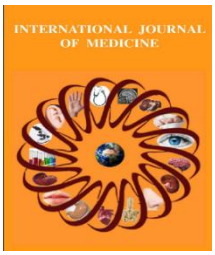

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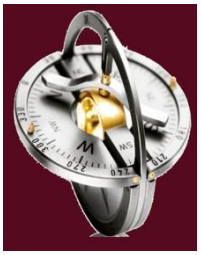

Original Research

Comparative evaluation of serum ferritin and transferrin saturation in patients with chronic kidney disease with or without anaemia.

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Abstract

Background: Anemia is a frequent complication of chronic kidney disease and results from inadequate erythropoietin production, inflammation, blood loss and impaired iron availability. Serum ferritin reflects stored iron but may increase during inflammation, whereas transferrin saturation indicates iron immediately available for erythropoiesis. Their combined assessment may improve the identification of absolute and functional iron deficiency in CKD. *Aim:* To compare serum ferritin and transferrin saturation levels in CKD patients with and without anemia and determine their relationships with hemoglobin concentration and CKD stage. *Materials and Methods:* This hospital-based comparative cross-sectional study included 100 adults with CKD, comprising 50 patients with anemia and 50 without anemia. Clinical information and laboratory parameters, including hemoglobin, serum ferritin, serum iron, total iron-binding capacity and transferrin saturation, were recorded. Absolute iron deficiency was defined as TSAT ≤20% accompanied by ferritin below the stage-specific threshold, while functional iron deficiency was defined as TSAT ≤20% with ferritin above this threshold. The groups were compared using the independent-samples *t*-test, chi-square test or Fisher's exact test. Correlation and multivariable logistic regression analyses were performed. A P value <0.05 was considered statistically significant. *Results:* Mean hemoglobin was significantly lower in CKD patients with anemia than in those without anemia (9.42±1.21 versus 13.48±1.08 g/dL; P<0.001). The anemic group had significantly lower serum ferritin (178.6±146.8 versus 263.4±171.5 ng/mL; P=0.009), serum iron (48.7±19.6 versus 76.3±25.8 µg/dL; P<0.001) and TSAT (17.4±7.1% versus 26.8±8.6%; P<0.001). TIBC did not differ significantly between the groups (P=0.266). TSAT ≤20% was present in 66.0% of anemic and 22.0% of non-anemic patients (OR=6.88; 95% CI: 2.84-16.67; P<0.001). Absolute iron deficiency was observed in 54.0% and 14.0%, respectively (OR=7.21; 95% CI: 2.71-19.18; P<0.001). Functional iron deficiency was not significantly different between the groups (28.0% versus 18.0%; P=0.235). Hemoglobin correlated positively with TSAT (r=0.52; P<0.001), serum iron (r=0.46; P<0.001) and ferritin (r=0.24; P=0.016), but negatively with CKD stage (r_s=-0.48; P<0.001). TSAT ≤20% remained an independent predictor of anemia (adjusted OR=5.36; 95% CI: 1.88-15.28; P=0.002). *Conclusion:* CKD patients with anemia had significantly lower serum ferritin, serum iron and TSAT and a greater burden of absolute iron deficiency than patients without anemia. TSAT was more strongly associated with hemoglobin and anemia than ferritin considered as a continuous measure. Combined assessment of ferritin and TSAT is therefore preferable for evaluating iron status and guiding the management of CKD-related anemia.

Keywords: *Chronic kidney disease; serum ferritin; transferrin saturation.*

Introduction

Chronic kidney disease (CKD) is a major public-health problem characterized by abnormalities of kidney structure or function persisting for at least three months and having implications for health. CKD is classified according to its cause, glomerular filtration rate and albuminuria category [1]. Anemia is one of the most frequent systemic complications of CKD, and its prevalence and severity increase progressively with declining renal function. The principal mechanism is inadequate renal production of erythropoietin; however, iron deficiency, chronic inflammation, shortened erythrocyte survival, nutritional deficiencies, occult blood loss and the effects of uremic toxins also contribute substantially. Anemia in CKD is associated with fatigue, reduced exercise capacity, impaired cognitive and physical functioning, poor quality of life, cardiovascular complications, hospitalization and increased mortality [2].

Iron deficiency in CKD may occur as absolute iron deficiency, in which total body iron stores are depleted, or functional iron deficiency, in which iron stores are adequate but iron cannot be efficiently mobilized for erythropoiesis. Repeated blood sampling, gastrointestinal blood loss, reduced dietary intake, impaired intestinal iron absorption and blood loss during hemodialysis contribute to absolute deficiency. Conversely, chronic inflammation increases hepatic hepcidin production, thereby reducing intestinal iron absorption and trapping iron within macrophages and hepatocytes. This produces iron-restricted erythropoiesis despite apparently adequate or elevated iron stores [3].

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Serum ferritin and transferrin saturation (TSAT) are the most widely used biochemical indicators for assessing iron status in CKD. Serum ferritin primarily reflects stored iron; however, it is also an acute-phase reactant and may be elevated in inflammation, infection, liver disease or malnutrition. Consequently, a normal or raised ferritin concentration does not reliably exclude iron-restricted erythropoiesis in CKD. TSAT represents circulating iron immediately available for erythropoiesis and is calculated from serum iron and total iron-binding capacity. Low TSAT may therefore indicate inadequate iron availability even when serum ferritin is normal or elevated [3,4].

The combined assessment of ferritin and TSAT assists in distinguishing absolute iron deficiency from functional iron deficiency. Absolute iron deficiency is commonly characterized by TSAT ≤20% with ferritin ≤100 ng/mL in nondialysis or peritoneal-dialysis CKD and ≤200 ng/mL in hemodialysis patients, whereas functional iron deficiency may present with TSAT ≤20% despite normal or increased ferritin [4]. Nevertheless, both parameters demonstrate biological and analytical variability and should be interpreted with hemoglobin concentration, inflammatory status, CKD stage and treatment history [5]. Comparing these indices between CKD patients with and without anemia may clarify alterations in iron storage and availability associated with anemia and facilitate appropriate iron evaluation and treatment.

