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## Comparing functional versus absolute iron deficiency in chronic kidney disease patients

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**Abstract**---Background: Chronic kidney disease (CKD) is a noteworthy public health concern, often leading to complications as kidney function declines. Anemia is a common early complication linked to reduced quality of life, increased cardiovascular risks, mortality, and progression to end-stage kidney disease. Iron deficiency is an adjustable risk factor for cardiovascular and renal damage. Two forms of iron deficiency exist absolute, characterized by depleted iron stores, and functional, with inaccessible iron stores despite normal or increased total body iron. The prevalence of Anemia in CKD patients ranges from 8.4% - 53%, but the specific prevalence of absolute and functional iron deficiency remains majorly unreported. Materials and methods: Demographic details, previous blood reports (Iron Profile including Serum Iron, Total iron binding capacity, Transferrin saturation, Ferritin), and medical and treatment history were taken. Data analysis was done on SPSS software. Results and Discussion: A total of 70 CKD patients were evaluated in this study. We compared functional and absolute iron deficiency in them. Both types raise the risk of cardiovascular hospitalization; however, absolute iron deficiency may be managed with medical means. These dual deficiencies coexist in a significant CKD population. Anemia in CKD stems from various factors, including erythropoietin deficiency and

disordered iron regulation. Traditional markers like serum ferritin and transferrin saturation have been used to differentiate between the two types of Anemia. Identifying the specific deficiency type can guide tailored therapeutic interventions, improving patient care and outcomes. Conclusion: Functional and Absolute Iron Deficiency Anemia were equally prevalent among CKD patients. Incorporating iron studies (serum ferritin, serum iron, TIBC, and TSAT) into routine assessments can prevent inappropriate iron therapy and guide the treatment of these anemias.

**Keywords**---comparing functional, absolute iron deficiency, chronic kidney disease patients.

## Introduction

Chronic kidney disease (CKD) is a noteworthy public health concern, giving rise to many complications as kidney function progressively diminishes. Anemia, in particular, stands out as one of the earliest complications in CKD, manifesting even in individuals with a glomerular filtration rate (GFR) below 70 mL/min/1.73 m<sup>2</sup> and worsening as renal function declines [1, 2]. The presence of Anemia in CKD is closely associated with a reduction in quality of life [3], heightened risks of cardiovascular diseases, all-cause mortality [3-5], and an increased likelihood of progressing to end-stage kidney disease (ESKD) [3].

Iron deficiency is a prevalent concern among individuals with CKD, encompassing both non-dialysis-dependent (ND) and dialysis-dependent patients, as it stands out as a significant, independently modifiable risk factor for cardiovascular and renal damage (6). The etiology of Anemia in CKD is multifaceted, with the foremost factor being the inadequate synthesis of erythropoietin by the impaired kidneys. Several contributory elements, including reduced red blood cell lifespan, a tendency towards bleeding disorders, iron deficiency, hyperparathyroidism, bone marrow fibrosis, and persistent inflammatory processes, compound Anemia. (7)

We recognize two distinctive forms of iron deficiency: absolute (or actual) and functional. Absolute iron deficiency is characterized by a stark depletion or even the absence of iron stores in vital tissues such as bone marrow, liver, and spleen, and it may be caused by reduced iron intake, decreased iron absorption in the intestines, GI blood loss, phlebotomy, dialysis and more. On the other hand, *functional iron deficiency* is defined as usual or increased total body iron stores, which paradoxically remain primarily inaccessible for erythropoiesis. This inaccessibility may be due to elevated levels of hepcidin due to chronic inflammation and reduced clearance in CKD. Hepcidin is a regulator of iron homeostasis, functions to impede the mobilization of iron stores from reticuloendothelial cells and hepatocytes to sustain erythropoiesis, essentially highlighting the disconnect between iron availability and its effective utilization in this form of iron deficiency (6,8). Hence, supplementation of iron in such patients is questionable.

The frequency of Anemia rose as the CKD advanced, going from 8.4% at stage 1 to 53.4% at stage 5. (9), whereas the prevalence of absolute and functional ID is not described yet (10). Hence, our study investigates Anemia's prevalence and association with absolute and functional Iron Deficiency Anemia (IDA) in CKD patients. Moreover, our research aims to explore the intricate relationships between these different forms of IDA and their potential connections with end-stage kidney disease (ESKD), mortality, and hospitalizations due to cardiovascular issues. We will also see the effect of Iron supplements on both anemias and barriers to iron therapy.

