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BASELINE SERUM FERRITIN AS AN EXPLORATORY PREDICTOR OF HEMOGLOBIN TARGET ACHIEVEMENT DURING ESA THERAPY IN CHILDREN WITH CHRONIC KIDNEY DISEASE

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ABSTRACT

Background: Anemia is a common complication of pediatric chronic kidney disease, CKD, and erythropoiesis-stimulating agents, ESAs, are frequently used to improve hemoglobin levels. Serum ferritin is commonly used to assess iron status, but its role as a predictor of hemoglobin target achievement during ESA therapy in children with CKD remains unclear. **Aim:** This study explored whether baseline serum ferritin could predict hemoglobin target achievement during ESA therapy in children with CKD. **Methods:** This multicenter, open-label, randomized, active-controlled trial was conducted between October 2019 and September 2020 at pediatric nephrology centers in Dhaka, Bangladesh. Children aged 1 to 18 years with CKD stages 3, 4, 5, or 5D, baseline hemoglobin 8 to <11 g/dL, TSAT >20%, and adequate baseline iron stores were randomized to receive either subcutaneous darbepoetin alfa, 0.75 µg/kg/week, or recombinant human erythropoietin beta, 100 IU/kg three times weekly. Target hemoglobin achievement was defined as at least one recorded hemoglobin value ≥11 g/dL during the 48-week follow-up. Hemoglobin response, ferritin trajectory, and receiver operating characteristic, ROC, performance of baseline ferritin were assessed. **Results:** All 44 randomized participants completed follow-up; 19 received darbepoetin alfa and 25 received rHuEPO beta. Baseline ferritin did not differ significantly between groups, 295.81 ± 325.89 ng/mL versus 416.45 ± 282.56 ng/mL, p=0.206. At 16 weeks, mean hemoglobin was identical in both groups, 10.53 g/dL, p=1.000. At 48 weeks, hemoglobin was higher in the darbepoetin alfa group, 11.19 ± 0.67 g/dL versus 10.75 ± 0.63 g/dL, p=0.033, with a greater mean rise from baseline, 2.64 g/dL versus 1.92 g/dL, p=0.004. Ferritin declined in both groups, but the magnitude of decline did not differ significantly. Baseline ferritin showed modest, non-significant discrimination for target hemoglobin achievement, AUC 0.631, 95% CI 0.458 to 0.804, p=0.161. The exploratory cutoff was 292 ng/mL, with sensitivity 63.2%, specificity 64.0%, PPV 63.2%, and NPV 64.0%. **Conclusion:** Baseline serum ferritin demonstrated limited standalone predictive value for hemoglobin target achievement during ESA therapy in children with CKD. The identified cutoff should be interpreted as hypothesis-generating rather than clinically definitive.

KEYWORDS: Chronic kidney disease; Children; Serum ferritin; Erythropoiesis-stimulating agents; Hemoglobin target.

INTRODUCTION

Chronic kidney disease, CKD, in children is uncommon compared with adult CKD, but it carries a disproportionate long-term burden because affected children face impaired growth, neurocognitive and school disruption, cardiovascular risk, progression to kidney failure, and lifelong dependence on specialized renal care. Global estimates vary widely because pediatric CKD is under-recognized in many settings, but available registry-based evidence suggests that the burden is substantial and unevenly distributed across health systems. Harambat et al. described the epidemiology of pediatric CKD and emphasized that reliable data are limited outside established registries.[1]

In a low- and middle-income country setting, Amanullah et al. reported that most children presented late, with 72.5% presenting in CKD stages 3 to 5, and adverse outcomes were 4.5 times higher in children with CKD stages 3 to 5 than in those with earlier-stage disease.[2] This late-presentation pattern is directly relevant to South Asian pediatric nephrology practice, where anemia, malnutrition, hypertension, and delayed referral frequently coexist at the time of diagnosis.