AIM
To compare serum ferritin and transferrin saturation levels in patients with chronic kidney disease with and without anemia.

OBJECTIVES
1. To estimate serum ferritin and transferrin saturation levels in CKD patients with anemia.
2. To estimate serum ferritin and transferrin saturation levels in CKD patients without anemia.
3. To compare iron-status parameters between the two groups and determine their association with hemoglobin concentration and CKD stage.

Materials and Methods
Source of Data
The study participants were recruited from patients attending the nephrology and general medicine outpatient departments or admitted to the medical and nephrology wards of the study institution. Patients with a confirmed diagnosis of CKD who fulfilled the eligibility criteria during the study period were considered for enrolment. Clinical information and laboratory findings were obtained through patient interviews, physical examination, hospital records and analysis of collected blood samples.

Study Design
A hospital-based, comparative cross-sectional study was conducted among patients with CKD. Participants were divided into two groups according to their hemoglobin concentration:

- **Group A:** CKD patients with anemia, n=50.
- **Group B:** CKD patients without anemia, n=50.

Study Location
The study was conducted in the Department of General Medicine/Nephrology in collaboration with the Department of Biochemistry and the Central Clinical Laboratory.

Study Duration
The study was conducted over 12 months. This period included participant recruitment, clinical assessment, laboratory investigations, data entry and statistical analysis.

Sample Size
A total of **100 patients with CKD** were included. The sample consisted of 50 patients with anemia and 50 patients without anemia. Eligible patients were enrolled consecutively until the required sample size was achieved.
Where an analytical calculation was required, the sample size could be justified using the formula for comparing two independent means: where at a 5% significance level, for 80% power, represented the anticipated pooled standard deviation and represented the minimum clinically meaningful difference. After allowing for incomplete data, the final sample was fixed at 100 participants.

Inclusion Criteria
1. Patients aged 18 years or older.
2. Patients of either sex.
3. Patients diagnosed with CKD based on abnormalities of kidney structure or function persisting for at least three months.
4. Patients belonging to CKD stages G3-G5, based on estimated glomerular filtration rate.
5. Patients willing to provide written informed consent.
6. Availability of hemoglobin, serum ferritin, serum iron and total iron-binding capacity measurements.
7. For the anemia group, hemoglobin was below the sex-specific diagnostic threshold.
8. For the non-anemia group, hemoglobin was equal to or above the corresponding threshold.

Exclusion Criteria
1. Acute kidney injury or acute kidney disease without established CKD.
2. Active bleeding or a history of major blood loss during the preceding three months.
3. Blood transfusion during the preceding three months.
4. Oral or intravenous iron therapy initiated or changed during the preceding three months.
5. Known hematological malignancy, aplastic anemia, hemolytic anemia, thalassemia, sickle-cell disease or other hereditary anemia.
6. Active infection, sepsis or clinically evident acute inflammatory illness.
7. Chronic liver disease or active malignancy likely to alter serum ferritin.
8. Recent major surgery or trauma.
9. Pregnancy or lactation.
10. Incomplete clinical or laboratory information.
11. Patients who declined consent.

Operational Definitions
Chronic kidney disease: CKD was defined as abnormalities of kidney structure or function persisting for at least three months, with implications for health. The estimated glomerular filtration rate was calculated using a validated creatinine-based equation, and CKD was categorized as G3a, G3b, G4 or G5 [1].

Anemia: In nonpregnant adults aged 15-65 years, anemia was defined as hemoglobin below 13.0 g/dL in males and below 12.0 g/dL in females, consistent with WHO guidance [2]. Appropriate age- and pregnancy-specific thresholds were applied when relevant.

Transferrin saturation: TSAT was calculated as:
Absolute iron deficiency: Absolute deficiency was defined as TSAT ≤20% with serum ferritin ≤100 ng/mL in nondialysis CKD or ≤200 ng/mL in hemodialysis patients.

Functional iron deficiency: Functional or iron-restricted deficiency was defined as TSAT ≤20% with serum ferritin above the threshold for absolute deficiency.

Procedure and Methodology

Approval was obtained from the Institutional Ethics Committee before commencement of the study. Patients with CKD attending the selected departments were screened for eligibility. The study purpose and procedures were explained in the participant's preferred language, and written informed consent was obtained.

A detailed history was recorded regarding age, sex, duration and cause of CKD, hypertension, diabetes mellitus, dietary pattern, gastrointestinal symptoms, menstrual history, previous bleeding, blood transfusion, dialysis status and medications. Particular attention was given to oral or intravenous iron, erythropoiesis-stimulating agents and vitamin supplementation.
A general and systemic examination was performed. Pallor, edema, blood pressure, nutritional status and clinical evidence of infection, inflammation, bleeding or chronic liver disease were documented. CKD stage was assigned using the estimated glomerular filtration rate.

Venous blood was collected for complete blood count, serum ferritin, serum iron, total iron-binding capacity, serum creatinine, blood urea nitrogen, albumin and other relevant biochemical investigations. C-reactive protein was measured wherever feasible to assist with the interpretation of elevated ferritin.
Patients were classified into anemia and non-anemia groups using hemoglobin concentration. Serum ferritin and TSAT were compared between the two groups. Iron-status patterns were further categorized as absolute iron deficiency, functional iron deficiency or no biochemical iron deficiency. Associations of ferritin and TSAT with hemoglobin, CKD stage, dialysis status and inflammatory markers were evaluated.

Sample Processing

Approximately 5-7 mL of venous blood was collected under aseptic precautions, preferably in the morning and before iron administration or a dialysis session.

