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# The influence of genetic variants of *IL-6 (-174 G/C)* and *INFγ (+874 A/T)* and their impact on anemic Sudanese children with kidney failure

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## Abstract

**Objectives** To investigate the influence of genetic variants IL-6 (-174 G/C) and interferon-gamma (IFNγ) (+874 A/T) on beta-globin gene expression, inflammation markers such as C-reactive protein (CRP), and their diagnostic impact on anemic Sudanese children with kidney failure.

**Results** Severe and moderate anemia were observed in 88.9% of children aged 5–15 years. Semi-quantified molecular analysis of allele-specific genomic content (Lane%) revealed a correlation with disease severity. For interferon-gamma (+874 A/T), the AA genotype expressed the highest beta-globin gene Lane% value (5.22 ± 2.15), with beta-globin gene expression showing diagnostic utility at an area under the curve (AUC) of 0.646 (95% confidence interval (CI): 0.472–0.820). For IL-6 (-174 G/C), the CC genotype exhibited the highest Lane% value (5.82 ± 2.34), and Lane% content was more diagnostic compared to beta-globin gene expression, with an AUC of 0.715 (95% CI: 0.471–0.959). C-reactive protein showed significant diagnostic value as a marker of inflammation, with AUC values for interferon-gamma at 0.618 (95% CI: 0.443–0.793) and IL-6 at 0.663 (95% CI: 0.502–0.823). These findings highlight the role of IL-6 and interferon-gamma genetic variants in the severity of anemia and their diagnostic potential in children with kidney failure.

**Keywords** Anemia, β-globin mRNA expression, C-reactive protein (CRP), End-stage kidney disease (ESKD), Erythropoietin-stimulating agents (ESAs), Genetic variants

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## Introduction

End-Stage Kidney Disease (ESKD) is a major clinical condition frequently complicated by Anemia of Chronic Disease (ACD), primarily driven by insufficient erythropoietin production. To manage this anemia, erythropoietin-stimulating agents (ESAs) are the recommended therapy. However, a subset of patients demonstrates hypo-responsiveness, defined as the inability to achieve target hemoglobin levels despite receiving high doses of ESAs. This phenomenon is strongly linked to underlying inflammation, which disrupts erythropoiesis and iron metabolism [1, 2].

Pro Inflammatory cytokines such as *Interleukin-6* (*IL6*) and *Interferon-gamma* (*IFN* γ) play pivotal roles in this inflammatory milieu. Genetic variants in these cytokines influence their transcriptional regulation, cytokine release, and subsequent therapeutic responses to ESAs [2 3]. Among these, the *IL6* (-174 G/C) and *IFN* γ (+874 A/T) promoter variants have been implicated in systemic inflammation and the dysregulation of erythropoiesis. Specifically, the +874 T allele of *IFN* γ is associated with heightened transcriptional activity, while the *IL6* G/C variants significantly modulates *IL6* expression levels, exacerbating the inflammatory state and contributing to ACD [4, 5].

Markers such as β-globin mRNA expression and C-reactive protein (CRP) levels serve as key indicators of inflammation and therapeutic response in patients with ESKD [6, 7]. These biomarkers provide critical insights into the underlying pathophysiological mechanisms and may guide the optimization of treatment strategies.

This study evaluates the influence of *IL6* (-174 G/C) and *IFN* γ (+874 A/T) genetic variants on treatment outcomes and inflammatory status in 45 anemic Sudanese children with ESKD undergoing hemodialysis. We hypothesize that these genetic variants impact anemia management by modulating inflammatory pathways, potentially necessitating adjunctive anti-inflammatory therapies and tailored rHuEPO dosing strategies, particularly in cases with elevated CRP levels [7].

## Materials and methodology

### Study design

This study was a prospective, observational cross-sectional analysis conducted across three teaching hospitals in Khartoum State: Soba University Hospital, Gaafar Ibn Ouf Children's Hospital, and Omdurman Children's Hospital 'Mohammed Elamin Hamid'. The study spanned from January 2019 to February 2020.

