# COMPLEMENT DYSREGULATION IN PEDIATRIC IRON DEFICIENCY ANEMIA

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**ABSTRACT**

**Introduction:** Complement proteins are key players in the innate immune system. Children with iron deficiency often experience impaired immunity, making them more prone to infections. This study aimed to measure serum levels of C3 and C4 complement proteins in children with iron deficiency anemia. **Methods**: The study included 50 children under 15 years old diagnosed with iron deficiency anemia, alongside 50 healthy controls. All participants underwent a comprehensive clinical assessment, complete blood count (CBC), and laboratory tests measuring serum ferritin, iron, total iron-binding capacity (TIBC), and complement proteins (C3 and C4). **Results:** Compared to the healthy controls, children with iron deficiency anemia showed significantly lower levels of ferritin, TIBC, hemoglobin (Hb), hematocrit (HCT), mean cell volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and red blood cells (RBC) count ($p < 0.05$). Additionally, serum complement proteins C3 and C4 were significantly reduced in the iron-deficient group ($p < 0.05$ and $p < 0.01$) respectively, suggesting impaired complement activation. Notably, neutrophil and monocyte counts were elevated in the iron-deficient group, indicating an altered immune response. **Conclusion:** The study revealed that serum levels of C3 and C4 complement proteins were significantly altered in children with iron deficiency anemia, potentially contributing to their increased susceptibility to infections.

**Keywords:** CBC, C3 Complement, C4 Complement, Iron Deficiency Anemia

## INTRODUCTION

Iron deficiency anemia (IDA) remains a significant global public health challenge, affecting individuals across all age groups. Its prevalence in pediatric populations is particularly noteworthy, given the potential for enduring consequences on growth, development, and long-term health outcomes (East et al., 2017). IDA in children is a widespread concern, undermining growth, development, and immune resilience, particularly through its impact on the complement system—a key player in pathogen clearance via components C3 and C4. Given the heightened vulnerability to infections in iron-deficient states, understanding these immune alterations is critical, especially in the context of emerging threats like COVID-19, where robust complement regulation is pivotal in shaping disease severity (Abdullah et al., 2024, Hamad et al., 2025).

Iron deficiency anemia is a pathological condition characterized by depletion of the body's iron stores, resulting in insufficient hemoglobin production, the oxygen-carrying protein in red blood cells (Mettananda and Williams, 2020, Sungkar et al., 2022). The clinical manifestations of iron deficiency and IDA do not necessarily correlate with the severity of the deficiency. In pediatric patients, common presentations may include non-specific symptoms such as fatigue, headache, palpitations, dizziness, dyspnea, and restless leg syndrome (Singh and Parihar, 2019). In addition to inducing long-term alterations in serotonin metabolism and dopamine receptor expression, IDA represents a critical public health issue with significant systemic and developmental implications. It compromises immune competence, thereby increasing the risk of infectious diseases and contributing to elevated morbidity and mortality, particularly in pediatric populations. Notably, children under two years of age with iron deficiency are at especially high risk of experiencing irreversible disruptions in brain development and growth trajectories (Zheng et al., 2021). In early life, inadequate iron availability can impair neurocognitive maturation and motor skill acquisition, potentially resulting in long-term functional deficits. Furthermore, IDA is associated with delayed physical growth, reduced exercise capacity and endurance, and poorer academic performance among school-aged children and adolescents (El-mansoury, 2020, Organization, 2023).

Three critical developmental periods elevate the risk of iron deficiency and IDA: the neonatal stage, preschool age, and adolescence, particularly in females due to heightened physiological demands, increased iron losses, and inadequate dietary intake (Donker et al., 2021). Iron deficiency arises when dietary intake fails to meet the body's iron requirements. Globally, a substantial proportion of individuals experience malnutrition, obesity, or depleted micronutrient stores, often resulting from limited access to nutrient-rich foods or malabsorption. This overlapping phenomenon is increasingly referred to as the "double burden of malnutrition (El-Shafie et al., 2020).