Anemia is one of the most frequent and clinically important complications of pediatric CKD. Wong et al. reported anemia in 36.6% of children with CKD, with prevalence increasing as kidney function declined.[3] Fadrowski et al., using baseline data from the chronic kidney disease in Children cohort, showed that hemoglobin declined more steeply when measured glomerular filtration rate fell below approximately 43 mL/min/1.73 m^2.[4] Staples et al. further demonstrated that anemia in pediatric predialysis CKD was associated with increased hospitalization risk, supporting its relevance beyond laboratory classification.[5] Lee et al. (2019), in the KNOW-Ped CKD study, also showed that anemia and iron deficiency are common in children with CKD and are influenced by kidney function, nutritional status, and iron-related biochemical parameters.[6] Recent reviews continue to identify anemia management as a central therapeutic challenge in pediatric CKD because children differ from adults in growth demands, iron utilization, inflammation, dialysis exposure, and acceptable hemoglobin targets.[7]

Erythropoiesis-stimulating agents, ESAs, remain a major component of anemia treatment in children with CKD, particularly when endogenous erythropoietin deficiency, iron-restricted erythropoiesis, or advanced kidney dysfunction limits spontaneous hemoglobin recovery. Bruce et al., in a systematic review of ESA use in children with CKD, identified 58 eligible studies covering 54 cohorts and 3895 children, and concluded that available ESA preparations were generally efficacious, while also emphasizing individualization and caution in apparent ESA resistance.[8] Schaefer et al., in a prospective registry of darbepoetin alfa use in 319 children with CKD anemia, found no new safety signals during up to 2 years of observation and reported effective anemia management based on hemoglobin concentrations and transfusion requirements.[9] More recent comparative evidence has also examined epoetin alfa and darbepoetin in children, but pediatric trials remain limited in size and heterogeneity remains substantial.[10] Hemoglobin targets in children remain less evidence-secure than in adults; Hattori noted that the KDIGO-suggested pediatric hemoglobin target of 11 to 12 g/dL was based on limited pediatric evidence, while Rheault et al. found that hemoglobin ≥12 g/dL was not associated with increased cardiovascular morbidity in children receiving hemodialysis.[11,12]

Iron status is a key determinant of erythropoietic response during ESA therapy, but conventional markers are imperfect in CKD. Serum ferritin is widely used because it is accessible and reflects storage iron under stable conditions; however, it is also an acute-phase reactant and may increase in inflammation, infection, malnutrition-inflammation states, and reduced kidney function. Hayes reviewed the limitations of conventional iron indices in pediatric CKD and highlighted the need to interpret ferritin and transferrin saturation with caution.[13] Atkinson et al. found that higher serum ferritin was associated with lower hemoglobin in children with non-dialysis CKD, suggesting that ferritin may reflect disease severity or inflammation rather than iron sufficiency alone.[14] Atkinson et al. further showed that higher hepcidin was associated with lower hemoglobin and increased risk of incident anemia, particularly at lower GFR.[15] Akchurin et al. provided additional mechanistic support by implicating interleukin-6-mediated inflammation in juvenile CKD anemia.[16] Meza et al. also showed that anemia may remain resistant to oral iron therapy in a substantial proportion of children with CKD, reinforcing that iron markers do not always predict hemoglobin correction.[17] Despite these observations, targeted pediatric evidence evaluating baseline serum ferritin as a predictor of hemoglobin target achievement during ESA therapy is scarce. This absence of focused literature provides the rationale for the present exploratory study, which assessed whether baseline serum ferritin could help identify children with CKD who achieved at least one hemoglobin value ≥11 g/dL during 48 weeks of ESA therapy.

METHODS

This study was a multicenter, open-label, randomized, active-controlled trial conducted between October 2019 and September 2020 at the Departments of Pediatric Nephrology at the Bangladesh Institute of Child Health, Dhaka Shishu Hospital, and Bangladesh Medical University, Dhaka. The study cohort comprised children aged 1 to 18 years with diagnosed chronic kidney disease (CKD) stages 3, 4, and 5 who were dialysis-independent, and stage 5D children receiving maintenance hemodialysis. Eligible participants had an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2, baseline hemoglobin between 8 and less than 11 g/dL, transferrin saturation (TSAT) greater than 20%, and adequate baseline iron stores defined as serum ferritin >100 ng/mL for dialysis-independent patients or >200 ng/mL for dialysis-dependent patients. Exclusion criteria included the need for acute blood transfusion, receipt of a blood transfusion within the prior month, uncontrolled hypertension, active systemic infection, and severe hyperparathyroidism (intact PTH >1200 pg/mL). Ethical approval was obtained from the institutional ethical review committee, and informed written consent was secured from the legal guardians of all participants prior to enrollment.