- Approximately 2 mL was collected in an ethylenediaminetetraacetic acid tube for complete blood count.
- The sample was gently mixed and analyzed using a calibrated automated hematology analyzer.
- Hemoglobin, hematocrit, red-cell count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration and red-cell distribution width were recorded.
- The remaining blood was collected in a plain or serum-separator tube.
- It was allowed to clot and was centrifuged at approximately 3,000 revolutions per minute for 10 minutes.
- Serum was separated and analyzed promptly. When immediate analysis was not possible, it was stored according to the reagent manufacturer's recommendations.
- Serum ferritin was measured using a validated chemiluminescent immunoassay or immunoturbidimetric method.
- Serum iron was measured using a standardized colorimetric method.
- Total iron-binding capacity was measured directly or calculated from serum iron and unsaturated iron-binding capacity.
- TSAT was calculated from serum iron and total iron-binding capacity.
- Serum creatinine was measured by an enzymatic or isotope-dilution mass-spectrometry-traceable method.
- Internal quality-control samples were analyzed daily, and the laboratory participated in external quality-assurance procedures.

Hemolyzed, lipemic, improperly labelled or inadequately collected specimens were rejected, and repeat samples were obtained whenever feasible.

Data Collection

Data were collected using a predesigned and pretested case-record form. The form included:

1. Demographic characteristics: age, sex, residence and socioeconomic information.
2. Clinical characteristics: CKD duration, etiology, stage, comorbidities and dialysis status.
3. Treatment history: iron therapy, erythropoiesis-stimulating agents, vitamin supplementation and transfusion.
4. Hematological findings: hemoglobin and red-cell indices.
5. Iron parameters: serum ferritin, serum iron, total iron-binding capacity and TSAT.
6. Biochemical findings: creatinine, eGFR, urea, albumin and C-reactive protein.
7. Classification of anemia and iron-deficiency status.

Each form was checked for completeness. Data were coded, anonymized and entered into a password-protected electronic database. A proportion of entries was cross-checked against source documents to minimize transcription errors.

Statistical Methods

Data were analyzed using IBM SPSS Statistics version 21.0. Continuous variables were assessed for normality using the Shapiro-Wilk test and graphical methods. Normally distributed data were summarized as mean and standard deviation, whereas skewed variables, particularly serum ferritin, were summarized as median and interquartile range. Categorical variables were presented as frequencies and percentages.

Serum ferritin and TSAT were compared between CKD patients with and without anemia. The independent-samples Student's *t*-test was used for normally distributed variables, while the Mann-Whitney *U* test was used for skewed variables. Categorical variables were compared using the chi-square test or Fisher's exact test. Mean or median differences, odds ratios and corresponding 95% confidence intervals were reported.

Correlation between hemoglobin and iron parameters was evaluated using Pearson's or Spearman's correlation coefficient, as appropriate. Comparisons across CKD stages were performed using one-way analysis of variance or the Kruskal-Wallis test. Multivariable logistic regression was used to determine whether low TSAT and abnormal ferritin were independently associated with anemia after adjusting for age, sex, CKD stage, dialysis status, diabetes, serum albumin and inflammation. Adjusted odds ratios with 95% confidence intervals were reported. All tests were two-tailed, and $P<0.05$ was considered statistically significant.

Results

Table 1: Comparison of serum ferritin and transferrin saturation between CKD patients with and without anemia (N=100)

Parameter	CKD with anemia (n=50), n (%) or Mean (SD)	CKD without anemia (n=50), n (%) or Mean (SD)	Effect estimate (95% CI)	Test of significance	P value
Hemoglobin, g/dL	9.42 (1.21)	13.48 (1.08)	MD=-4.06 (-4.52 to -3.60)	Welch's t=-17.70	<0.001*
Serum ferritin, ng/mL	178.6 (146.8)	263.4 (171.5)	MD=-84.80 (-148.20 to -21.40)	Welch's t=-2.66	0.009*

Serum iron, µg/dL	48.7 (19.6)	76.3 (25.8)	MD=-27.60 (-36.71 to -18.49)	Welch's t=-6.03	<0.001*
TIBC, µg/dL	289.4 (61.7)	302.8 (58.6)	MD=-13.40 (-37.27 to 10.47)	t=-1.12	0.266
Transferrin saturation, %	17.4 (7.1)	26.8 (8.6)	MD=-9.40 (-12.53 to -6.27)	Welch's t=-5.96	<0.001*
TSAT ≤20%	33 (66.0)	11 (22.0)	OR=6.88 (2.84-16.67)	χ^2=19.50	<0.001*
Low ferritin†	27 (54.0)	7 (14.0)	OR=7.21 (2.71-19.18)	χ^2=17.80	<0.001*
Absolute iron deficiency‡	27 (54.0)	7 (14.0)	OR=7.21 (2.71-19.18)	χ^2=17.80	<0.001*
Functional iron deficiency§	14 (28.0)	9 (18.0)	OR=1.77 (0.68-4.59)	χ^2=1.41	0.235
No biochemical iron deficiency	9 (18.0)	34 (68.0)	OR=0.10 (0.04-0.25)	χ^2=25.61	<0.001*

†Ferritin ≤100 ng/mL in nondialysis CKD or ≤200 ng/mL in hemodialysis patients.
‡TSAT ≤20% accompanied by low ferritin.

§TSAT ≤20% with ferritin above the threshold for absolute deficiency.
MD: mean difference; TIBC: total iron-binding capacity; TSAT: transferrin saturation; OR: odds ratio. *Statistically significant at P<0.05.