### **Objectives**

Physicians or nephrologists should make a thoughtful decision regarding the assessment and workup for appropriate iron supplementation.

### **Material & Methods**

**Study Type & Ethical Consideration:** This study is a cross-sectional study conducted in a hospital that caters to the population of Uttar Pradesh and Bihar. Proper informed consent was taken from patients or their legal guardians. The study was conducted at BRD Medical College.

### **Inclusion Criteria**

- Patients aged 18 years and above with a confirmed diagnosis of chronic kidney disease (CKD) stages I-V as per the kidney disease: Improving Global Outcomes (KDIGO) guidelines.
- Patients with documented hemoglobin levels.
- Patients with records of iron status markers, including serum ferritin and transferrin saturation (TSAT).

### **Exclusion Criteria**

- Patients with acute kidney injury (AKI).
- Pediatric patients (below 18 years of age).
- Patients with a history of hematological disorders or chronic inflammatory conditions like autoimmune disorders, Rheumatoid Arthritis, and SLE.
- An individual who has been diagnosed with cancer and has kidney dysfunction.

**Data Collection:** Clinical data, including patient demographics, comorbidities, laboratory results, prescribed medications, and relevant medical history, were collected. All data will be anonymized to ensure patient confidentiality and adherence to data protection regulations.

### **Definitions**

**CKD Staging:** The CKD stages were determined using estimated glomerular filtration rate (eGFR) and albuminuria levels according to KDIGO guidelines. Anemia was defined as Hb < 13 gm/dl in males and < 12 gm/dl in females, while

WHO defined *Anemia* as a condition characterized by the number of red blood cells (RBC) or their oxygen-carrying capacity is not adequate to meet physiologic needs (11,12).

*Absolute Iron Deficiency Anemia* was defined as transferrin saturation (TSAT) < 20% and ferritin < 100ng/ml. *Functional Iron Deficiency Anemia* was defined as TSAT < 20% and ferritin 100-500 ng /ml. Ferritin levels > 500ng/ml and TSAT <20% were considered separate categories due to the higher risk of adverse outcomes. (10)

### Data Analysis

Descriptive statistics were used to report patient demographics and characteristics. Data analysis was conducted using statistical software like R or SPSS. Prevalence rates of Anemia, absolute, and functional iron deficiency will be calculated. Associations between different forms of iron deficiency and clinical outcomes, such as mortality and hospitalization risks, will be explored through appropriate statistical tests and models, such as logistic regression and survival analysis.

### Results

Our study had a total sample population of 70 patients with a mean age of  $49 \pm 15.12$  years (standard deviation). Our study population majorly comprised of males as we had 46 (65.71%) males and 24 (34.28%) females. The mean weight of participants was  $62.406 \pm 7.87$  Kg. The stage-wise distribution of patients is shown in Figure I.

