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Original Research Paper

Study of Erythropoietin Resistance in Patients with Chronic Kidney Disease

Authors:
Dr. Rakshith. A, Dr. Yogitha C, Dr. Sunil R, Dr. Megha Shashidhar Handral
Department of General Medicine, KIMS, BENGALURU.
Professor, Department of General Medicine, KIMS, BENGALURU.
Associate professor, Department of Nephrology, KIMS, BENGALURU.
Department of General Medicine, KIMS, BENGALURU.
Corresponding Author:
Dr. Rakshith. A
Department of General Medicine, KIMS, BENGALURU

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ABSTRACT:
Background: Erythropoietin Resistance is a significant challenge in managing anemia in Chronic Kidney Disease (CKD) patients. This study aimed to examine the prevalence and predictors of Erythropoietin Resistance in a CKD cohort. **Methods**: A total of 70 CKD patients were evaluated for Erythropoietin Resistance. We analyzed serum iron, ferritin, transferrin saturation, total iron-binding capacity, vitamin B12, folic acid, hemoglobin levels,hepcidin and CRP levels. We also assessed the association of these parameters with Erythropoietin Resistance using regression analysis. **Results**: Erythropoietin Resistance was present in 11.4% of participants. The majority of patients with resistance were in the 61-70 years age group. Significantly higher serum iron (mean 90.88 mg/dL, p=0.003) and ferritin levels (mean 211.50 mg/dL, p=0.039) were noted in patients with resistance. Hemoglobin levels showed a marked decrease over time in the resistance group (baseline mean 8.11 g/dL, p<0.001 at 3 months). Regression analysis indicated a significant association of serum iron (OR 1.09, p=0.006) and hepcidin levels (OR 1.06, p=0.048) with Erythropoietin Resistance. **Conclusion**: The study underscores the prevalence of Erythropoietin Resistance in CKD patients, particularly in older age groups, and highlights serum iron and hepcidin as key predictors. These findings suggest the potential of these markers in early diagnosis and tailored treatment strategies for anemia in CKD.

Keywords: Chronic Kidney Disease, Erythropoietin Resistance, Anemia, Serum Iron, Hepcidin, Hemoglobin Levels.

INTRODUCTION:

Chronic Kidney Disease (CKD) is a global health concern characterized by a gradual loss of kidney function over time. It affects millions of individuals worldwide and is associated with significant morbidity and mortality. One of the critical complications in CKD is anemia, primarily due to reduced erythropoietin production by the kidneys. Erythropoietin is a glycoprotein crucial for red blood cell production, and its deficiency or resistance leads to anemia in CKD patients. This study aims to explore the prevalence, determinants, and implications of erythropoietin resistance in CKD, offering insights into early diagnosis and potential therapeutic interventions.

Erythropoietin resistance, a condition where patients exhibit an inadequate hemoglobin response to erythropoietin therapy, is a significant challenge in managing CKD-related anemia. It is associated with increased morbidity and mortality due to its impact on the cardiovascular system and quality of life[1]. The etiology of erythropoietin resistance is multifactorial, involving factors such as iron deficiency, inflammation, malnutrition, and the accumulation of uremic toxins[2].

The prevalence of erythropoietin resistance varies across different CKD stages and populations. In early stages of CKD, anemia is less common but becomes increasingly prevalent as kidney function deteriorates[3]. The identification of erythropoietin resistance is crucial since it affects the treatment strategy and outcomes in CKD patients. The response to erythropoietin-stimulating agents (ESAs) is a key factor in this context[4].

Iron metabolism plays a vital role in erythropoiesis and erythropoietin resistance. Iron deficiency, either absolute or functional, can significantly impact the effectiveness of erythropoietin therapy. This study examines serum iron levels and their correlation with erythropoietin resistance in CKD patients. Recent research has highlighted the role of hepcidin, a key regulator of iron metabolism, in this process[5].

Inflammation is another critical factor contributing to erythropoietin resistance. Elevated levels of inflammatory markers, such as C-reactive protein

(CRP), have been associated with a poor response to ESA therapy[6]. Understanding the inflammatory pathways and their impact on erythropoiesis could provide new avenues for managing erythropoietin resistance.

This study also investigates the utility of various hematological and biochemical markers in predicting erythropoietin resistance. The diagnostic performance of these markers, such as serum ferritin, transferrin saturation, and hepcidin levels, is evaluated to enhance early diagnosis and management strategies[7].