### Participants

The study included anemic Sudanese children aged 2–15 years with hemoglobin levels ≤ 11.0 g/dl, diagnosed with end-stage kidney disease (ESKD), and undergoing regular hemodialysis. Children with hemoglobin levels ≥ 12.0 g/dl, congenital hemoglobinopathies, or cancer-associated anemia were excluded. Participants were admitted to specialized nephrology and dialysis units and monitored for six months following treatment. Informed written consent was obtained from participants' guardians, and ethical approval was secured from the Research Ethics Committee (REC) of the Ministry of Health, Khartoum State.

### Pharmacological treatment

Treatment involved administering erythropoietin-stimulating agents (Epoetin beta, Recormon® 4000 IU/ml) at a dose of 150 units/kg/week [1] along with intravenous iron sucrose (100 mg/ml). Dosage adjustments were made following the guidelines of the UK Kidney Association (UKKA), which aligns with the National Institute for Health and Care Excellence (NICE) guidelines for anemia management in chronic kidney disease (CKD) in children, adolescents, and adults [8].

### Study design and area

The study employed a prospective, observational cross-sectional design, conducted over a one-year period. A total coverage sampling technique was utilized, enrolling 51 children diagnosed with ESKD who were receiving hemodialysis and recombinant human erythropoietin (rHuEPO). Six participants were excluded due to rural relocation, preparation for kidney transplantation, or death. A control group was not included due to ethical concerns and the difficulties of obtaining blood samples from healthy children.

### Sample size and statistical methods

A power analysis was conducted to confirm that the sample size provided 80% statistical power with a significance level of 0.05, ensuring reliable detection of significant differences and correlations. Statistical analyses were performed using SPSS version 16.0. Methods included multiple regression analysis and descriptive statistics (mean ± standard deviation, frequencies, percentages). Odds ratios (OR) with 95% confidence intervals (CI) were calculated where applicable.

The following analyses were applied:

- **Marginal Homogeneity Test**: Compared hemoglobin categories at the first and sixth months of follow-up.
- **ANOVA and Fisher's Exact Test**: Compared genetic lane content and mRNA genetic expression across groups, with Fisher's test applied when expected frequencies were < 5.
- **Receiver Operating Characteristic (ROC) Curves**: Plotted true positive versus false positive rates for

Lane content of polymorphisms, β-globin mRNA expression, and C-reactive protein (CRP) levels.

### Laboratory procedures

#### *Complete blood count (CBC)*

CBC was performed monthly for six months, targeting a hemoglobin level of 11.0–12.0 g/dl per NKF-KDOQI guidelines. Anemia severity was classified using WHO criteria [9]:

- **Severe**: Hb < 7.0 g/dl.
- **Moderate**: Hb 7.0–9.9 g/dl.
- **Mild**: Hb 10.0–11.4 g/dl (children aged 5–11 years).

Participants were divided into two age groups: 6–59 months and 5–15 years. Peadiatrics units care is provided up to 15 years old.

#### *Molecular analysis of inflammatory cytokines*

Genetic analysis of *IFN* γ (+ 874 A/T) and *IL6* (-174 G/C) variants was performed using Amplification Refractory Mutation System Polymerase Chain Reaction (ARMS-PCR) [10]. PCR products were separated via electrophoresis and analyzed using Totallab software version 1.0.1 [11]. Data on primer sequences and PCR conditions are available in the Supplementary file.

### β-Globin mRNA analysis

Quantification of β-globin mRNA expression was conducted using reverse transcription PCR (RT-PCR). The relative expression was calculated using the 2^-ΔΔCt method, with values ranging from 1.2 to 5.3.