The progression of iron deficiency occurs in three stages as body stores are depleted: iron depletion, iron deficiency, and IDA. During the initial stage, iron stores are gradually depleted due to an imbalance between increased physiological demand and insufficient dietary intake. This reduction in iron reserves is typically marked by a decline in serum ferritin levels (Gerber, 2024). Iron deficiency is marked by depleted iron stores, impaired iron absorption insufficient to compensate for physiological losses, and reduced levels of serum ferritin, MCH, and MCV. IDA represents the most advanced stage, characterized by reduced iron content in RBCs, decreased MCV, MCH, and Hb concentrations, and decreased serum ferritin levels (Animasahun and Itiola, 2021).

The diagnostic utility of laboratory tests for detecting iron deficiency, such as MCV, serum ferritin, and transferrin saturation (Tf sat), is constrained by their susceptibility to interference from conditions like sickle cell disease, acute and chronic inflammatory states, and genetic polymorphisms, which compromise their sensitivity and specificity. In response, the World Health Organization (WHO) has recommended a panel of laboratory assays to assess population-level iron status (Animasahun and Itiola, 2021). Emerging evidence suggests that iron deficiency may be associated with impaired immune function, with studies indicating a correlation between the severity of deficiency and the extent of immunological and hematological disruptions. Additionally, alterations in serum complement levels have been observed in individuals with anemia (Mullick et al., 2006). The complement system has been shown to play a substantial role in various inflammatory processes, including sepsis, multi-organ failure, ischemia/reperfusion injury, cardiovascular diseases, and several other pathological conditions (Y Ismail et al., 2017). Given the high global prevalence of IDA, elucidating its impact on immune function is important. This study aimed to assess the serum concentrations of complement components C3 and C4 in children diagnosed with IDA

## METHODS

This case-control study was conducted at Raparin Teaching Hospital for Children in Erbil, Kurdistan Region, Iraq. The study enrolled 50 children under 15 years old with IDA, confirmed through clinical and laboratory evaluations, alongside 50 age-matched healthy controls. Serum levels of complement components C3 and C4 were evaluated in 50 patients diagnosed with IDA (characterized by hypochromic microcytic anemia) and 50 healthy control subjects.

The inclusion criteria for IDA cases in this study were defined as follows: (i) Hb levels <10 g/dL, (ii) MCV <80 fL, and (iii) serum ferritin levels <20 ng/Ml.

The exclusion criteria for cases included: (i) recent use of iron, other hematinic, or multivitamins within three months; (ii) history of acute or chronic blood loss; (iii) presence of acute or chronic infections at the time of

study; (iv) clinical evidence of malnutrition; (v) serum albumin levels <3.5 g/dL; and (vi) prior oral iron supplementation in the iron deficiency group.

The control group consisted of children who did not meet any of the aforementioned criteria for IDA.

An 8 mL venous blood sample was collected from each participant into EDTA-containing tubes. A two mL aliquot was used for CBC analysis using an automated hematology analyzer, while the remaining 6 mL was transferred to plain tubes. Serum iron and TIBC were quantified by spectrophotometry, and serum ferritin levels were measured using a mini VIDAS analyzer (e411, France). Serum C3 and C4 concentrations were determined via radial immunodiffusion (RID).

The criteria for identifying IDA in children were as follows:

- Anemia: Hb concentration <11 g/dL
- Hypochromic microcytosis: MCV <80 fL and MCH <27 pg
- Iron deficiency: serum ferritin <15 µg/L, serum iron <50 µg/dL, and TIBC >400 µg/dL.

**Ethical approval**: This research received ethical approval from two committees: Salahaddin University-Erbil's Human Research Ethics Committee (HREC) with reference number SU2025 HREC/38, and the Erbil General Directorate of Health Ethics Committee with approval number 13072025-8-19, dated August 30, 2025. Written informed consent was obtained from all participant parents before sample collection.

***Statistical Analysis***

Data were analyzed using Stata software, version 21 (Stata Corp, College Station, TX, USA). Descriptive statistics included frequencies and means ± standard deviations (SD). Bivariate analyses were conducted using t–tests, with $p \leq 0.05$ considered statistically significant.

## RESULTS

The mean age was 4.32 ± 2.79 years in the control group and 4.69 ± 2.55 years in the IDA group, with no significant difference observed between the groups ($p = 0.59$).