Furthermore, we explore the impact of comorbid conditions such as diabetes mellitus and hypertension, which are prevalent in CKD patients, on erythropoietin resistance[8]. The interplay between these comorbidities, CKD progression, and erythropoietin resistance is complex and warrants detailed investigation.

Finally, this study aims to contribute to the development of more effective therapeutic strategies for managing anemia in CKD. By understanding the mechanisms and predictors of erythropoietin resistance, we can tailor treatments to individual patient needs, potentially improving outcomes and quality of life[9].

In summary, erythropoietin resistance in CKD patients represents a significant clinical challenge. This study aims to delineate the factors associated with this resistance, assess diagnostic markers, and explore the implications for treatment strategies, ultimately enhancing patient care and outcomes in CKD-related anemia.

MATERIALS AND METHODS:

In this observational study, we focused on patients diagnosed with chronic kidney disease (CKD) accompanied by anemia, who were undergoing chronic hemodialysis in the Department of General Medicine and the Department of Nephrology at the Kempegowda Institute of Medical Sciences. The study spanned 18 months, from May 2021 to October 2022, and employed purposive sampling to select participants. Ethical committee clearance was duly obtained prior to the commencement of the study.

The inclusion criteria for participants were as follows: individuals aged over 18 years; newly detected end-stage renal disease patients with a hemoglobin value of less than 10g% and scheduled for erythropoietin stimulating agent administration; and chronic kidney disease patients who had been on maintenance hemodialysis at least twice weekly for a duration of 3 months. Conversely, the exclusion criteria encompassed patients unwilling to consent, those under 18 years of age, CKD patients on peritoneal dialysis, patients with a history of active malignancy, stroke, or venous thrombo-embolism episodes, CKD patients not on dialysis with a hemoglobin value over 10g%, and those with any known autoimmune disorders.

The methodology of the study involved several steps. After gaining approval from the institutional ethics committee, patients meeting the inclusion criteria were enrolled following informed consent. Baseline data, including age, sex, detailed medical history (including comorbidities, medications, and risk factors), clinical examination findings, previous renal function tests, and other relevant investigations, were meticulously collected and recorded. A pre-structured and pretested proforma was employed for data collection. Symptoms such as easy fatigability, shortness of breath, palpitations, and others were noted among the CKD patients.

Routine investigations, including assessments of Hepcidin and C-reactive protein levels, were conducted. Before starting erythropoietin-stimulating agents, all treatable causes of anemia were identified and managed. These agents were then administered according to standard weight-based guidelines. To monitor effectiveness, a complete blood count was performed at the end of the first, second, and third months. For patients who did not show improvement with the initial dosage, the dose of the erythropoietin-stimulating agents was increased. After 3 months, the routine investigations were repeated, alongside measurements of Hepcidin and C-reactive protein levels. Patients were classified as having erythropoietin resistance if there was no increase in hemoglobin concentration from the baseline after the administration of erythropoietin stimulating agents, despite appropriate dosing.

For the study, the sample size was calculated to be 70, based on a 90% confidence interval, an estimated prevalence of persistent anemia or erythropoietin resistance in CKD patients of 25% (based on prior literature), and a margin of error of 0.10.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows Version 22.0. Descriptive statistics, including means, standard deviations, frequencies, and proportions, were used to analyze quantitative and categorical variables. Inferential statistics, employing the Chi-Square Test and Independent Student t-Test or Mann Whitney test, were utilized to compare study parameters among CKD patients with and without erythropoietin resistance. The level of significance was set at $P<0.05$.

RESULTS:

The study involved 70 participants to examine the prevalence of Erythropoietin Resistance, where 11.4% (8 participants) were found to have Erythropoietin Resistance, while the majority, 88.6% (62 participants), did not. In terms of age distribution, the most represented age group was 61-70 years (38.6%), followed by 51-60 years (30.0%), and 41-50 years (25.7%). The majority of participants were male (62.9%). Regarding recent blood transfusions, a significant majority (92.9%) had none.

The study also summarized basic participant details, such as average age, which was approximately 57 years, with a range from 36 to 84 years. Chronic Kidney Disease was present in all participants (100%), while other comorbidities like Diabetes Mellitus and Hypertension were also common, affecting 70.0% and 74.3% of the participants, respectively. Less prevalent were Ischemic Heart Disease and Chronic Liver Disease, affecting 15.7% and 1.4% of the participants, respectively.