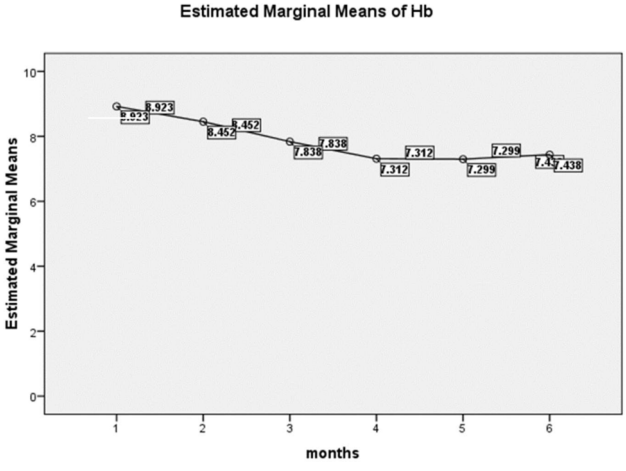


**Fig. 1** Trends in hemoglobin levels: estimated marginal means of hemoglobin (Hb) levels over the six-month follow-up period in Sudanese children with end-stage kidney disease (ESKD) undergoing treatment with erythropoietin-stimulating agents (ESAs)

### C-reactive protein (CRP) analysis

CRP levels were measured using a semi-quantitative latex slide agglutination assay, employing a two-fold dilution process for enhanced precision [12]. Details and more information of methodology is provided in supplementary file.

### Inclusion and exclusion criteria

- **Inclusion Criteria**: Anemic children ≤ 15 years with hemoglobin levels ≤ 11.0 g/dl and a confirmed diagnosis of ESKD.
- **Exclusion Criteria**: Children with hemoglobin levels ≥ 12.0 g/dl, congenital hemoglobinopathies, cancer-associated CKD, or treatments interfering with iron uptake [13].

## Results

Despite the administration of Erythropoietin-Stimulating Agents (ESAs), anemia persisted among the studied Sudanese children with ESKD, with severity ranging from moderate to severe, as depicted by the estimated marginal means of hemoglobin levels (Fig. 1). This persistence highlights the need for further investigation into the role of genetic variants in pro-inflammatory cytokines, *Interferon-gamma* (*IFN*γ), and *Interleukin-6* (*IL6*), on treatment response.

### INFγ and β-globin gene expression

The *INFγ* TT genotype was the most common (37.8%) among the participants. The AA genotype exhibited the highest genomic content (Lane % = 5.22 ± 2.15), whereas the TT genotype demonstrated the highest mean β-globin gene expression (3.31 ± 1.10), as detailed in Table 1. However, statistical analysis revealed no significant differences in genomic content or β-globin expression across *INFγ* genotypes ($P = 0.079$ and $P = 0.291$, respectively).

### IL-6 and β-globin gene expression

The *IL6* GC genotype was the most prevalent (53.3%), with the highest β-globin expression (2.98 ± 0.96). The CC genotype exhibited the highest genomic content (Lane % = 5.82 ± 2.34). Similar to *INFγ*, no significant differences were observed in β-globin expression between the *IL6* genotypes ($P = 0.197$ and $P = 0.638$, respectively), as shown in Table 1.

### ROC analysis

Receiver operating characteristic (ROC) analysis revealed that genomic content (Lane %) was a stronger diagnostic marker for *IFN* γ (AUC = 0.646) and *IL6* (AUC = 0.715) in relation to β-globin gene expression. In comparison, CRP demonstrated significant diagnostic values (AUC = 0.618

**Table 1** Genotypic distribution and Mean values: frequency, genomic content (Lane %), and β-globin gene expression levels (2^-ΔΔCt) for Interferon-gamma (*IFNγ*) and Interleukin-6 (*IL6*) genotypes in Sudanese children with end-stage kidney disease (ESKD)

| Genotype | Frequency (%) | Genomic content (Lane %)(Mean ± SD) | Sig.(genomic content) | β-globin gene expression (2^-ΔΔCt) | Sig.(β-globin expression) |
|---|---|---|---|---|---|
| IFγ AA | 28.90% | 5.20 ± 2.10 | 0.079 | 2.70 ± 1.00 | 0.291 |
| IFγ TA | 33.30% | 3.70 ± 1.40 | | 2.80 ± 0.80 | |
| IFγ TT | 37.80% | 4.50 ± 1.50 | | 3.30 ± 1.00 | |
| IL-6 GC | 53.30% | 4.30 ± 1.60 | 0.197 | 2.90 ± 0.90 | 0.638 |
| IL-6 CC | 11.10% | 5.80 ± 2.30 | | 3.40 ± 1.00 | |
| IL-6 GG | 35.60% | 4.20 ± 1.70 | | 2.80 ± 1.10 | |