Participants were randomized according to the study protocol to receive either subcutaneous darbepoetin alfa, 0.75 µg/kg/week, or recombinant human erythropoietin beta, 100 IU/kg three times weekly. The primary therapeutic target was achievement and maintenance of a hemoglobin level between 11 and 12 g/dL. Clinical and biochemical parameters, including complete blood counts and iron profiles, were monitored biweekly during the initial treatment phase and subsequently at regular follow-up intervals throughout the 48-week study period.

For the present exploratory analysis, all 44 randomized participants who completed the 48-week follow-up were included in the longitudinal evaluation of hemoglobin response and ferritin trajectory. Continuous variables were expressed as mean ± standard deviation and compared using independent-samples and paired-samples t-tests where appropriate. Target hemoglobin achievement was defined as at least one recorded hemoglobin value ≥11 g/dL during the 48-week follow-up period. To assess the exploratory predictive utility of baseline serum ferritin for target hemoglobin achievement, receiver operating characteristic (ROC) curve analysis was performed. The optimal exploratory serum ferritin cutoff was determined using the maximum Youden index, with corresponding sensitivity, specificity, positive predictive value, and negative predictive value calculated. Statistical significance was defined as a two-tailed p-value <0.05. All analyses were performed using SPSS version 23.0.

RESULTS

A total of 44 children with chronic kidney disease and renal anemia were randomized and included in the full cohort analysis. All 44 participants completed the 48-week follow-up. Of them, 19 received darbepoetin alfa and 25 received recombinant human erythropoietin beta.

Table 1: Baseline demographic and clinical characteristics of the study population.

Variable	Darbepoetin alfa, n=19	rHuEPO beta, n=25
Age		
1-5 years	2, 10.5%	5, 20.0%
6-10 years	15, 78.9%	10, 40.0%
11-15 years	2, 10.5%	10, 40.0%
>15 years	0, 0.0%	0, 0.0%
Sex		
Male	5, 26.3%	13, 52.0%
Female	14, 73.7%	12, 48.0%
Socioeconomic status		
Lower income	13, 68.4%	11, 44.0%
Lower-middle income	6, 31.6%	14, 56.0%
Residence		
Rural	6, 31.6%	6, 24.0%
Urban	13, 68.4%	19, 76.0%
Blood pressure category		
Pre-hypertension	10, 52.6%	14, 56.0%
Stage I hypertension	8, 42.1%	10, 40.0%
Stage II hypertension	1, 5.3%	1, 4.0%
Nutritional status		
Underweight	15, 78.9%	20, 80.0%
Normal weight	4, 21.1%	5, 20.0%
Height-for-age		
<3rd percentile	14, 73.7%	16, 64.0%
3rd to 50th percentile	5, 26.3%	9, 36.0%
Baseline anemia severity		
Moderate anemia, Hb 8 to <10 g/dL	16, 84.2%	18, 72.0%
Mild anemia, Hb 10 to <11 g/dL	3, 15.8%	7, 28.0%

Note: Values are presented as n, %. Hb, hemoglobin; rHuEPO, recombinant human erythropoietin

The mean age of the cohort was 6.9 ± 3.3 years. Most children were female, 26 of 44, 59.1%, and the majority resided in urban areas, 32 of 44, 72.7%. Chronic undernutrition was common, with 35 children, 79.5%, classified as underweight and 30 children, 68.2%, having height-for-age below the 3rd percentile. Pre-hypertension was the most frequent blood pressure category, observed in 24 children, 54.5%. At baseline, anemia severity was moderate in 34 children, 77.3%, and mild in 10 children, 22.7%.

Table 2: Baseline biochemical and iron-status characteristics by treatment group.