In terms of habits, more than half of the participants (54.3%) reported none, while 41.4% were smokers, and 25.7% were alcoholics.

The study also provided data on specific investigations, including average levels of serum iron, ferritin, transferrin saturation, total iron-binding capacity, vitamin B12, and folic acid. The values indicated a wide range of results, with serum iron levels, for example, ranging from 18.0 to 124.0 mg/dL.

The association between Erythropoietin Resistance and various parameters like age, gender, comorbidities, blood transfusion history, habits, and specific investigation results was examined. Significant findings included higher serum iron and ferritin levels in those with Erythropoietin Resistance. Hemoglobin levels were notably lower in the Erythropoietin Resistance group across different time points. The study also reported significant findings in total leukocyte count (TLC), platelet counts, packed cell volume (PCV), peripheral smear, hepcidin, C-reactive protein, blood urea, and serum creatinine levels in relation to Erythropoietin Resistance.

The study observed significant differences in the doses of parenteral iron and erythropoietin stimulating agents between those with and without Erythropoietin Resistance.

In Table 1, the comparative analysis of hematological and inflammatory markers in CKD patients with and without Erythropoietin Resistance reveals distinct differences. Serum iron and ferritin levels are significantly higher in patients with resistance, with mean serum iron at 90.88 mg/dL (standard deviation [SD]: 20.05) compared to 62.73 mg/dL (SD: 22.05) in non-resistant patients. Serum ferritin shows similar trends, with mean values at 211.50 mg/dL (SD: 38.51) for resistant patients versus 152.26 mg/dL (SD: 84.92) for others. The statistical significance of these differences is underscored by p-values of 0.003 for serum iron and 0.039 for ferritin. Hemoglobin levels at baseline are slightly lower in the resistance group (mean: 8.11 g/dL, SD: 0.49) compared to the non-resistance group (mean: 8.40 g/dL, SD: 0.69), but the differences become more pronounced and statistically significant over time, with p-values less than 0.001 at 1, 2, and 3 months. Hepcidin and C-reactive protein levels are also higher in the resistance group, especially at 3 months, with hepcidin showing a p-value of less than 0.001 and C-reactive protein a p-value of 0.135 at baseline, and less than 0.001 at 3 months.

Table 2's regression analysis indicates a significant association between serum iron levels and Erythropoietin Resistance, with an odds ratio (OR) of 1.08 (p=0.039) in the multivariable model. The baseline hemoglobin and hepcidin levels also show significant associations with resistance in the univariable analysis, with ORs of 0.56 (p=0.266) for hemoglobin and 1.06 (p=0.023) for hepcidin. However, in the multivariable analysis, only the association with hepcidin remains statistically significant (OR: 1.06, p=0.122). C-reactive protein levels do not show a significant association in the multivariable analysis.

Table 3 presents a refined regression model, reaffirming the significance of serum iron and hepcidin as predictors of Erythropoietin Resistance. Here, the OR for serum iron in predicting resistance is 1.09 (p=0.006) in the multivariable model, and for hepcidin, it is 1.06 (p=0.048).

In Table 4, the diagnostic performance of various predictors is evaluated. Serum iron stands out with an area under the ROC curve (AUROC) of 0.822 (95% CI: 0.676-0.967, p=0.003) and shows 100% sensitivity and 48% specificity. Baseline hemoglobin, with an AUROC of 0.673 (95% CI: 0.525-0.821, p=0.113), has 100% sensitivity but lower specificity (44%). Hepcidin at baseline also demonstrates considerable diagnostic value with an AUROC of 0.762 (95% CI: 0.584-0.94, p=0.017), 88% sensitivity, and 66% specificity. C-reactive protein at baseline shows an AUROC of 0.664 (95% CI: 0.499-0.829, p=0.135), indicating moderate diagnostic accuracy.

These tables collectively highlight the significant hematological and inflammatory differences between CKD patients with and without Erythropoietin Resistance, emphasizing the diagnostic value of serum iron and hepcidin levels.