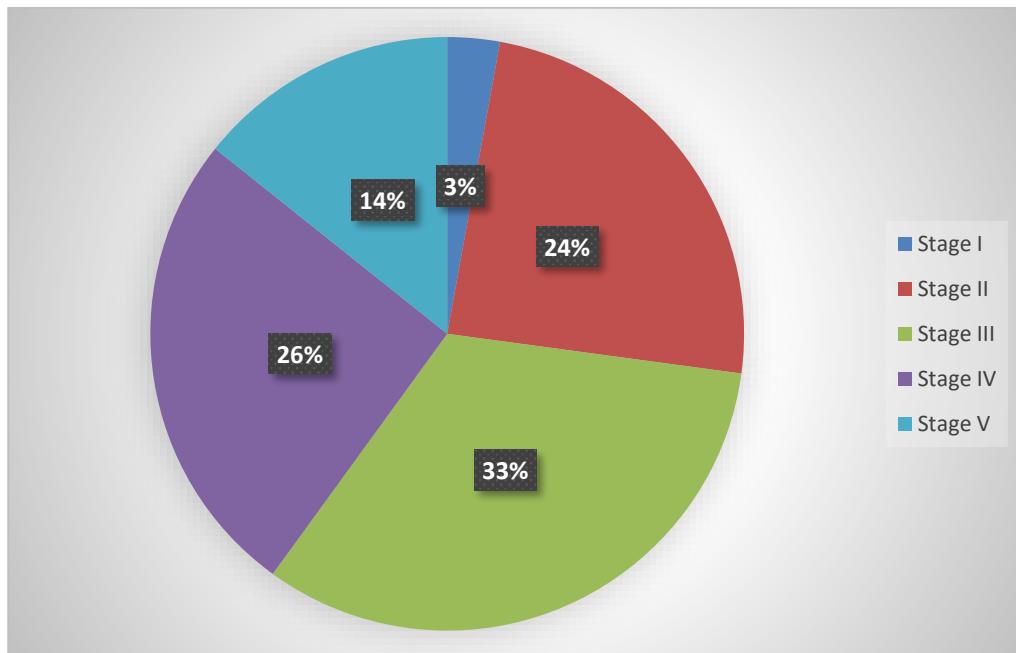


Figure 1; Patient distribution in different CKD stages.

We divided our patients into two categories and considered Stage I-II as one category, which included 19 (27.14%) people, and Stage III-V category had 51(72.85 %) people. The serum Creatinine value ranged from 1.0 to 19.0 mg/dL with a mean creatinine of  $7.93 \pm 4.48$  mg/dl. Serum urea levels ranged from 17.90 to 322.90 mmol/L with a mean of  $94.51 \pm 67.62$  mmol/l. Nearly fifty-five percent (i.e., 39) of our patients were on maintenance dialysis.

All our participants were anemic with mean Hemoglobin of  $7.920 \pm 2.088$  gm/dl according to the criteria for Anemia defined by KDIGO in CKD patients (11,12). Distribution of various Iron parameters (i.e., Serum Iron levels, Total Iron Binding Capacity (TIBC), TSAT, Ferritin). (Table I)

	Serum Iron	TIBC	TSAT	Ferritin
Median	55.700	560.000	10.600	104.300
Mean	62.100	535.107	12.793	122.683
Std. Deviation	44.381	151.259	14.125	130.706
Minimum	6.700	129.000	1.600	7.800
Maximum	228.000	890.000	89.000	567.800

Table I; Various Iron Parameters in our sample population

Thirty-three (47.14%) had TSAT < 20% and Ferritin < 100ng/ml classified as Absolute Iron deficiency anemia. Out of thirty-three, 20 (60.6%) were on hemodialysis. Twenty-seven (81.81%) were on iron supplementation. Thirty-three (47.14 %) had TSAT <20 % and ferritin levels 100-500ng/ml, defined as functional iron deficiency anemia. Out of thirty-three, 16 (48.48 %) were on hemodialysis. Twenty-seven (81.81%) were on iron supplementation. Two (2.8%) people having ferritin levels >500ng/ml and TSAT < 20 % classified into separate categories because of the higher risk of adverse outcomes and increased mortality was reported as per previous studies (10) Two (2.8%) had ferritin levels 100-500 ng/ml but TSAT >20%; thus, they were not classified in either category. No Iron deficiency anemia was seen, likely other causes of Anemia present. Thirty four (48.6%) of the 70 patients exhibited a transferrin saturation (TSAT) level below 10%. This marked a significant prevalence, with 34 patients falling into this category. Distribution of Ferritin and TSAT across our population is divided into two categories based on CKD stages (Table II & III)

Table II; Distribution of Ferritin levels in our sample population

CKD Stage	Ferritin Category	Frequency	Percentage
stage I-II	100-500	10	55.556
	<100	8	44.444
	>500	0	0.000
	Total	18	100.000
stage III-V	100-500	25	48.077
	<100	25	48.077
	>500	2	3.846
	Total	52	100.000

Table III; Distribution of TSAT in our sample population

CKD Stage	TSAT Category	Frequency	Percent
stage I-II	<20%	15	83.333
	>20%	3	16.667
	Total	18	100.000
stage III-V	<20%	45	86.538
	>20%	7	13.462
	Total	52	100.000

Traditionally Iron profile is used to differentiate between functional and absolute iron deficiency anemia (Table I) (7)

Table IV; Different parameters of iron study in functional and absolute iron deficiency anemia