Variable	Darbepoetin alfa, n=19	rHuEPO beta, n=25	p-value
Hematological and iron profile			
Hemoglobin, g/dL	8.55 ± 0.60	8.83 ± 1.23	0.327
Serum ferritin, ng/mL	295.81 ± 325.89	416.45 ± 282.56	0.206
Transferrin saturation, %	24.82 ± 7.86	27.67 ± 12.79	0.368
Mineral metabolism			
Calcium, mmol/L	2.07 ± 0.33	2.50 ± 1.19	0.096
Inorganic phosphate, mmol/L	2.47 ± 1.34	2.66 ± 0.67	0.576
Parathyroid hormone, pg/mL	895.9 ± 714.7	741.3 ± 506.6	0.429
Inflammatory and nutritional markers			
C-reactive protein, mg/L	5.7 ± 0.87	4.5 ± 0.83	<0.001
Albumin, g/L	34.88 ± 8.32	36.71 ± 4.50	0.394
Renal biochemical parameters			
Potassium, mmol/L	4.12 ± 0.36	4.91 ± 0.42	<0.001
Serum creatinine, mg/dL	4.82 ± 0.93	3.84 ± 1.98	0.036
Blood urea, mg/dL	50 ± 20.21	71 ± 21.22	0.002

Note: Values are presented as mean ± SD. rHuEPO, recombinant human erythropoietin.

Baseline hemoglobin, serum ferritin, transferrin saturation, calcium, phosphate, parathyroid hormone, and albumin did not differ significantly between the two treatment groups. However, C-reactive protein, potassium, serum creatinine, and blood urea differed significantly between groups. Baseline ferritin was numerically higher in the rHuEPO beta group than in the darbepoetin alfa group, but this difference was not statistically significant, 416.45 ± 282.56 ng/mL versus 295.81 ± 325.89 ng/mL, p=0.206.

Table 3: Hemoglobin response during ESA therapy.

Variable	Darbepoetin alfa, n=19	rHuEPO beta, n=25	Treatment difference	p-value
Baseline hemoglobin, g/dL	8.55 ± 0.60	8.83 ± 1.23	-0.28	0.327
Hemoglobin at 16 weeks, g/dL	10.53 ± 0.88	10.53 ± 0.63	0.00	1.000
Change from baseline to 16 weeks, g/dL	1.98	1.70	0.28	0.429
Hemoglobin at 48 weeks, g/dL	11.19 ± 0.67	10.75 ± 0.63	0.44	0.033
Change from baseline to 48 weeks, g/dL	2.64	1.92	0.72	0.004

Note: *Values are presented as mean ± SD or mean change. Treatment difference represents darbepoetin alfa minus rHuEPO beta. ESA, erythropoiesis-stimulating agent; rHuEPO, recombinant human erythropoietin.*

At 16 weeks, mean hemoglobin increased similarly in both treatment groups. The darbepoetin alfa group increased from 8.55 ± 0.60 g/dL to 10.53 ± 0.88 g/dL, while the rHuEPO beta group increased from 8.83 ± 1.23 g/dL to 10.53 ± 0.63 g/dL. The between-group difference in hemoglobin change was not statistically significant, p=0.429.

At 48 weeks, in the full cohort analysis, the darbepoetin alfa group had a greater mean hemoglobin increase than the rHuEPO beta group, 2.64 g/dL versus 1.92 g/dL, p=0.004. Mean hemoglobin at 48 weeks was 11.19 ± 0.67 g/dL in the darbepoetin alfa group and 10.75 ± 0.63 g/dL in the rHuEPO beta group, p=0.033.