Table 1 compares the iron profile of CKD patients with and without anemia. As expected, mean hemoglobin was significantly lower in patients with anemia than in those without anemia (9.42±1.21 versus 13.48±1.08 g/dL), with a mean difference of -4.06 g/dL (95% CI: -4.52 to -3.60; P<0.001). The anemic group also had significantly lower serum ferritin (178.6±146.8 versus 263.4±171.5 ng/mL; MD=-84.80; 95% CI: -148.20 to -21.40; P=0.009), serum iron (48.7±19.6 versus 76.3±25.8 µg/dL; MD=-27.60; 95% CI: -36.71 to -18.49; P<0.001) and TSAT (17.4±7.1% versus 26.8±8.6%; MD=-9.40%; 95% CI: -12.53 to -6.27; P<0.001). Mean TIBC did not differ significantly between the groups (289.4±61.7 versus 302.8±58.6 µg/dL; P=0.266). A TSAT ≤20% was observed in 66.0% of anemic patients compared with 22.0% of non-anemic patients, corresponding to 6.88-times higher odds among anemic patients (95% CI: 2.84-16.67; P<0.001). Low ferritin and absolute iron deficiency were each present in 54.0% of anemic patients and 14.0% of non-anemic patients (OR=7.21; 95% CI: 2.71-19.18; P<0.001). Functional iron deficiency was more frequent in the anemic group, although the difference was not statistically significant (28.0% versus 18.0%; OR=1.77; P=0.235). Conversely, the absence of biochemical iron deficiency was substantially less common in anemic patients than in non-anemic patients (18.0% versus 68.0%; OR=0.10; 95% CI: 0.04-0.25; P<0.001).

Table 2: Serum ferritin and transferrin saturation profile among CKD patients with anemia (n=50)

Iron-status parameter	n (%) or Mean (SD)	95% CI	Reference value used for testing	Test of significance	P value
Hemoglobin, g/dL	9.42 (1.21)	9.08-9.76	12.0 g/dL	One-sample t=-15.08	<0.001*
Serum ferritin, ng/mL	178.6 (146.8)	136.9-220.3	100 ng/mL	One-sample t=3.79	<0.001*
Serum iron, µg/dL	48.7 (19.6)	43.1-54.3	60 µg/dL	One-sample t=-4.08	<0.001*
TIBC, µg/dL	289.4 (61.7)	271.9-306.9	300 µg/dL	One-sample t=-1.21	0.231
Transferrin saturation, %	17.4 (7.1)	15.4-19.4	20%	One-sample t=-2.59	0.013*
TSAT ≤20%	33 (66.0)	52.2%-77.6%	50%	One-sample z=2.26	0.024*
TSAT 21%-30%	11 (22.0)	12.8%-35.2%	50%	One-sample z=-3.96	<0.001*
TSAT >30%	6 (12.0)	5.6%-23.8%	50%	One-sample z=-5.37	<0.001*
Ferritin below stage-specific threshold†	27 (54.0)	40.4%-67.0%	50%	One-sample z=0.57	0.572
Ferritin above stage-specific threshold	23 (46.0)	33.0%-59.6%	50%	One-sample z=-0.57	0.572
Absolute iron deficiency	27 (54.0)	40.4%-67.0%	50%	One-sample z=0.57	0.572
Functional iron deficiency	14 (28.0)	17.5%-41.7%	50%	One-sample z=-3.11	0.002*
No biochemical iron deficiency	9 (18.0)	9.8%-30.8%	50%	One-sample z=-4.53	<0.001*

†Ferritin ≤100 ng/mL in nondialysis CKD or ≤200 ng/mL in hemodialysis patients. Continuous variables were tested against the stated clinically relevant reference value; categorical proportions were tested against a reference proportion of 50%.
*Statistically significant at P<0.05.

Table 2 presents the iron-status profile of the 50 CKD patients with anemia. Their mean hemoglobin was 9.42±1.21 g/dL (95% CI: 9.08-9.76), which was significantly below the reference value of 12.0 g/dL (P<0.001). Mean serum ferritin was 178.6±146.8 ng/mL (95% CI: 136.9-220.3) and was significantly higher than the reference value of 100 ng/mL (P<0.001), indicating that ferritin alone did not adequately reflect available iron in all patients. Mean serum iron was significantly below 60 µg/dL (48.7±19.6 µg/dL; P<0.001), while mean TSAT was significantly below 20% (17.4±7.1%; 95% CI: 15.4-19.4; P=0.013). TIBC did not differ significantly from the reference value of 300 µg/dL (P=0.231). Overall, 33 patients (66.0%; 95% CI: 52.2%-77.6%) had TSAT ≤20%, significantly exceeding the reference proportion of 50% (P=0.024). TSAT values of 21%-30% and >30% were found in 22.0% and 12.0% of patients, respectively. Ferritin was below the stage-specific threshold in 54.0% of patients, whereas 46.0% had ferritin above this threshold. Absolute iron deficiency was identified in 27 patients (54.0%), functional iron deficiency in 14 (28.0%) and no biochemical iron deficiency in only nine (18.0%). Thus, 82.0% of anemic CKD patients had either absolute or functional iron deficiency, emphasizing the prominent contribution of impaired iron stores or availability to anemia.

Table 3: Serum ferritin and transferrin saturation profile among CKD patients without anemia (n=50)