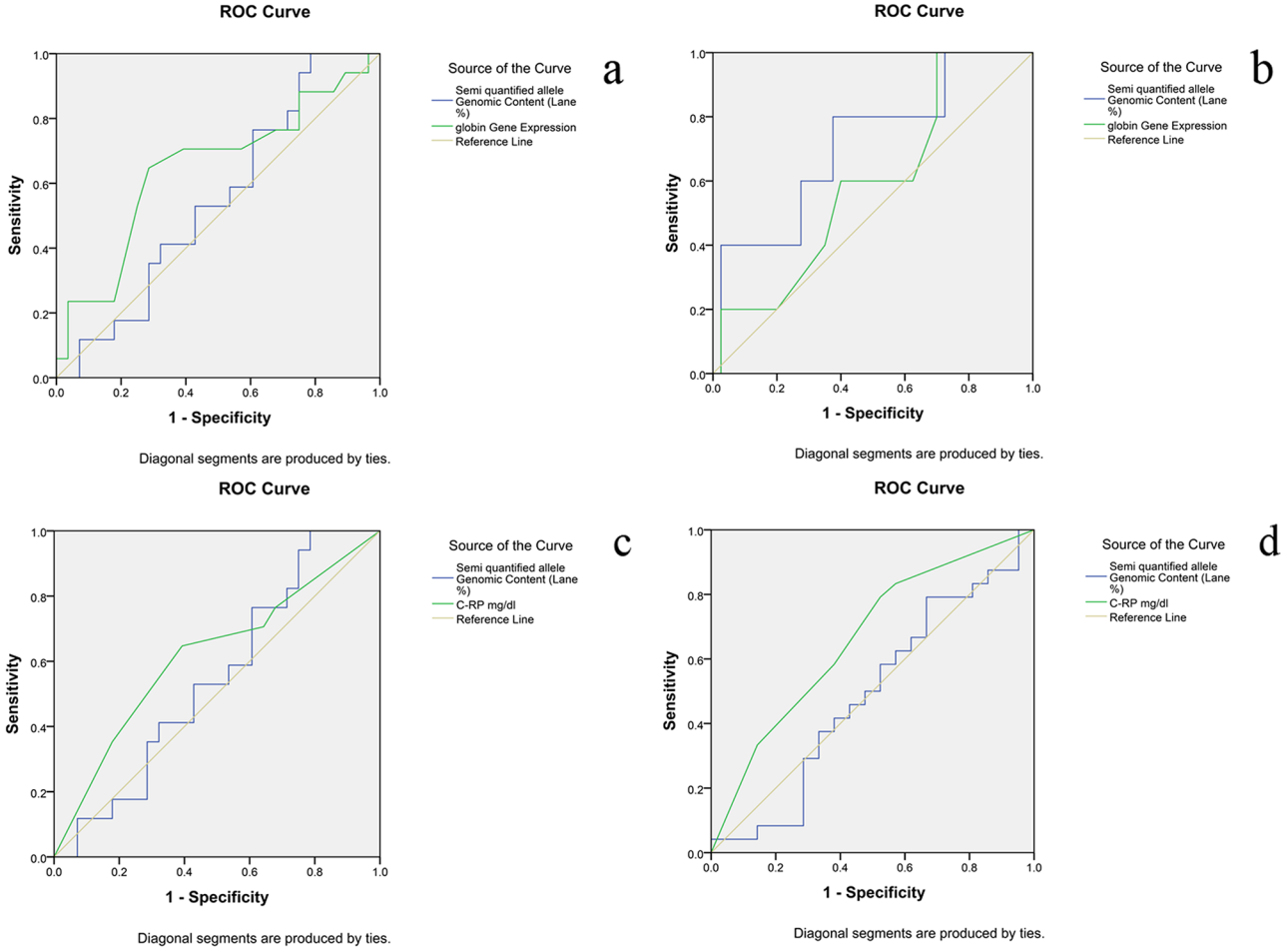


**Fig. 2** Receiver operating characteristic (ROC) curves for diagnostic markers. (**a**) Genomic content (Lane %) and β-globin gene expression versus *IFNγ* polymorphisms. (**b**) Genomic content (Lane %) and β-globin gene expression versus *IL6* polymorphisms. (**c**) Genomic content (Lane %) and CRP (mg/dl) versus *IFN γ* polymorphisms. (**d**) Genomic content (Lane %) and CRP (mg/dl) versus *IL6* polymorphisms. The gray-yellow line indicates the reference line (AUC = 0.5). The green line indicates the semi-quantified allele genomic content (Lane %). The blue line indicates the CRP (mg/dl). Axes Labels: X-axis: Specificity(False Positive Rate). Y-axis: Sensitivity(True Positive Rate). Each curve demonstrates diagnostic performance in distinguishing inflammatory and genetic profiles of Sudanese children with ESKD

for *IFN* γ and AUC = 0.663 for *IL6*) relative to genomic content, as illustrated in Fig. 2.

Table 2 summarizes the diagnostic performance of various markers analyzed through receiver operating characteristic (ROC) curves. The area under the curve (AUC) values, along with their 95% confidence intervals, provide insights into the discriminatory ability of each marker. These findings reveal that β-globin expression, particularly in the context of IL6 polymorphisms, demonstrates superior diagnostic capabilities compared to CRP levels. The data support the exploration of β-globin expression as a more reliable marker in this clinical setting.