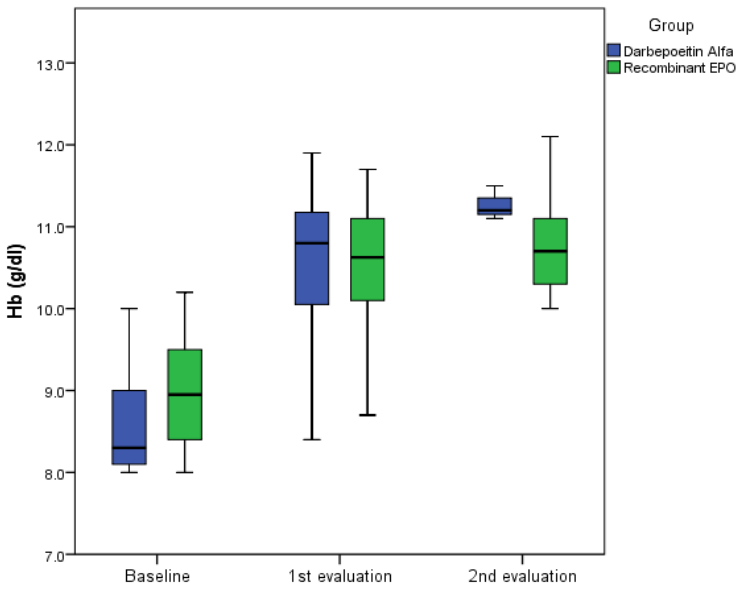

Table 4: Serum ferritin trajectory during ESA therapy.

Variable	Darbepoetin alfa, n=19	rHuEPO beta, n=25	p-value
Baseline ferritin, ng/mL	295.81 ± 325.89	416.45 ± 282.56	0.206
Ferritin at 16 weeks, ng/mL	129.32 ± 53.21	226.36 ± 184.97	0.033
Change from baseline to 16 weeks, ng/mL	-166.49	-190.09	0.808
Ferritin at 48 weeks, ng/mL	153.53 ± 62.41	211.27 ± 95.78	0.020
Change from baseline to 48 weeks, ng/mL	-142.28	-205.18	0.528

Note: Values are presented as mean ± SD or mean change. ESA, erythropoiesis-stimulating agent; rHuEPO, recombinant human erythropoietin.

Serum ferritin declined in both treatment groups during ESA therapy. Although absolute ferritin levels were lower in the darbepoetin alfa group at both 16 weeks and 48 weeks, the magnitude of ferritin decline from baseline did not differ significantly between treatment groups. At 16 weeks, the mean ferritin reduction was -166.49 ng/mL in the darbepoetin alfa group and -190.09 ng/mL in the rHuEPO beta group, p=0.808. At 48 weeks, the corresponding reductions were -142.28 ng/mL and -205.18 ng/mL, p=0.528.

Figure : 1:

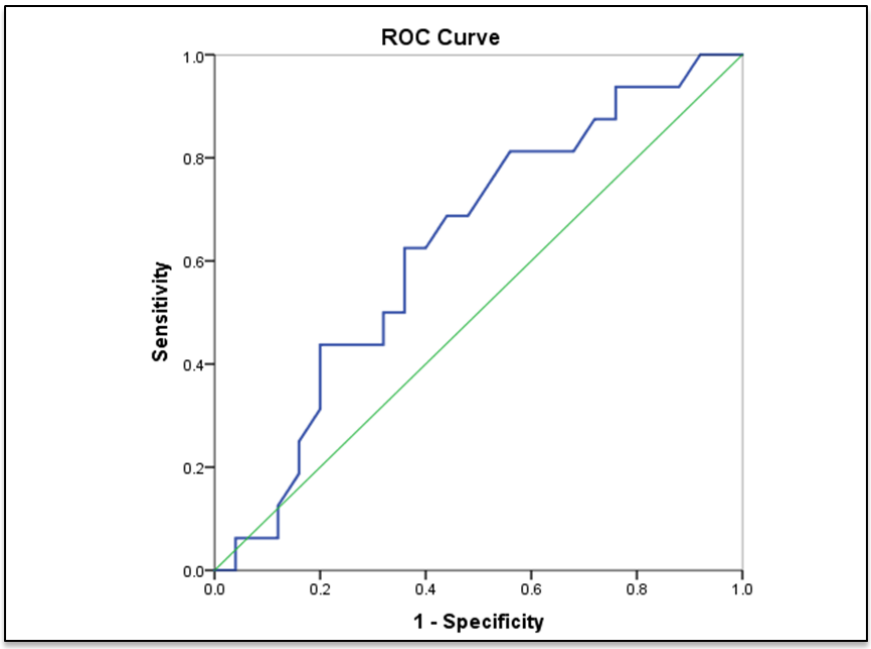

Table 5: Exploratory ROC performance and optimal baseline serum ferritin cutoff for hemoglobin target achievement during follow-up.