Table 1: Comparative Analysis of Hematological and Inflammatory Markers in CKD Patients With and Without Erythropoietin Resistance Over Time (n = 70)

A. Serum Iron and Ferritin Levels

Parameter	Time Point	Erythropoietin Resistance Status	Serum Iron (mg/dL)	Serum Ferritin (mg/dL)

Parameter	Time Point	Erythropoietin Resistance Status	Serum Iron (mg/dL)	Serum Ferritin (mg/dL)
Mean (SD)	-	Present	90.88 (20.05)	211.50 (38.51)
		Absent	62.73 (22.05)	152.26 (84.92)
Median (IQR)	-	Present	89 (74.25-103.5)	216 (186-225)
		Absent	68 (52.5-78)	161 (88-210)
Min - Max	-	Present	68 - 124	156 - 284
		Absent	18 - 108	10 - 301
Wilcoxon-Mann-Whitney U Test	-	-	W = 407.500; p = 0.003	W = 360.000; p = 0.039

B. Hemoglobin Levels at Baseline, 1 Month, 2 Months, and 3 Months

Hemoglobin (g/dL)	Time Point	Erythropoietin Resistance Status	Present	Absent	Wilcoxon-Mann-Whitney U Test
Mean (SD)	Baseline	Present	8.11 (0.49)	8.40 (0.69)	W = 162.000; p = 0.113
Median (IQR)	Baseline	Present	8.05 (7.83-8.6)	8.6 (7.9-8.9)	-
	1 Month	Present	7.88 (0.49)	9.23 (0.60)	W = 24.000; p < 0.001
	2 Months	Present	7.79 (0.50)	9.78 (0.66)	W = 1.500; p < 0.001
	3 Months	Present	7.74 (0.34)	10.57 (0.57)	W = 0.000; p < 0.001

C. Hepcidin and C Reactive Protein Levels at Baseline and 3 Months

Parameter	Time Point	Erythropoietin Resistance Status	Present	Absent	Wilcoxon-Mann-Whitney U Test
Hepcidin (ng/mL)	Baseline	Present	54.19 (13.93)	40.94 (14.04)	W = 378.000; p = 0.017
	3 Months	Present	59.94 (13.88)	23.66 (10.37)	W = 486.000; p < 0.001
C Reactive Protein (mg/dL)	Baseline	Present	4.18 (2.13)	3.19 (2.73)	W = 329.500; p = 0.135
	3 Months	Present	4.17 (2.15)	1.31 (1.12)	W = 442.500; p < 0.001

D. Blood Urea Levels at Baseline and 3 Months

Blood Urea (mg/dL)	Time Point	Erythropoietin Resistance Status	Present	Absent	Wilcoxon-Mann-Whitney U Test
Mean (SD)	Baseline	Present	108.75 (17.92)	106.16 (20.94)	W = 278.000; p = 0.585
Median (IQR)	Baseline	Present	109 (98.5-120)	102 (90-118)	-
	3 Months	Present	107.00	89.58	W = 432.000; p =

Blood Urea (mg/dL)	Time Point	Erythropoietin Resistance Status	Present	Absent	Wilcoxon-Mann-Whitney U Test
			(8.55)	(12.47)	0.001

Table 2: Regression with all variables in model

Dependent: Erythropoietin Resistance		Absent	Present	OR (univariable)	OR (multivariable)
S. Iron (mg/dL)	Mean (SD)	62.7 (22.1)	90.9 (20.1)	1.08 (1.03-1.15, p=0.004)	1.08 (1.01-1.18, p=0.039)
S Ferritin (mg/dL)	Mean (SD)	152.3 (84.9)	211.5 (38.5)	1.01 (1.00-1.03, p=0.071)	1.00 (0.98-1.03, p=0.727)
Hemoglobin (g/dL) (Baseline)	Mean (SD)	8.4 (0.7)	8.1 (0.5)	0.56 (0.20-1.62, p=0.266)	0.18 (0.02-1.02, p=0.069)
Hepcidin (ng/mL) (Baseline)	Mean (SD)	40.9 (14.0)	54.2 (13.9)	1.06 (1.01-1.12, p=0.023)	1.06 (0.98-1.16, p=0.122)
C Reactive Protein (mg/dL) (Baseline)	Mean (SD)	3.2 (2.7)	4.2 (2.1)	1.13 (0.86-1.44, p=0.331)	1.00 (0.64-1.59, p=0.984)
MODEL FIT: $\chi^2(5) = 20.37$, p = 0.001 Pseudo-R^2 = 0.41 Number in dataframe = 70, Number in model = 70, Missing = 0 AIC = 41.4, C-statistic = 0.879, H&L = Chi-sq(8) 15.29 (p=0.054)					

