study were informed in their favourite languages about the nature of the research and how it would be conducted. They were also required to sign a written consent to join them. The privacy of the patients was preserved throughout, and all lab samples were anonymised and analysed thereafter.

Statistical Analysis

All the data were input into Microsoft Excel and then checked using SPSS version 26. It used mean and standard deviations to highlight continuous variables, and percentages to represent categorical variables. When applicable, we compared groups using one-way ANOVA or the independent t-test. To identify significant differences between subgroups, post hoc testing was used. Using Pearson correlation coefficients, we aimed to investigate the connections among hepcidin, cytokines, iron indicators, haemoglobin status, and parasite density. We further subjected ourselves to additional statistical modelling to identify independent variables that may explain the severity of anaemia. The p-value was considered significant below 0.05.

Results

Finally, 160 patients who met the requirements were included in the final analysis. The infection with Plasmodium falciparum caused the majority of the cases (59), establishing itself in 94 cases. Plasmodium vivax infection (37%, n = 59) had become the second most prevalent cause. Mixed infections comprised 4 percent (n= 7) of the cases. The mean age of the participants in the study was 34.8 years, and 61% (n = 98) were men. The pattern of malaria species distribution showed no significant difference between males and females (chi-square = 1.84, p = 0.39), indicating that sex was no longer a significant factor in the distribution of Plasmodium species among the enrolled subjects.

Hematologic Discoveries and Patterns of Anaemia

The average haemoglobin level was 8.9 ± 1.5 g/dL, indicating that the majority of individuals in the study were anaemic. According to WHO guidelines, 25% of patients (n = 40) were severely anaemic. Patients with Plasmodium falciparum infection had significantly lower haemoglobin levels than those with Plasmodium vivax infection (8.6 ± 1.4 g/dL vs. 9.3 ± 1.6 g/dL; p = 0.002). Changes in the red cell indices were also large. With severe anaemia, the number of RBCs was significantly lower, the RDW was considerably higher, and thrombocytopenia was highly evident. As the degree of parasitemia increased, haemoglobin decreased in a definite alternating fashion [Table 1]. The results demonstrated that parasitemia was negatively correlated with haemoglobin (r = -0.55, p < 0.001), indicating that the burden of parasitism markedly increased anaemia intensity.

Table 1: Results of blood tests performed on study participants

Parameter	Total (n=160)	Mild/Moderate Anemia (n=120)	Severe Anemia (n=40)	p-value
Hemoglobin (g/dL)	8.9 ± 1.5	9.4 ± 1.2	7.1 ± 0.6	<0.001
RBC count (million/µL)	3.28 ± 0.46	3.41 ± 0.39	2.87 ± 0.40	<0.001
Platelet count (×10⁹/L)	128 ± 46	139 ± 40	98 ± 34	<0.001
RDW (%)	15.9 ± 2.5	15.4 ± 2.1	17.5 ± 3.2	0.001

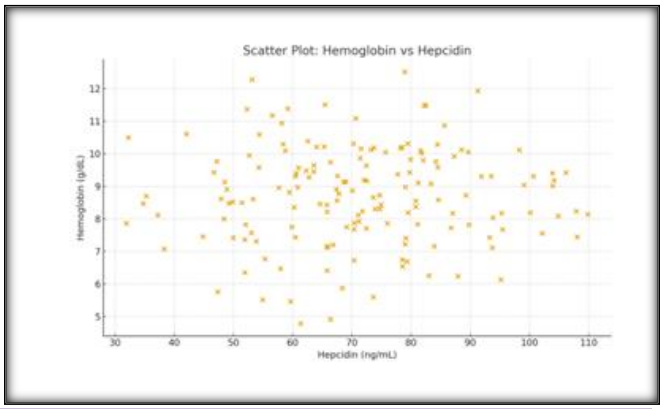

Figure 1: Negative correlation between hemoglobin & hepcidin

Iron Metabolism Parameters

Hepcidin levels in the study population were extremely high, with a mean of 79.2 ± 20.6 ng/mL. Hepcidin levels were significantly greater in severely anemic individuals compared to mildly or moderately anemic patients (92.5 ± 17.8 versus 74.3 ± 18.9 ng/mL, which is significant at p 0.001) [Figure 1]. Serum iron levels in severely anaemic patients were significantly lower, with a mean of 29.8 +/- 9.4 ug/dl, compared to mildly moderate anaemic patients, whose levels had a mean of 38.7 +/- 11.0 ug/dl (p < 0.001). There was a significant reduction in total iron-binding capacity, and transferrin saturation was significantly reduced in the severely anemic group. Ferritin levels rose considerably over the course of the cohort, and the highest

levels were observed in severe anemia [Figure 1& 2]. These findings indicate that iron sequestration is a result of inflammation rather than iron deficiency.

Johnson et al. (2002) reported a negative correlation between hepcidin and hemoglobin, just as [Figure 1] shows in our case.