**Table 2** Diagnostic performance of markers based on receiver operating characteristic (ROC) analysis

| Diagnostic marker | AUC | 95% CI lower | 95% CI upper | Interpretation |
|---|---|---|---|---|
| β-globin expression (IFNγ) | 0.646 | 0.472 | 0.82 | Fair discrimination |
| β-globin expression (IL6) | 0.592 | 0.471 | 0.959 | Poor discrimination |
| CRP levels (IFNγ) | 0.618 | 0.443 | 0.793 | Fair discrimination |
| CRP levels (IL6) | 0.663 | 0.502 | 0.823 | Fair discrimination |

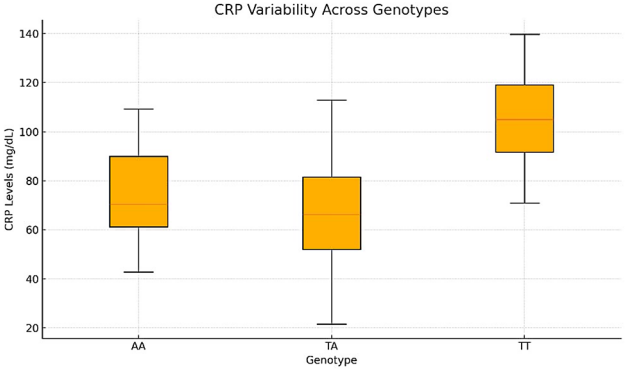


**Fig. 3** C-reactive protein (CRP) levels across different genotypes. The box plot show cases the variability in CRP levels across genotypes (AA, TA, TT): Median line in each box represents the central tendency (median) of CRP levels. Boxes illustrate the interquartile range (IQR), showing the spread of the middle 50% of the data. Whiskers extend to the data points within 1.5 times the IQR. Outliers (dots beyond whiskers) highlight extreme CRP values within each genotype. This plot emphasizes the wider variability in CRP levels for the TA and TT genotypes, with TT showing both higher median and overall CRP levels

### C-reactive protein (CRP) levels across different genotypes

Figure 3 illustrates the variability in C-reactive protein (CRP) levels across different genotypes (AA, TA, and TT). The median CRP levels and interquartile ranges demonstrate significant variation among the genotypes.