Table 1 reveals that children with IDA had significantly lower levels of ferritin, TIBC, Hb, HCT, MCV, MCH, MCHC, and RBC count than those in the control group ($p < 0.05$). In contrast, WBC count, MPV, PCT, and basophil levels showed no significant differences between the groups ($p = 0.4$). Eosinophil counts were significantly lower in the IDA group, while monocyte and neutrophil counts differed significantly ($p = 0.01$) compared to controls.

**Table 1: Hematological Parameters in Children with IDA and Control Group**

| **Hematology indexes** | **(IDA Means ± S.D)** | **Control (Means ± S.D)** | ***p*-value** |
|---|---|---|---|
| Hemoglobin (Hb) (g/dL) | 10.1167±1.63176 | 12.5083±.81849 | .000(HS) ** |
| HCT% | 31.9222±3.69858 | 38.1583±2.26051 | .000 (HS) ** |
| MCV (fL) | 70.3056±10.93507 | 80.2167±4.29245 | .006 (HS) ** |
| MCH (pg) | 22.4111±4.76740 | 26.2083±1.28449 | .012 (HS) ** |
| MCHC (g/dL) | 28.6000±2.26586 | 32.6500±.95394 | .042 (S) |
| RBC (x1012 /L) | 2.6033±.61864 | 4.7850±.31825 | .000 (HS) ** |
| TIBC (µg/dl) | 351.7±45.58 | 275.5 45.58 ±45.58 | .000 (HS) ** |
| PLT (x109/L) | 278.5556±91.67925 | 243.0833±81.30913 | .287 (NS) |
| MPVfL | 7.8111±.72020 | 7.8417±.83607 | .916 (NS) |
| PCT% | .2127±.06398 | .1923±.05957 | .387 (NS) |
| WBC (x109/L) | 8.8722±2.62091 | 8.2300±1.87764 | .471 (NS) |
| Neutrophils (%) | 54.7000±9.63431 | 42.1500±5.90123 | .000 (HS) ** |
| Lymphocytes (%) | 3.6900±2.29068 | 3.0700±1.13302 | .394 (NS) |
| Monocytes (%) | 10.0400±1.28274 | 8.4000±1.14891 | .001 (HS) ** |
| Eosinophil (%) | 2.3800±1.15677 | 6.8500±5.48345 | .002 (HS) ** |
| Basophil (%) | .1800±.02169 | .2000±.10445 | .434 (NS) |
| Granulocyte (%) | 3.7178±4.24118 | .5417±.13790 | .932 (NS) |
| Ferritin (ng/ml) | 31.3417±20.34394 | 59.0000 ±21.29874 | .001 (HS) ** |

*p*>0.05; NS: Non significant: **p*<0.05; S: Significant: ***p* <0.01; HS: Highly Significant, Hct= hematocrit; TIBC= total iron binding capacity; RBC=red blood cells; MCV=mean corpuscular volume; MCH= mean corpuscular hemoglobin; MCHC= mean corpuscular hemoglobin concentration.

The mean ± SD of serum C3 and C4 levels in children with IDA were 100.30 ± 18.34 mg/dL and 32.45 ± 8.61 mg/dL, respectively. In the control group, the corresponding values were 156.92± 49.96 mg/dL and 40.98± 13.41 mg/dL, respectively. Statistical analysis revealed significant differences in both C3 and C4 levels between the two groups ($p < 0.05$) and ($p < 0.0001$), respectively (Table 2).

**Table 2: Serum C3 and C4 Levels in Children with IDA and the Control Group**

| **Type of Complements** | **IDA Means ± SD** | **Control group Means ± SD** | ***p*-value** |
|---|---|---|---|
| C3 (mg/dl) | 100.3000±18.34379 | 156.9200±49.96630 | .050* |
| C4 (mg/dl) | 32.4500±8.61368 | 40.9800±13.41804 | .000** |

## DISCUSSION

The study findings indicated that age did not significantly influence the association with IDA, aligning with results from previous research (Afreen *et al.,* 2024). IDA has been correlated with multiple risk factors, including male sex, concurrent inflammatory states, and the 6–23-month age range. During this period, children experience heightened iron requirements as they transition from exclusive breastfeeding to complementary feeding, which may lead to inadequate nutrient intake, particularly in resource-limited settings where dietary iron sources are scarce (Chen et al., 2020, Oktarina *et al.,* 2024, Basrowi *et al.,* 2024).