Table 2: The iron metabolism parameters

Parameter	Mild/Moderate Anemia (n=120)	Severe Anemia (n=40)	p-value
Serum iron (µg/dL)	38.7 ± 11.0	29.8 ± 9.4	<0.001
TIBC (µg/dL)	251 ± 36	226 ± 41	0.003
Transferrin saturation (%)	11.9 ± 4.0	8.7 ± 3.4	<0.001
Ferritin (ng/mL)	521 ± 142	618 ± 161	<0.001
Hepcidin (ng/mL)	74.3 ± 18.9	92.5 ± 17.8	<0.001

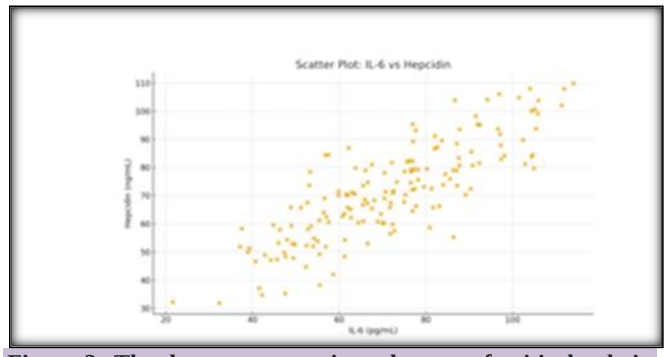

Figure 2: The data on comparisons between ferritin levels in groups differing by the degree of anemia.

Cytokine Profiles and correlation with Anemia.

There was a great improvement in the level of inflammatory cytokines among malaria patients. The mean IL-6 was 69.413 son. L. g/mL, and the means of TNF-A are 53.114 son. L. g/mL. The two cytokines had strong positive correlations with hepcidin (IL-6: r = 0.73, p < 0.001; TNF-ali: r = 0.67, p < 0.001) [Figure 3]. An anti-inflammatory cytokine, IL-10, showed a higher level, although it showed a lower correlation with hepcidin (r = 0.41, p < 0.001). The levels of C-reactive protein and ESR were consistently elevated, indicating an increased inflammatory response. There was a significant association based on the chi-square test (χ 2= 14.52, p < 0.001) between the high level of IL-6 and severe anaemia. This sanctions the assumption that anaemia is aggravated by the cytokine-induced inflammation [Table 3].

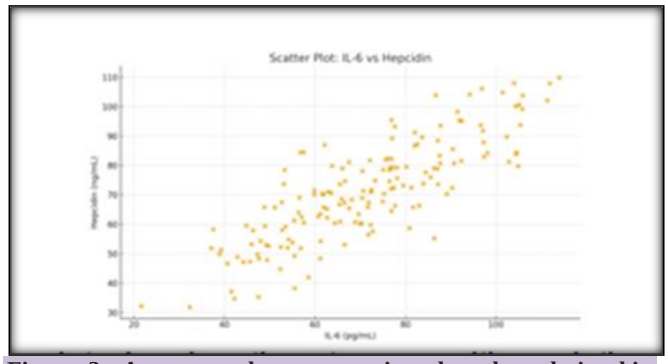

Figure 3: A scatter plot constructing that the relationship between IL-6 and hepcidin was found to be strongly positive.

Table 3: Cytokines & correlation hepcidin.

Marker	Mean ± SD	Correlation with Hepcidin (r)	p-value
IL-6 (pg/mL)	69.4 ± 18.7	0.73	<0.001
TNF-α (pg/mL)	53.1 ± 13.5	0.67	<0.001
IL-10 (pg/mL)	38.2 ± 12.6	0.41	<0.001
CRP (mg/L)	28.9 ± 10.7	0.46	<0.001

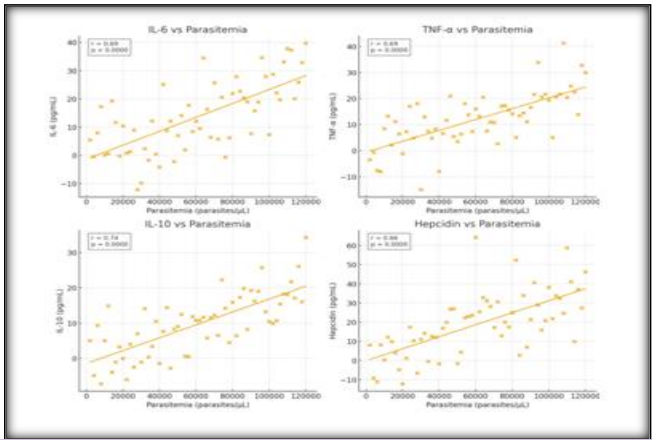

Figure 4: Multi-panel scatter plots of the relationships of cytokines and parasitemia.

Parasitemia and Trends of Biomarkers.

The various biochemical markers showed a consistent, clinically significant association with parasitemia. Those with high parasite density had significantly reduced haemoglobin levels, elevated iron indices, and reduced ferritin and hepcidin. As parasitemia intensity increased, IL-6 levels also increased gradually (r = 0.60, p < 0.001), indicating an inflammatory response. Parasitemia was found to have a double correlation with hepidin (r = 0.49, p = 0.001) [Figure 4]. The general conclusion from these findings is that the parasite burden suppresses inflammation, which, in turn, raises hepcidin levels and worsens anaemia through iron limitation and dysfunctional erythropoiesis.