Lab Parameter	Functional IDA	Absolute IDA
Serum Iron Level	Normal	Decreased
TIBC	Normal / Decreased	Increased
TSAT	Increased	Decreased
Ferritin	Increased	Decreased

Progression with worsening CKD stages leads to lower median serum iron levels, higher median ferritin levels, higher TSAT (Figure II), and lower TIBC (560 in Stage I – II and 547.17 in Stage III- V). Serum Iron shows a transition to absolute IDA. In contrast, all other parameters show a transition toward functional IDA with the progression of CKD stages. However, our study found the almost equal prevalence of Functional and Absolute IDA in both categories. (Table V)

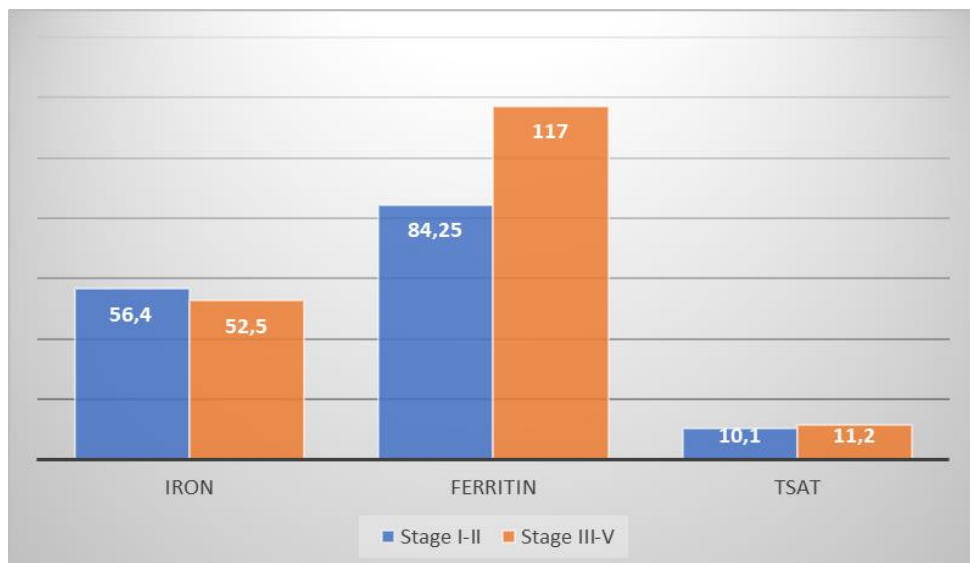


Figure II; Trends of Median of Serum Iron, Ferritin level and TSAT with progression of CKD stages.

Table V: Prevalence of Absolute IDA and Functional IDA in accordance to CKD Stages

	Absolute IDA; n (%)	Functional IDA; n (%)
CKD Stage I-II	8(47%)	25(51%)
CKD Stage III-V	9(53%)	24(49%)

## Discussion

The comparative analysis of functional and absolute iron deficiency in CKD patients revealed critical insights into managing and understanding iron metabolism in this population. Anemia in CKD patients typically results from a combination of factors, including erythropoietin deficiency, uremia-related inhibitors in circulation, and shortened red blood cell lifespan. Both absolute and functional iron deficiency increased the risk of cardiovascular hospitalization in CKD, while only functional iron deficiency and high ferritin levels raised mortality risk. Functional and absolute iron deficiency were found to coexist in a substantial portion of the CKD patient population. (10) . Our study observed a higher prevalence of iron deficiency, with 47% of patients presenting absolute iron deficiency and an equal percentage showing functional iron deficiency. This finding surpasses the results reported in a prior study conducted by Awan et al., where they reported lower rates of 30% for absolute iron deficiency and 19% for functional iron deficiency.

Eisenga et al. found that TSAT <10% is an independent predictor of unfavourable outcomes in CKD patients. (17) Our study revealed that 48.57% of 70 patients had TSAT <10%. Additionally, disordered iron regulation is gaining recognition as a significant contributor. Elevated hepcidin levels, associated with decreasing GFR, hinder iron release from enterocytes and the reticuloendothelial system through ferroportin (12,13). This results in increased tissue ferritin but insufficient circulating iron for erythropoiesis.