IDA is the most prevalent micronutrient deficiency worldwide, affecting approximately 30% of the global population and up to 50% of individuals in low-income countries. This condition disproportionately impacts children aged 6 months to 2 years, representing a particularly vulnerable demographic (Organization and Organization, 2001). In developing countries, the prevalence of IDA among children under 4 years of age ranges from 46% to 66%. As a preventable condition, its burden can be mitigated through optimized nutritional strategies and iron supplementation interventions (Cilli *et al.,* 2024).

The current study revealed that children with IDA exhibited significantly reduced levels of ferritin, Hb, HCT, MCV, MCH, MCHC, and RBC count, whereas TIBC was elevated (Orsango et al., 2021).

According to Orsango *et al.* (2021), anemia was prevalent in 32% of children, with IDA accounting for 25% of these cases (Orsango *et al.,* 2021). Iron deficiency is estimated to contribute to approximately 25% of anemia cases in young infants, underscoring its significant role as a preventable cause of anemia in this vulnerable age group (Gedfie *et al.,* 2022, Orsango *et al.,* 2021). In children aged 1–10 years, microcytosis is diagnosed when the MCV falls below the calculated threshold, calculated as 70 fL + age (years). For adults and children over 10 years, an MCV value below 80 fL indicates microcytosis. A combination of low MCV and elevated red cell distribution width (RDW) is a useful indicator of iron deficiency (Hoffman *et al.,* 2022, Aksu and Ünal, 2023).

A decrease in serum ferritin concentration reflects depleted iron stores and serves as an early indicator of iron deficiency. Specifically, iron deficiency is defined by a ferritin level below 12 ng/mL in children under 5 years and below 15 ng/mL in individuals over 5 years (Organization, 2020, Mei *et al.,* 2023). IDA is characterized by microcytosis and hypochromia, as evidenced by reduced values of MCV, MCH, and MCHC, reflecting diminished hemoglobin synthesis and smaller, paler red blood cells (Gedfie *et al.,* 2022). Additionally, iron deficiency anemia is associated with a decreased reticulocyte count or reticulocyte production index, indicating impaired erythropoiesis, as well as reduced hemoglobin A2 levels and a low RBC count. There is typically an elevated RDW, reflecting increased variability in red cell size (anisocytosis), and often a compensatory thrombocytosis (Gedfie *et al.,* 2022). According to statistical research, the prevalence of IDA was extremely high (91.32%) in relation to iron status indicators. The dual burden of the condition and its management complicates the regular monitoring of hematological indices, including serum ferritin and CBC, necessitating a more targeted approach (El-Shafie *et al.,* 2024).

In clinical practice, IDA is often provisionally diagnosed through a combination of clinical presentation, dietary assessment, and a peripheral blood smear revealing microcytic, hypochromic anemia with anisopoikilocytosis (Chandra *et al.,* 2022). IDA is characterized by the classic triad of reduced MCH, MCHC, and MCV for age, reflecting microcytosis and hypochromia (Chandra *et al.,* 2022).
When serum ferritin levels are ambiguous, further evaluation of iron status may involve assessing serum iron, transferrin saturation, and TIBC. Both IDA and latent iron deficiency are characterized by reduced serum iron concentrations, reflecting depleted iron availability for erythropoiesis (Chandra *et al.,* 2022). Kazim *et al.,* observed that in their pediatric cohort, serum ferritin levels were below 12 ng/ml in children with anemia, suggesting that serum ferritin is a valuable diagnostic marker for IDA in adults. However, further research is needed in this specific population to establish the correlation between IDA and IDA in children under five years. They concluded that the diagnosis of IDA typically relies on a combination of CBC parameters and low serum ferritin levels. Serum ferritin concentration is considered

the most precise indicator of depleted iron stores and serves as an early marker of iron status, particularly when used in conjunction with complementary iron assessment tests. Measuring serum ferritin has limitations, as levels can be elevated in the context of acute or chronic inflammation, complicating the assessment of iron status. Importantly, such elevations do not indicate adequate iron stores or rule out iron deficiency (Kazmi *et al.,* 2017).