- •The AA genotype exhibits a moderate range of CRP levels, with a median close to 70 mg/dL and variability extending from approximately 50 to 100 mg/dL.
- •The TA genotype shows a similar distribution pattern but with slightly lower variability compared to the AA genotype.
- •The TT genotype demonstrates the highest CRP levels, with a median exceeding 90 mg/dL and variability ranging up to 140 mg/dL.

This trend suggests that the TT genotype is associated with a more pronounced inflammatory response, as indicated by elevated CRP levels. These findings highlight the potential role of genotype-specific inflammatory markers in understanding disease progression and treatment responses. Further statistical analysis is required to confirm the significance of these observations.

### Correlation analysis

Weak negative correlations were identified between genomic content (Lane %) and both β-globin expression and CRP levels for *IFNγ* and *IL6* genotypes. However, these correlations were statistically insignificant ($P > 0.05$), indicating that while genetic variants influence inflammation and anemia progression, their direct impact on β-globin expression in this study remains inconclusive.

## Discussion

This study highlights the persistent anemia observed in Sudanese children with end-stage kidney disease (ESKD), despite treatment with Epoetin beta (Recormon® 4000 IU/ml) and intravenous iron sucrose (100 mg/ml). This persistent anemia underscores the need to investigate underlying factors, particularly given the long-life expectancy of pediatric patients. Consistent with KDIGO guidelines [14], our study monitored the response to therapy over six months, with severe and moderate anemia being prevalent, especially among female participants who manifested the lowest hemoglobin (Hb) levels.

Prior studies, such as those by Luo et al., have demonstrated that a lack of response to therapy at six months in lupus nephritis patients is predictive of poor long-term renal outcomes [15]. Similarly, our study identified variability in β-globin mRNA expression, as assessed by quantitative PCR, underscoring the complexities of evaluating marrow responsiveness to recombinant human erythropoietin (rHuEPO) [3].

### Genetic variants and inflammatory markers

This study explored the association between genetic variants of pro-inflammatory cytokines (*IL6* and *IFN* γ), CRP levels, and marrow response to rHuEPO. The weak negative correlations observed between semi-quantified genomic content (Lane %) of *IFN* γ and *IL6* with both β-globin gene expression and CRP levels reflect the intricate role of inflammatory pathways in anemia progression among ESKD patients. ROC analysis further established CRP as a superior diagnostic marker for predicting hypo-responsiveness to Epoetin beta therapy.

Inflammation-induced hypo-responsiveness to erythropoietin-stimulating agents (ESAs) is well-documented and has been linked to pro-inflammatory cytokines, such as *IL6* and *IFN* γ. These cytokines antagonize the action of erythropoietin (EPO) by inhibiting erythroid progenitor cells and disrupting iron metabolism [16]. Specifically, these cytokines inhibit erythroid precursor growth and downregulate EPO receptor mRNA expression, contributing to ESA resistance. Our study observed that the

*IL6* GC genotype was the most frequent and correlated with elevated β-globin gene expression and CRP levels, findings that align with previous research linking the *IL6* -174 C variant to increased *IL6* production and reduced ESA efficacy [17, 18].

The *IFN*γ variant also demonstrated notable impacts. The TT genotype was associated with higher β-globin gene expression and CRP levels, consistent with studies showing that the + 874 T allele predisposes individuals to stronger NF-κB binding under inflammatory conditions [19]. Conversely, the AA genotype, linked to lower *IFN*γ production, corresponded with reduced β-globin gene expression [20]. These findings suggest that *IFN*γ plays a critical role in modulating ESA responsiveness, as observed in other chronic disease-related anemias [21]. However, limited significance in the current study correlations ($P > 0.05$) undermines some conclusions. Additional multivariate analyses might clarify the interaction between genetic variants, CRP levels, and β-globin expression.