Parameter	Value
Analysis population	Full cohort, n=44
Outcome	At least one Hb ≥11 g/dL during the 48-week follow-up
Predictor	Baseline serum ferritin
AUC	0.631
Standard error	0.088
95% CI	0.458 to 0.804
p-value	0.161
Best exploratory cutoff, ng/mL	292
Sensitivity	0.632 (12/19)
Specificity	0.640 (16/25)
PPV	0.632 (12/19)
NPV	0.640 (16/25)
Youden index	0.272

Note: ROC, receiver operating characteristic; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

ROC analysis showed that baseline serum ferritin had modest, non-significant discriminatory ability for target hemoglobin achievement, defined as at least one recorded hemoglobin value ≥11 g/dL during the 48-week follow-up period. The AUC was 0.631, 95% CI 0.458 to 0.804, p=0.161. The maximum Youden index identified an exploratory ferritin cutoff of 292 ng/mL, with sensitivity 63.2%, specificity 64.0%, positive predictive value 63.2%, and negative predictive value 64.0%. Given the modest AUC and non-significant p-value, this cutoff should be interpreted as hypothesis-generating rather than clinically definitive.

DISCUSSION

In this randomized open-label trial of 44 children with CKD and renal anemia, all participants completed 48 weeks of ESA therapy, allowing full-cohort assessment of hemoglobin response and ferritin trajectory. The main finding was that baseline serum ferritin showed only modest and statistically non-significant discriminatory ability for hemoglobin target achievement, defined as at least one recorded hemoglobin value ≥11 g/dL during follow-up. The ROC-derived AUC was 0.631, with a wide 95% CI of 0.458 to 0.804 and p=0.161. The exploratory cutoff of 292 ng/mL produced limited classification performance, with sensitivity 63.2%, specificity 64.0%, PPV 63.2%, NPV 64.0%, and a Youden index of 0.272. These findings suggest that baseline ferritin may carry some signal, but it is not sufficiently strong as a standalone predictor of hemoglobin target achievement in this cohort.

This modest predictive performance is consistent with the known limitations of ferritin interpretation in pediatric CKD. Hayes emphasized that serum ferritin and transferrin saturation are commonly used to assess iron status, but both are affected by inflammation and may not accurately reflect bioavailable iron for erythropoiesis.[13] In the CKiD cohort, Atkinson et al. found that higher ferritin was associated with lower hemoglobin, indicating that ferritin may reflect CKD severity, inflammation, or iron sequestration rather than iron sufficiency alone.[14] Similarly, Atkinson et al. showed that higher hepcidin was associated with lower hemoglobin and greater risk of anemia, particularly at lower GFR.[15] Therefore, the non-significant AUC observed in the present study is biologically plausible and supports a cautious interpretation of ferritin as an exploratory rather than definitive marker.

The baseline iron-status profile also supports this interpretation. Baseline ferritin was numerically higher in the rHuEPO beta group than in the darbepoetin alfa group, 416.45 ± 282.56 ng/mL versus 295.81 ± 325.89 ng/mL, but the difference was not statistically significant, p=0.206. Baseline TSAT was also comparable, 27.67 ± 12.79% versus 24.82 ± 7.86%, p=0.368. However, CRP differed significantly between groups, 5.7 ± 0.87 mg/L in the darbepoetin alfa group and 4.5 ± 0.83 mg/L in the rHuEPO beta group, p<0.001. This is important because inflammation can elevate ferritin independent of usable iron stores. Akchurin et al. showed that interleukin-6 contributes to anemia in juvenile CKD through mechanisms including hypoferremia, renal fibrosis, and alteration of the erythropoietin axis.[16] Recent pediatric hemodialysis data also link inflammatory burden, including CRP, with ESA hyporesponsiveness.[18]