Discussion

This study examined the relationships among iron metabolic

dysregulation, inflammatory cytokines, hepcidin, and the degree of anaemia in adult patients with malaria. The results have also shown that malaria-associated anaemia is a significant consequence of inflammation-induced disruption of iron homeostasis rather than only a consequence of hemolysis or red cell death. Raised hepcidin, together with highly raised IL-6 and TNF-α, was a consistent biochemical pattern in severe anaemic patients, highlighting the importance of the inflammatory environment in the pathogenesis of malaria anaemia.

In his research, hepcidin levels were significantly higher in individuals with severe anaemia than in those with mild or moderate anaemia. The results are consistent with previous research showing that hepcidin is a crucial downstream mediator of cytokine-mediated inflammation, namely IL-6, which initiates hepcidin synthesis in the liver via the JAK-STAT signalling pathway.[11] This strong relationship between IL-6 and hepcidin in this cohort is consistent with earlier studies suggesting that IL-6, which antagonises iron levels during acute malaria infection, is associated with hypoferremia and reduced red blood cell production.[12] The study's TNF-α increase corroborates the idea that inflammatory stress suppresses bone marrow activity and shortens erythrocyte lifespan, which in turn contributes to the sharp decline in haemoglobin seen in acute infections.[13]

This cohort of iron revealed the general distribution curve of iron loss due to inflammation. The serum ferritin and transferrin saturation levels were very low in very anaemic patients with elevated serum ferritin. Similar results were reported in malaria populations in Africa and Southeast Asia, suggesting that ferritin increase was an indicator of acute-phase responses rather than iron deficiency.[14,15] The isoelectric saturation of transferrin against a high level of ferritin can be considered as an indicator of functional iron deficiency. It is a time of iron that is available to undergo erythropoiesis, yet ferroportin is inhibited by hepcidin.[16]

This biochemical scenario was evident in this study, and it may be a reason why anaemia related to malaria can be extremely acute even in an iron-deficient person.

The observed relationship between parasite burden and anaemia severity is consistent with prior clinical studies showing that high parasitemia is associated with heightened inflammatory responses, elevated cytokine levels, and impaired erythropoiesis.[17] The researchers in the current study determined that positively correlated with parasitemia were IL-6 and hepcidin levels, and the haemoglobin levels were negatively correlated. This means that parasite biomass initiates an inflammatory response, elevating hepcidin levels and promoting hyperanemic complications. These compounds interplay to visualise the speed with which malaria causes anaemia and could result in further deterioration even after parasite clearance in the presence of high hepcidin levels.

The research findings have clinical value. Increased levels of hepcidin could delay the restoration of haemoglobin levels despite effective antimalarial therapy, as has been demonstrated in previous longitudinal studies.[18] This raises essential questions about when and how it is safe to administer iron to people residing in malaria-prone regions. Iron given at an inflammatory stage can be futile or harmful as it can be sequestered, but iron given at the convalescent stage can have superior advantages. Understanding the temporal dynamics of hepcidin can have important implications for clinical practice and health guidelines in the population.

Another important result of the present study is the presence of the anti-inflammatory cytokine IL-10, which showed a moderate increase but a comparatively weaker relationship with anaemia markers. This likely indicates an immunomodulatory response aimed at reducing excessive inflammation. This has previously occurred in mild and severe malaria.[19] However, the amount of IL-10 in this case could not counteract the strong pro-inflammatory effects of IL-6 and TNF-alpha, and, as a result, hepcidin remained significantly elevated in most cases.

Overall, the results of the present research support the argument that malaria anaemia is a complex disease with numerous causes, including parasite load, inflammatory cytokines, and iron metabolism. The relationship between inflammation, iron restriction, and the extent of anaemia became an important connection for hecidin. The data reveal that cytokine profiling is widely used for patients at risk of anaemia, thereby enabling focused monitoring. Longitudinal studies can provide better insight into hepcidin kinetics after treatment and inform strategies to maximise iron supplementation and erythropoietic recovery in patients with malaria.

Conclusion

This paper underlines the central position of hepcidin in the development of anaemia and progression in adults with malaria. The strong relationship among elevated hepcidin, elevated inflammatory cytokines, and reduced iron supply demonstrates the effects of inflammation on iron metabolism during acute infection. The ongoing elevated levels of IL-6 and TNF-α, and the dramatic declines in serum iron and transferrin saturation, despite increasing ferritin levels, point to functional iron deficiency as a significant contributing factor to malaria-related anaemia. The effects of parasite burdens on inflammation and hepcidin can demonstrate the complex and interactive nature of these pathways. The findings suggest that measuring hepcidin and cytokine levels, along with traditional haematological and iron markers, can help identify patients at increased risk of severe anaemia and support them more effectively. Future longitudinal studies could clarify the role of hepcidin in recovery and determine whether there is an opportunity to implement specific interventions to improve the demonstrated erythropoietic recovery after therapy.

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Conflicts of interest

There are no conflicts of interest.

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