The association between *IL6* and CRP levels in our study is consistent with the findings of Panichi et al., who identified *IL6* as a strong predictor of ESA resistance and a marker for higher ESA dose requirements [22]. However, our results diverge from those of Won et al., who suggested that *IL6* alone, rather than CRP, is the most reliable predictor of ESA hypo-responsiveness in hemodialysis patients [23]. In this prospective observational study, CRP demonstrated greater diagnostic value than *IL6* polymorphisms, emphasizing the importance of targeting inflammatory pathways in managing anemia in ESKD.

### Physiological implications and treatment strategies

Our findings indicate that genetic variants of *IL6* and *IFN*γ significantly influence ESA treatment efficacy. *IL6*, a key mediator of inflammation, stimulates hepcidin production, reducing iron availability and impairing erythropoiesis [16, 23]. Elevated *IL6* levels, particularly in patients with the GC and CC genotypes, are associated with higher ESA resistance due to inflammatory disruptions in iron metabolism.

Similarly, *IF*γ, particularly the TT variant, has been linked to heightened inflammatory responses that negatively impact erythropoiesis by directly inhibiting erythroid precursor cells [24, 25]. These genetic variants interact with pro-inflammatory pathways, contributing to hypo-responsiveness to ESA therapy in ESKD patients. As Badura et al. have explained, elevated levels of inflammatory biomarkers, including *IL1*, *IL6*, *IF*γ, CRP, and TNF-α, are key contributors to CKD progression and associated anemia [26].

Targeting these pathways with anti-inflammatory therapies may mitigate ESA resistance and improve anemia management. For instance, IL-6 inhibitors (e.g., tocilizumab), methylxanthine derivatives such as pentoxifylline, and antioxidants like vitamin E-coated polysulfone have shown promise in reducing inflammation and enhancing ESA responsiveness. Additionally, treatments with vitamin D analogs and receptor activators have demonstrated improved outcomes, particularly among hemodialysis patients [27].

### Study limitations

This study has several limitations. The absence of a control group limits the study's ability to draw comparative insights between anemic ESKD patients and non-anemic or healthy children. Moreover, the small sample size and the study's confinement to a specific geographical area limit the generalizability of the findings to the broader Sudanese pediatric ESKD population.Furthermore, the absence of a comprehensive genetic database for the Sudanese population restricts the ability to accurately characterize genetic variations.

## Conclusion

Our study underscores the critical role of *IL6* and *IFN*γ genetic variants in influencing ESA treatment responses in children with ESKD. Future research should focus on integrating genetic, inflammatory, and therapeutic insights to develop personalized medicine approaches. These efforts could enhance the precision of anemia management and improve clinical outcomes for pediatric ESKD patients.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13104-025-07095-5.

Supplementary Material 1

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#### Author contributions

*A.A. formulated the proposal, collected the data, carried out all the laboratory investigations including the molecular genetic studies, conducted data analysis, and drafted the manuscript. S.E. participated as a certified trainer and technical assistant in supervising the process of conventional ARMS-PCR work, he also contributed scientifically in selecting primers, and master mix, identifying sequence alignment, and writing the manuscript. N.A. contributed as a specialist in treating and following up with patients and contributed to writing the manuscript. N.M. is the second supervisor, and co-mentor of the research thesis and contributed to writing the manuscript. N.H. is the main supervisor, refined the research concept, supervised data collection and

analysis, logistically supported the research, and contributed to writing the manuscript.All authors read and approved the final manuscript.

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**Data availability**
All data supporting the findings of this study are available in the paper and its Supplementary Information section.

## Declarations

**Ethics approval and consent to participate**
The study has been approved by the Research Ethics Committee (REC) at Karary University(KU -2018-13), Soba University Hospital Ethical Committee, and the REC of the Ministry of Health- Khartoum State, Sudan. Informed consent to participate was obtained from the parents or legal guardians of all the participants. A written statement (Arabic language) was applied to all patients' crowns providing confidentiality and anonymity with all study data. Participants participated voluntarily, free from any coercion, and ensured with their to right to withdraw at any time. Permission was taken from the administration of hospitals in the study area. All research staff and participants were informed fully about the purpose, methods, and intended use of the study

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

**Conflict of interest**
The authors declare that they have no conflict of interest.

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