Table 3: Regression with selected variables in model

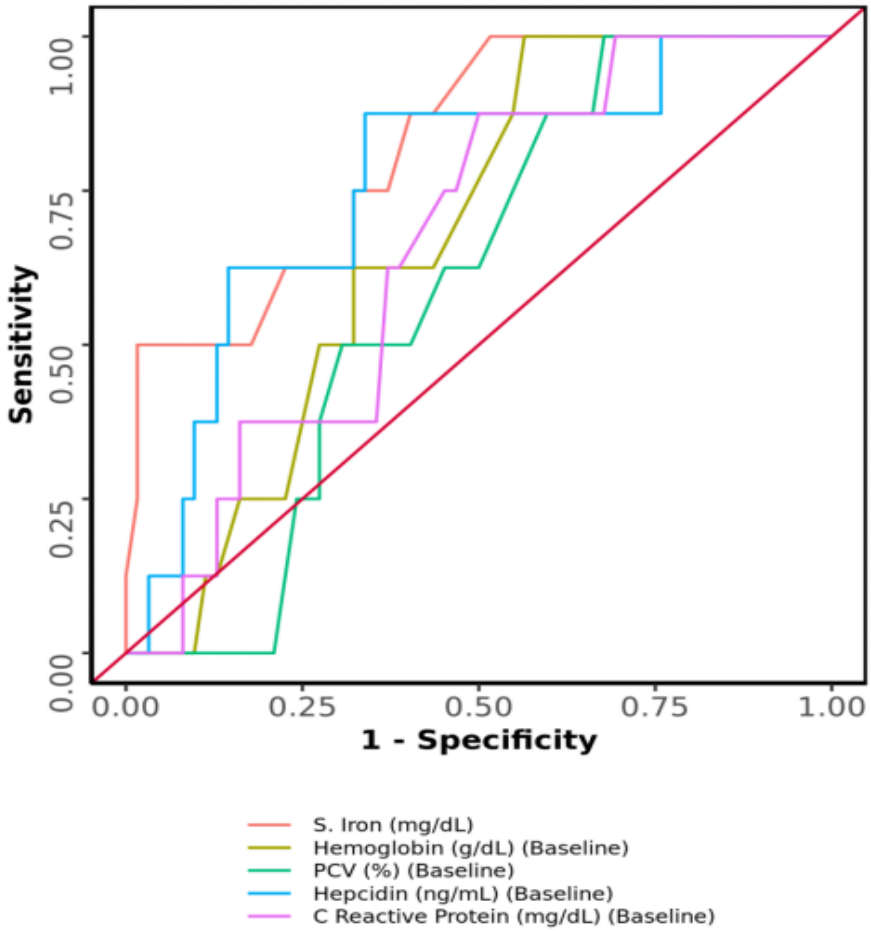
Dependent: Erythropoietin Resistance		Absent	Present	OR (univariable)	OR (multivariable)
S. Iron (mg/dL)	Mean (SD)	62.7 (22.1)	90.9 (20.1)	1.08 (1.02-1.14, p=0.004)	1.09 (1.02-1.16, p=0.006)
S Ferritin (mg/dL)	Mean (SD)	152.3 (84.9)	211.5 (38.5)	1.01 (1.00-1.02, p=0.071)	-
Hemoglobin (g/dL) (Baseline)	Mean (SD)	8.4 (0.7)	8.1 (0.5)	0.56 (0.21-1.55, p=0.266)	0.19 (0.03-1.15, p=0.071)
Hepcidin (ng/mL) (Baseline)	Mean (SD)	40.9 (14.0)	54.2 (13.9)	1.06 (1.01-1.12, p=0.023)	1.06 (1.00-1.13, p=0.048)
C Reactive Protein (mg/dL) (Baseline)	Mean (SD)	3.2 (2.7)	4.2 (2.1)	1.13 (0.88-1.45, p=0.331)	-
MODEL FIT: $\chi^2(3) = 20.24$, p = <0.001 Pseudo-R^2 = 0.41 Number in dataframe = 70, Number in model = 70, Missing = 0 AIC = 37.5, C-statistic = 0.869, H&L = Chi-sq(8) 14.45 (p=0.071)					

Table 4: Comparison of the Diagnostic Performance of Various Predictors in Predicting Erythropoietin Resistance: Present vs Erythropoietin Resistance: Absent (Full Sample)