Iron-status parameter	n (%) or Mean (SD)	95% CI	Reference value used for testing	Test of significance	P value
Hemoglobin, g/dL	13.48 (1.08)	13.17-13.79	12.0 g/dL	One-sample t=9.69	<0.001*
Serum ferritin, ng/mL	263.4 (171.5)	214.7-312.1	100 ng/mL	One-sample t=6.74	<0.001*
Serum iron, µg/dL	76.3 (25.8)	69.0-83.6	60 µg/dL	One-sample t=4.47	<0.001*
TIBC, µg/dL	302.8 (58.6)	286.1-319.5	300 µg/dL	One-sample t=0.34	0.737
Transferrin saturation, %	26.8 (8.6)	24.4-29.2	20%	One-sample t=5.59	<0.001*
TSAT ≤20%	11 (22.0)	12.8%-35.2%	50%	One-sample z=-3.96	<0.001*
TSAT 21%-30%	21 (42.0)	29.4%-55.8%	50%	One-sample z=-1.13	0.258
TSAT >30%	18 (36.0)	24.1%-49.9%	50%	One-sample z=-1.98	0.048*
Ferritin below stage-specific threshold†	7 (14.0)	6.9%-26.2%	50%	One-sample z=-5.09	<0.001*
Ferritin above stage-specific threshold	43 (86.0)	73.8%-93.1%	50%	One-sample z=5.09	<0.001*
Absolute iron deficiency	7 (14.0)	6.9%-26.2%	50%	One-sample z=-5.09	<0.001*
Functional iron deficiency	9 (18.0)	9.8%-30.8%	50%	One-sample z=-4.53	<0.001*
No biochemical iron deficiency	34 (68.0)	54.2%-79.2%	50%	One-sample z=2.55	0.011*

†Ferritin ≤100 ng/mL in nondialysis CKD or ≤200 ng/mL in hemodialysis patients. Continuous variables were tested against the stated reference value; categorical proportions were tested against 50%.

*Statistically significant at P<0.05.

Table 3 summarizes the iron-status profile of the 50 CKD patients without anemia. Their mean hemoglobin was 13.48±1.08 g/dL (95% CI: 13.17-13.79), significantly above the reference value of 12.0 g/dL (P<0.001). Mean serum ferritin was 263.4±171.5 ng/mL (95% CI: 214.7-312.1), while mean serum iron was 76.3±25.8 µg/dL; both were significantly above their respective reference values (P<0.001). Mean TSAT was also significantly above 20% (26.8±8.6%; 95% CI: 24.4-29.2; P<0.001). In contrast, mean TIBC was comparable to the reference value of 300 µg/dL (302.8±58.6 µg/dL; P=0.737). TSAT ≤20% was found in 11 patients (22.0%), while 21 (42.0%) had TSAT of 21%-30% and 18 (36.0%) had TSAT >30%. Only seven patients (14.0%) had ferritin below the stage-specific threshold, whereas 43 (86.0%) had ferritin above it (P<0.001). Absolute and functional iron deficiencies were identified in 14.0% and 18.0% of patients, respectively. Most patients without anemia 34 (68.0%; 95% CI: 54.2%-79.2%) had no biochemical iron deficiency, which was significantly greater than the reference proportion of 50% (P=0.011).

Table 4: Relationship of iron-status parameters with hemoglobin concentration, anemia and CKD stage (N=100)

Analysis	Estimate	95% CI	Test of significance	P value
Correlation between hemoglobin and serum ferritin	r=0.24	0.05-0.41	Pearson's t=2.45	0.016*
Correlation between hemoglobin and TSAT	r=0.52	0.36-0.65	Pearson's t=6.04	<0.001*
Correlation between hemoglobin and serum iron	r=0.46	0.29-0.60	Pearson's t=5.13	<0.001*
Correlation between hemoglobin and TIBC	r=0.11	-0.09-0.30	Pearson's t=1.10	0.274
Correlation between hemoglobin and CKD stage	r_s=-0.48	-0.61 to -0.31	Spearman's test	<0.001*
Correlation between TSAT and CKD stage	r_s=-0.39	-0.54 to -0.21	Spearman's test	<0.001*
Correlation between ferritin and CKD stage	r_s=0.21	0.01-0.39	Spearman's test	0.036*
TSAT ≤20% and presence of anemia	Unadjusted OR=6.88	2.84-16.67	Wald χ^2=17.96	<0.001*
Low ferritin and presence of anemia	Unadjusted OR=7.21	2.71-19.18	Wald χ^2=15.63	<0.001*
TSAT ≤20% as an independent predictor of anemia†	Adjusted OR=5.36	1.88-15.28	Wald χ^2=9.90	0.002*
Low ferritin as an independent predictor of anemia†	Adjusted OR=4.11	1.35-12.51	Wald χ^2=6.19	0.013*
Each one-stage increase in CKD severity†	Adjusted OR=1.91	1.13-3.24	Wald χ^2=5.79	0.016*
Ferritin per 50-ng/mL increase†	Adjusted OR=0.91	0.79-1.04	Wald χ^2=1.89	0.169
TSAT per 1% increase†	Adjusted OR=0.88	0.82-0.94	Wald χ^2=14.08	<0.001*

†Multivariable logistic regression adjusted for age, sex, diabetes mellitus, dialysis status, CKD stage, serum albumin and C-reactive protein.

CKD-stage-wise comparison

CKD stage	Number of patients, n (%)	Hemoglobin, Mean (SD), g/dL	Ferritin, Mean (SD), ng/mL	TSAT, Mean (SD), %	Anemia present, n (%)
G3a	17 (17.0)	12.72 (1.83)	196.4 (137.8)	26.9 (8.2)	6 (35.3)
G3b	23 (23.0)	11.98 (2.14)	207.8 (149.6)	23.8 (8.7)	9 (39.1)
G4	29 (29.0)	11.21 (2.41)	224.7 (161.3)	20.9 (8.4)	16 (55.2)
G5/G5D	31 (31.0)	10.37 (2.38)	253.6 (181.7)	18.1 (7.6)	19 (61.3)
Overall test	**100 (100.0)**	**F=4.52; P=0.005***	**F=0.62; P=0.605**	**F=4.16; P=0.008***	**χ^2=4.02; P=0.259**

For stage-wise continuous comparisons, one-way ANOVA was used. The chi-square test for trend may additionally be applied to anemia prevalence across ordered CKD stages.: Pearson's correlation coefficient; : Spearman's rank correlation coefficient; OR: odds ratio.

*Statistically significant at P<0.05.