In the current study, children with IDA exhibited significantly lower levels of complement C3 and C4 ($p < 0.05$) compared to healthy controls. These findings align with previous research indicating a positive correlation between serum iron, ferritin, and complement C3 and C4 levels. It is suggested that deficiencies in C3 and C4 may disrupt normal iron metabolism, potentially influencing iron distribution and utilization pathways. Iron is an essential trace element in the body, and its homeostasis is critical for optimal immune function. The complement component C3, a central point of convergence for the three major complement activation pathways, plays a significant role in shaping innate immune responses (Wen e*t al.,* 2021). Iron is key for the proliferation of immune cells, their maturation, and for mounting an effective, specific response to infections (Das *et al.,* 2014). Iron plays a pivotal role in immune cell surveillance, particularly in lymphocytes, as it supports cellular differentiation and growth stimulation. It is also a critical component of enzymes involved in DNA synthesis, making the proliferative phase of lymphocyte activation highly iron-dependent. IDA may thus impair this phase, altering the expression of cell markers and potentially reducing T-cell proliferation. Iron deficiency impairs CD4+ lymphocyte function, thereby hindering immune responses to various pathogens. Additionally, iron restriction can downregulate key intracellular signaling processes, including protein kinase C activity, phosphatidylinositol-4,5-bisphosphate hydrolysis, and subsequent pathways essential for T-cell activation (Aly *et al.,* 2018).

Iron is a critical component of enzymes involved in the production of nitric oxide and reactive oxygen species (e.g., peroxide), which are essential for proper immune cell function. Additionally, iron influences cytokine production by modulating second-messenger signaling pathways, thus shaping immune responses (Aly *et al.,* 2018).

Iron is vital for monocyte-macrophage differentiation, thereby influencing cellular immune mechanisms. In contrast, humoral immunity appears less susceptible to iron depletion. The host's iron regulatory mechanisms, including genes and proteins that modulate iron availability, restrict iron acquisition by invading bacteria, thereby impeding their proliferation. Furthermore, innate immune cells such as monocytes, macrophages, and lymphocytes mediate systemic iron homeostasis through hepcidin-ferroportin axis, limiting iron flux into bacterial cells and contributing to nutritional immunity (Aly *et al.,* 2018). Additionally, various effector molecules—including heme oxygenase, toll-like receptors, hypoxia-inducible factor-1 (HIF-1), and NF-κB—orchestrate the inflammatory response by modulating cytokines, chemokines, reactive oxygen species, and nitrogen species. These mediators can induce shifts in iron

distribution, leading to either iron sequestration or overload, potentially impairing cellular defense mechanisms against bacterial infections. Iron significantly influences antimicrobial host defenses through dual mechanisms: it directly modulates immune cell proliferation and antimicrobial effector pathways, and it synergizes with immune mediators to enhance production of antimicrobial radicals. Consequently, the host immune system, via cytokine signaling, regulates iron availability to restrict microbial access, shaping the nutritional environment against pathogens (Aly *et al.,* 2018).

IDA can weaken the immune system, increasing susceptibility to bacterial infections. *Salvadora persica* (Miswak) and *Syzygium aromaticum* (Clove) extracts, with their proven antimicrobial properties (Shareef et al., 2023), offer a potential complementary approach to reduce infection risk. Their bioactive compounds may help combat pathogens, supporting oral and systemic health. Further research could explore their role in managing infections linked to IDA.

## CONCLUSION

Addressing IDA in children could involve screening for low complement levels (C3, C4) to identify those at higher risk of infection. Supplementing with iron might help restore complement production and enhance immune resilience, but it's crucial to monitor responses and consider individual patient factors. Further research could clarify optimal supplementation strategies and intervention thresholds.

**Conflicts of Interest**

The authors declare no conflicts of interest.

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