Both ESA groups showed clinically meaningful hemoglobin improvement. At 16 weeks, hemoglobin increased similarly in the darbepoetin alfa and rHuEPO beta groups, reaching 10.53 ± 0.88 g/dL and 10.53 ± 0.63 g/dL, respectively, with no between-group difference, p=1.000. The mean change from baseline to 16 weeks was also not significantly different, 1.98 g/dL versus 1.70 g/dL, p=0.429. This finding is consistent with the systematic review and meta-analysis by Bertazza Partigiani et al., which found no significant difference in hemoglobin improvement between epoetin alfa and

darbepoetin over 21 to 28 weeks.[10] Bruce et al. similarly concluded that ESAs are generally effective in pediatric CKD, but emphasized heterogeneity in study designs, dosing, populations, and outcome definitions.[8]

At 48 weeks, the darbepoetin alfa group showed a greater hemoglobin response than the rHuEPO beta group. Mean hemoglobin was 11.19 ± 0.67 g/dL versus 10.75 ± 0.63 g/dL, p=0.033, and the mean rise from baseline was 2.64 g/dL versus 1.92 g/dL, p=0.004. This finding is clinically relevant, but it should not be interpreted as definitive superiority because the sample size was small and baseline inflammatory and renal biochemical differences were present. Schaefer et al., in a prospective registry of 319 children receiving darbepoetin alfa, found no new safety signals over up to 2 years and reported effective anemia management based on hemoglobin concentrations and transfusion requirements.[9] Therefore, the present 48-week finding is compatible with existing darbepoetin effectiveness data, but requires confirmation in larger pediatric trials with adjustment for inflammation, dialysis status, ESA dose modification, and iron supplementation.

Serum ferritin declined in both groups during ESA therapy. From baseline to 16 weeks, the mean ferritin reduction was -166.49 ng/mL in the darbepoetin alfa group and -190.09 ng/mL in the rHuEPO beta group, p=0.808. From baseline to 48 weeks, reductions were -142.28 ng/mL and -205.18 ng/mL, respectively, p=0.528. Although follow-up ferritin levels were lower in the darbepoetin alfa group at 16 and 48 weeks, the magnitude of ferritin decline did not differ significantly between treatments. This pattern may reflect increased iron utilization during erythropoiesis, but ferritin dynamics should be interpreted cautiously. Meza et al. reported that hemoglobin and TSAT improved after oral iron therapy in children with CKD, while ferritin did not change significantly, and anemia remained resistant in approximately 30% of children.[17] This supports the view that ferritin change alone does not reliably capture erythropoietic response.

Overall, this study suggests that baseline serum ferritin has limited standalone value for predicting hemoglobin target achievement during ESA therapy in children with CKD. The findings are best interpreted as exploratory and hypothesis-generating. They support the need for future pediatric studies evaluating ferritin together with TSAT, CRP, hepcidin, dialysis adequacy, nutritional status, ESA dose intensity, and longitudinal iron supplementation data.

Limitations of The Study

This study was limited by the small sample size, open-label design, and exploratory nature of the ferritin-based ROC analysis. Although all participants completed 48 weeks of follow-up, baseline differences in inflammatory and renal biochemical parameters, particularly CRP, serum creatinine, and blood urea, may have influenced ferritin interpretation and hemoglobin response. The analysis did not include multivariable adjustment for inflammation, dialysis status, ESA dose changes, iron supplementation, or hepcidin, so the ferritin cutoff should be considered hypothesis-generating only.

CONCLUSION

Baseline serum ferritin showed modest and statistically non-significant discriminatory ability for hemoglobin target achievement during ESA therapy in children with CKD. An exploratory cutoff of 292 ng/mL demonstrated limited predictive performance, with sensitivity 63.2%, specificity 64.0%, PPV 63.2%, and NPV 64.0%, and should not be interpreted as a validated clinical threshold. Both ESA regimens improved hemoglobin over 48 weeks, while darbepoetin alfa was associated with a greater mean hemoglobin rise at 48 weeks than rHuEPO beta. Overall, baseline ferritin may provide limited supportive information, but it should be interpreted together with other markers of iron availability, inflammation, renal function, nutritional status, and treatment exposure.

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