Table 4 evaluates the relationships between iron-status parameters, hemoglobin, anemia and CKD severity. Hemoglobin showed a weak but statistically significant positive correlation with serum ferritin (r=0.24; 95% CI: 0.05-0.41; P=0.016), a moderate positive correlation with TSAT (r=0.52; 95% CI: 0.36-0.65; P<0.001) and a moderate positive correlation with serum iron (r=0.46; 95% CI: 0.29-0.60; P<0.001). The correlation between hemoglobin and TIBC was weak and statistically non-significant (r=0.11; P=0.274). Hemoglobin decreased significantly with advancing CKD stage (r_s=-0.48; 95% CI: -0.61 to -0.31; P<0.001), and TSAT likewise declined with increasing CKD severity (r_s=-0.39; P<0.001). In contrast, ferritin showed a weak positive correlation with CKD stage (r_s=0.21; P=0.036), possibly reflecting inflammation, reduced iron mobilization or previous iron exposure in advanced CKD.

In the unadjusted analysis, TSAT ≤20% was associated with 6.88-times higher odds of anemia (95% CI: 2.84-16.67; P<0.001), while low ferritin was associated with 7.21-times higher odds (95% CI: 2.71-19.18; P<0.001). After adjustment for demographic and clinical covariates,

TSAT ≤20% remained an independent predictor of anemia (adjusted OR=5.36; 95% CI: 1.88-15.28; P=0.002), as did low ferritin (adjusted OR=4.11; 95% CI: 1.35-12.51; P=0.013). Each one-stage increase in CKD severity increased the adjusted odds of anemia by 91% (adjusted OR=1.91; 95% CI: 1.13-3.24; P=0.016). Every 1% increase in TSAT reduced the adjusted odds of anemia by approximately 12% (adjusted OR=0.88; 95% CI: 0.82-0.94; P<0.001). Ferritin considered as a continuous variable was not independently associated with anemia (adjusted OR per 50-ng/mL increase=0.91; P=0.169), indicating that TSAT may provide a more consistent measure of iron availability in CKD.

CKD-stage-wise comparison

The stage-wise analysis demonstrated a progressive reduction in hemoglobin and TSAT with advancing CKD. Mean hemoglobin decreased from 12.72±1.83 g/dL in stage G3a to 10.37±2.38 g/dL in G5/G5D, and this difference was statistically significant (ANOVA F=4.52; P=0.005). Similarly, mean TSAT declined from 26.9±8.2% in stage G3a to 18.1±7.6% in G5/G5D (F=4.16; P=0.008). Mean ferritin increased from 196.4±137.8 ng/mL in G3a to 253.6±181.7 ng/mL in G5/G5D, although the overall difference was not statistically significant (F=0.62; P=0.605). The prevalence of anemia increased from 35.3% in G3a and 39.1% in G3b to 55.2% in G4 and 61.3% in G5/G5D. However, the overall categorical comparison did not reach statistical significance (χ^2=4.02; P=0.259).

Discussion

Comparison of serum ferritin and TSAT between CKD patients with and without anemia

The present study demonstrated substantially impaired iron availability among CKD patients with anemia. Compared with patients without anemia, anemic participants had significantly lower mean hemoglobin (9.42±1.21 vs. 13.48±1.08 g/dL), serum ferritin (178.6±146.8 vs. 263.4±171.5 ng/mL), serum iron (48.7±19.6 vs. 76.3±25.8 µg/dL) and TSAT (17.4±7.1% vs. 26.8±8.6%). In contrast, TIBC did not differ significantly between the groups. These findings support the multifactorial nature of CKD-related anemia, in which reduced erythropoietin production coexists with absolute or functional iron deficiency. Batchelor et al. (2020)[1] similarly described iron deficiency as a major contributor to anemia in CKD because of impaired intestinal absorption, chronic blood loss, inflammation and hepcidin-mediated sequestration of iron within the reticuloendothelial system.

The mean TSAT of 17.4% in the anemic group was below the conventional 20% threshold for iron-restricted erythropoiesis. Gafter-Gvili et al. (2019)[2] identified TSAT ≤20% with low ferritin as absolute iron deficiency, whereas TSAT ≤20% with preserved or raised ferritin represented functional iron deficiency. The lower TSAT and serum iron observed in the present anemic group therefore indicated reduced circulating iron immediately available for erythropoiesis. Hain et al. (2023)[3] emphasized that TSAT may be more informative than ferritin alone in inflammatory CKD because ferritin can remain normal or elevated despite inadequate iron delivery to the bone marrow.

Low ferritin and absolute iron deficiency were each observed in 54.0% of anemic patients compared with 14.0% of non-anemic patients, producing 7.21-times higher odds among those with anemia. The proportion of absolute iron deficiency in the anemic group was higher than the 8%-18% reported across stages G3-G5 in the multinational CKD Outcomes and Practice Patterns Study by Wong et al. (2020)[4]. This difference could be explained by the present study's deliberate inclusion of equal numbers of anemic and non-anemic patients, the use of a higher ferritin threshold for hemodialysis patients, regional differences in nutrition and iron treatment, and inclusion of patients with advanced CKD or dialysis dependence. CKDopps used ferritin <100 ng/mL and TSAT <20% to define absolute deficiency in nondialysis patients, whereas the present study used a ferritin threshold of ≤200 ng/mL for hemodialysis patients.

Functional iron deficiency was found in 28.0% of anemic patients and 18.0% of those without anemia, although the difference was not statistically significant. The CKDopps analysis by Wong et al. (2020)[4] reported incongruent iron indices, including low TSAT with preserved ferritin, in approximately 15%-34% of patients. Thus, the present prevalence of functional deficiency was within the range observed internationally. The absence of a significant between-group difference may have resulted from the relatively small sample, heterogeneous inflammatory status or prior exposure to oral iron, intravenous iron and erythropoiesis-stimulating agents.