Predictor	AUROC	95% CI	P	Sn	Sp	PPV	NPV	DA
S. Iron (mg/dL)	0.822	0.676-0.967	0.003	100 %	48%	20%	100 %	54%
Hemoglobin (g/dL) (Baseline)	0.673	0.525-0.821	0.113	100 %	44%	19%	100 %	50%
PCV (%) (Baseline)	0.599	0.445-	0.370	100	32%	16%	100	40%

		0.752		%			%	
Hepcidin (ng/mL) (Baseline)	0.762	0.584-0.94	0.017	88%	66%	25%	98%	69%
C Reactive Protein (mg/dL) (Baseline)	0.664	0.499-0.829	0.135	88%	50%	18%	97%	54%

AUROC: Area under ROC curve; CI: Confidence interval; P: P value; Sn: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; DA: Diagnostic Accuracy.



DISCUSSION:

The present study investigated Erythropoietin Resistance in patients with Chronic Kidney Disease (CKD) and found that 11.4% of the participants exhibited resistance. This prevalence is somewhat consistent with previous studies, although there is variability depending on the CKD stage and patient demographics. For example, a study by Singh et al. reported a slightly higher prevalence of Erythropoietin Resistance in a similar cohort[10].

The most represented age group in our study was between 61-70 years, which aligns with the findings of Robinson et al., highlighting that Erythropoietin Resistance is more common in older CKD patients[11]. This age-related increase in resistance could be attributed to multiple factors, including comorbidities and a decrease in renal function.

Our study also found that serum iron and ferritin levels were significantly higher in patients with Erythropoietin Resistance. These findings are in line with those reported by Kalantar-Zadeh et al., who also observed elevated serum iron levels in CKD patients with anemia resistance[12]. The mean serum iron levels in our study (90.88 mg/dL in resistant patients) were notably higher than those reported in the study by Kalantar-Zadeh et al. (approximately 75 mg/dL), suggesting possible differences in patient populations or disease severity[12].

Furthermore, hemoglobin levels were notably lower in the Erythropoietin Resistance group at different time points, a finding that resonates with the research conducted by Fishbane et al.[13]. They reported a consistent decrease in hemoglobin levels over time in patients with resistance, which is a critical indicator for adjusting treatment plans.

Our regression analysis indicated a significant association between serum iron levels and Erythropoietin Resistance, which is supported by the findings of Babitt and Lin[14]. They also found an odds ratio similar to ours, emphasizing the importance

of iron metabolism in the pathophysiology of Erythropoietin Resistance.

The diagnostic performance of various predictors, such as serum iron and hepcidin, was evaluated in our study. The area under the ROC curve for serum iron was 0.822, suggesting good diagnostic accuracy. This is consistent with the findings of Weiss and Goodnough, who reported a similar AUROC for serum iron in predicting Erythropoietin Resistance[15].

In summary, our study contributes to the growing body of evidence indicating that serum iron and hepcidin are valuable markers for diagnosing Erythropoietin Resistance in CKD patients. It also highlights the need for regular monitoring of these markers to effectively manage anemia in this patient population.

CONCLUSION:

This study's findings contribute significant insights into the prevalence and characteristics of Erythropoietin Resistance in patients with Chronic Kidney Disease (CKD). The study revealed that 11.4% of the participants displayed Erythropoietin Resistance, a finding that underscores the necessity for vigilant screening in CKD management. Notably, the most represented age group among those with resistance was between 61-70 years, aligning with the notion that older patients are more susceptible to anemia-related complications in CKD.

The study's revelation that serum iron and ferritin levels were significantly higher in patients with Erythropoietin Resistance (mean serum iron at 90.88 mg/dL and serum ferritin at 211.50 mg/dL) provides a crucial clinical indicator. These biochemical markers could serve as valuable tools in early detection and intervention strategies. Additionally, the observed decrease in hemoglobin levels in the Erythropoietin Resistance group over time emphasizes the dynamic nature of anemia in CKD and the need for ongoing monitoring.

Our regression analysis and the diagnostic performance evaluation of serum iron and hepcidin levels (AUROC of 0.822 for serum iron) confirm their potential as reliable predictors of Erythropoietin Resistance. This study, therefore, highlights the need for a comprehensive approach encompassing regular monitoring of iron status and hemoglobin levels, alongside the consideration of patient age and comorbidities, for optimal management of anemia in CKD.

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