Ferritin was significantly lower in the anemic group, but the mean remained above 100 ng/mL. This apparent discrepancy illustrates why ferritin should not be interpreted in isolation. Ferritin is an acute-phase reactant and may increase in association with inflammation, infection, liver dysfunction, malnutrition and recent intravenous iron administration. Lopez et al. (2016)[5] and Rohr et al. (2023)[6] observed that the diagnostic interpretation of ferritin becomes more difficult in chronic inflammatory disease and recommended its combined assessment with TSAT. The large standard deviations of ferritin in both study groups further suggest considerable biological heterogeneity.

TIBC was slightly lower in anemic patients, but the difference was not statistically significant. Le Viet Thang et al. (2020)[7] reported lower TIBC in CKD than in healthy controls and found that TIBC was weakly positively correlated with hemoglobin and serum albumin and negatively correlated with creatinine and inflammation. In the present investigation, the absence of a significant difference may indicate similar transferrin concentrations, nutritional status and inflammatory burden in the two groups. Alternatively, opposing effects of absolute deficiency, which may increase TIBC, and inflammation or protein-energy wasting, which may decrease TIBC, could have reduced the overall difference.

Iron profile among CKD patients with anemia

Among anemic patients, mean serum iron was significantly below 60 µg/dL, mean TSAT was significantly below 20%, and 66.0% had TSAT ≤20%. Absolute iron deficiency was present in 54.0%, while functional deficiency was present in another 28.0%; consequently, 82.0% of anemic patients exhibited some form of biochemical iron restriction. This finding is consistent with the central role of abnormal iron metabolism in renal anemia. Le Viet Thang et al. (2020)[7] found overall iron deficiency in 44.0% of 175 Vietnamese patients with nondialysis CKD, with the proportion increasing from 22.6% in stage G3 to 50.5% in stage G5. Their mean hemoglobin of 9.71±2.26 g/dL was also comparable to the mean of 9.42±1.21 g/dL observed in the present anemic group.

The higher overall iron-deficiency burden in the present anemic group may reflect restriction of the analysis to patients already meeting anemia criteria, inclusion of dialysis patients, or differences in iron-deficiency thresholds. Dialysis patients experience repeated circuit-related blood loss, laboratory phlebotomy and impaired gastrointestinal absorption, while ESA therapy increases marrow iron demand. These mechanisms may produce absolute deficiency even when the patient has previously received iron treatment.

Although mean ferritin was 178.6 ng/mL, nearly two-thirds of anemic patients had TSAT ≤20%. This discordance is characteristic of inflammation-mediated iron sequestration. In CKD, reduced renal clearance and inflammation increase circulating hepcidin, which suppresses ferroportin activity, decreases intestinal iron absorption and prevents the release of stored iron from macrophages. Goyal et al. (2017)[8] observed positive relationships between hepcidin, ferritin and TSAT in nondialysis CKD and demonstrated the complex interaction between inflammation and iron availability. Thus, a relatively preserved ferritin concentration did not exclude inadequate iron delivery for erythropoiesis in the current patients.

Functional iron deficiency was observed in 28.0% of anemic patients. Batchelor et al. (2020)[1] and Hain et al. (2023)[3] explained that functional deficiency may be suspected when TSAT is low despite normal or raised ferritin. Nevertheless, both biomarkers are affected by biological variability; ferritin changes with inflammation, while serum iron and TSAT show diurnal and short-term variation. Therefore, classification based on a single measurement should be interpreted alongside C-reactive protein, clinical inflammation, nutritional status and treatment history.

Only 18.0% of anemic patients had no biochemical iron deficiency. Their anemia may have resulted predominantly from inadequate erythropoietin synthesis, shortened erythrocyte survival, uremic marrow suppression, hyperparathyroidism, folate or vitamin B12 deficiency, occult blood loss, or other chronic diseases. This finding underscores that normal ferritin and TSAT do not exclude renal anemia and that iron indices form only one component of its evaluation.

Iron profile among CKD patients without anemia
Patients without anemia had a mean hemoglobin of 13.48±1.08 g/dL, mean ferritin of 263.4±171.5 ng/mL and mean TSAT of 26.8±8.6%. Most patients had ferritin above the stage-specific threshold, and 68.0% had no biochemical iron deficiency. Nevertheless, 14.0% had absolute and 18.0% had functional iron deficiency. Therefore, almost one-third of non-anemic patients showed evidence of disturbed iron status before the development of overt anemia.

This finding agrees with the concept that iron deficiency and anemia are related but distinct conditions. Guedes et al. (2021)[9] showed in nondialysis CKD that low TSAT, with either low or high ferritin, was associated with adverse clinical outcomes irrespective of hemoglobin status. A separate CKDopps analysis by Guedes et al. (2021)[10] found that low TSAT was associated with poorer physical health-related quality of life, including in patients whose ferritin was not low. These observations support evaluating iron status in CKD patients even before hemoglobin falls below the anemia threshold.

The 22.0% prevalence of TSAT ≤20% among non-anemic patients in the current study was lower than the 66.0% in anemic patients but was still clinically relevant. Wong et al. (2020)[4] likewise showed that iron deficiency was frequently present across nondialysis CKD stages and was not limited to patients with severe anemia. The preservation of hemoglobin in some iron-deficient patients may reflect earlier CKD stage, adequate endogenous erythropoietin, lower inflammatory burden or sufficient marrow iron availability at the time of testing.

Ferritin exceeded the stage-specific threshold in 86.0% of non-anemic patients. This may represent adequate iron stores, but it should not automatically be interpreted as iron sufficiency. Besarab and Drueke (2021)[11] cautioned that ferritin may not accurately represent usable marrow iron in advanced CKD, while TSAT becomes influenced by serum iron variability and reduced transferrin concentrations. Therefore, the 18.0% prevalence of functional deficiency in non-anemic patients was biologically plausible despite relatively high mean ferritin.

The one-sample tests in Tables 2 and 3 compared proportions with an arbitrary 50% benchmark. They describe whether each observed proportion differed from one-half of the respective group but should not be interpreted as evidence that 50% is a recognized clinical standard. The direct comparisons between anemic and non-anemic groups in Table 1 and the regression models in Table 4 provide stronger evidence regarding the study objectives.

Relationships with hemoglobin and CKD stage
Hemoglobin demonstrated a moderate positive correlation with TSAT (r=0.52) and serum iron (r=0.46), but only a weak positive correlation with ferritin (r=0.24). This pattern suggests that circulating iron availability was more closely related to erythropoiesis than the quantity of stored iron. Stancu et al. (2019)[12] similarly reported that hemoglobin was positively related to renal function, serum albumin and TSAT among nondialysis CKD patients. Le Viet Thang et al. (2020)[7] also found that hemoglobin <10 g/dL was associated with more than twice the odds of overall iron deficiency.

The weak ferritin-hemoglobin relationship may be explained by ferritin's dual role as an iron-storage protein and an inflammatory marker. A patient can consequently have a high ferritin concentration but limited iron availability. The present multivariable analysis supported this interpretation: ferritin considered continuously per 50-ng/mL increase was not independently associated with anemia, whereas every 1% increase in TSAT was associated with a 12% reduction in the adjusted odds of anemia.

TSAT ≤20% remained an independent predictor of anemia after adjustment for age, sex, diabetes, dialysis status, CKD stage, serum albumin and C-reactive protein (adjusted OR=5.36). Low ferritin also remained independently associated with anemia (adjusted OR=4.11). Collectively, these results suggest that both depleted stores and reduced available iron contributed to anemia, although TSAT was the more consistent continuous predictor. Guedes et al. (2021)[9] similarly found low TSAT to be a robust risk marker in nondialysis CKD, whereas relationships based on ferritin were less consistent.

Hemoglobin decreased progressively from 12.72 g/dL in G3a to 10.37 g/dL in G5/G5D, while TSAT declined from 26.9% to 18.1%. Each one-stage increase in CKD severity was independently associated with 1.91-times higher odds of anemia. Ryu et al. (2017)[13] reported a comparable stage-dependent increase in anemia prevalence in the KNOW-CKD cohort: 32.8% in G3a, 46.6% in G3b, 78.9% in G4 and 96.5% in G5. The current prevalence estimates were lower in G4 and G5/G5D, possibly because of the equal allocation of anemic and non-anemic participants, differences in ESA or iron therapy, and the much smaller sample.

Although anemia prevalence increased from 35.3% in G3a to 61.3% in G5/G5D, the categorical comparison did not reach significance. The absence of significance despite an apparent upward trend probably reflected small numbers within individual stages and limited statistical power. By contrast, the continuous decline in hemoglobin was significant, indicating that hemoglobin concentration retained more information than dichotomization into anemia present or absent.

Ferritin rose from 196.4 ng/mL in G3a to 253.6 ng/mL in G5/G5D, but the stage-wise difference was not significant. Rising ferritin alongside falling hemoglobin and TSAT is compatible with inflammation and hepcidin-mediated iron restriction rather than improving iron sufficiency. The overall findings therefore support combined interpretation of hemoglobin, ferritin and TSAT. Low ferritin remained useful for identifying depleted stores, whereas TSAT appeared more closely related to concurrent hemoglobin concentration and anemia risk.

Conclusion
Patients with chronic kidney disease and anemia had significantly lower serum ferritin, serum iron and transferrin saturation than CKD patients without anemia. A TSAT ≤20%, low ferritin and absolute iron deficiency were strongly associated with anemia, whereas TIBC and functional iron deficiency did not differ significantly between the groups. TSAT exhibited a stronger correlation with hemoglobin and remained a more consistent independent predictor of anemia than serum ferritin. Hemoglobin and TSAT progressively declined with advancing CKD stage, while ferritin showed a slight increase, possibly reflecting inflammation and impaired mobilization of stored iron. These findings emphasize that serum ferritin should not be interpreted alone in CKD because normal or elevated concentrations may coexist with inadequate circulating iron. Combined assessment of hemoglobin, serum ferritin and TSAT may enable earlier identification of absolute and functional iron deficiency and facilitate appropriate management of CKD-related anemia.

LIMITATIONS
The study had several limitations. Its cross-sectional design did not establish a temporal or causal relationship between abnormal iron parameters and the development of anemia. The relatively small sample of 100 patients, recruited from a single hospital, limited statistical power, subgroup analysis and generalizability. Equal allocation of patients with and without anemia did not represent the natural prevalence of anemia in the underlying CKD population. The inclusion of patients from different CKD stages and dialysis categories introduced clinical heterogeneity.

Serum ferritin and TSAT were assessed at a single time point and may have been influenced by biological variability, diurnal variation, inflammation, nutritional status and recent treatment. Ferritin is an acute-phase reactant and may not accurately represent available iron stores in patients with CKD. Although the adjusted analysis included C-reactive protein and other covariates, residual confounding from chronic inflammation, occult infection, blood loss and dietary iron intake could not be excluded. Information regarding the dose and duration of oral or intravenous iron and erythropoiesis-stimulating agents may not have been fully standardized.

More specific indicators of iron-restricted erythropoiesis, such as reticulocyte hemoglobin content, percentage of hypochromic red cells, soluble transferrin receptor and serum hepcidin, were not measured. Other causes of anemia, including erythropoietin deficiency, vitamin B12 or folate deficiency, hemolysis, hyperparathyroidism and occult gastrointestinal blood loss, were not comprehensively evaluated. Larger multicentric longitudinal studies with repeated measurements are required to confirm the findings and determine the prognostic and therapeutic relevance of the observed iron-status abnormalities.

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