The reliance on traditional markers such as serum ferritin and transferrin saturation may not be sufficient for distinguishing between functional and absolute iron deficiency. The central tenet of our study lies in acknowledging the coexistence of absolute and functional iron deficiencies in CKD patients. This duality signifies that the mere presence of Anemia in CKD is a multifaceted challenge, demanding nuanced and customized approaches. The clinical significance of this distinction is profound. By identifying and addressing these iron deficiencies more precisely, healthcare providers can tailor their interventions to each patient's unique iron status, thereby improving the quality of care.

The clinical implications of these two types of iron deficiency are paramount. Functional iron deficiency, characterized by a low transferrin saturation, may result from impaired iron utilization despite adequate iron stores, often attributed to chronic inflammation. Iron deficiency has been associated with reduced response to erythropoiesis-stimulating agents and suboptimal hemoglobin control in CKD patients. On the other hand, absolute iron deficiency, marked by low serum ferritin levels, suggests an inadequate iron supply and is linked to classic

iron deficiency Anemia. (9) Identifying the specific type of iron deficiency in CKD patients may guide more precise therapeutic interventions.

Tailoring therapeutic strategies to the type of iron deficiency is an emerging concept. Even when absolute iron deficiency is absent according to current criteria, administering iron supplements can raise hemoglobin levels and alleviate Anemia. (15,16) Functional iron deficiency may necessitate anti-inflammatory and erythropoiesis-stimulating agent adjustments, while absolute iron deficiency may require more aggressive iron replacement therapy. (10)

Future research in this field should focus on developing more sensitive and specific diagnostic markers for iron deficiency in CKD patients. Moreover, prospective studies with larger cohorts and more extended follow-up periods can provide a more comprehensive understanding of the clinical course and outcomes associated with these distinct types of iron deficiency.

In summary, our study paves the way for a deeper understanding of iron deficiency in CKD by distinguishing between absolute and functional iron deficiencies. This distinction offers a unique perspective that could revolutionize the management of iron-related complications in CKD. With further research and a commitment to personalized approaches, the prospects for enhanced patient care and improved outcomes in CKD appear brighter than ever. The paradigm shift we propose in our study marks an essential step towards this overarching goal, offering hope for a future where CKD patients receive precisely the care they need.

### **Review of literature**

Awan et al found that in CKD, the presence of Anemia has been closely linked to adverse patient outcomes. Notably, two forms of iron deficiency anemia (IDA), absolute and functional IDA, and their associations with outcomes have garnered attention.

A study involving 933,463 CKD patients revealed that 20.6% experienced anemia. Among those with Anemia, 23.6% had transferrin saturation (TSAT), Ferritin measured, with 30% diagnosed with absolute IDA and 19% with functional IDA. Interestingly, while absolute IDA was not directly associated with increased mortality, it was correlated with a higher risk of cardiovascular hospitalization at 1- and 2-year intervals. In contrast, functional IDA was linked to elevated mortality and heightened risks of cardiovascular hospitalization at the same intervals. Moreover, elevated ferritin levels (>500 ng/mL) were associated with an increased mortality risk (10).

Furthermore, Eisenga et al research has indicated within the CKD patient population that low transferrin saturation (TSAT), particularly TSAT<10%, is a robust predictor of adverse outcomes. This underlines the importance of prioritizing TSAT as a marker of iron status over serum ferritin in clinical practice for CKD patients (17).



An analysis of 6766 CKD patients in Brazil, France, Germany, and the USA highlighted international variations in anemia assessment and management practices. Hemoglobin and iron status monitoring fell short of recommended frequencies, and anemic patients with iron deficiency often went untreated. This underscores the need for enhanced CKD care practices (18).

In Ireland, a cross-sectional study conducted in specialist nephrology clinics assessed the management of Anemia in CKD. The prevalence of Anemia increased with CKD progression but exhibited variations among clinical sites. Iron deficiency was familiar, yet treatment was infrequent, with testing for iron deficiency often overlooked. This study revealed discrepancies in clinical guidelines and low utilization of effective treatments (19).

Iron deficiency, whether absolute or functional, is pivotal in Anemia associated with advanced CKD. Blood loss, poor iron absorption, and chronic inflammation are common risk factors for both types. However, conventional biomarkers for diagnosing iron deficiency Anemia (IDA) have their limitations, posing challenges. This review delves into IDA pathophysiology, diagnostic tests, treatment guidelines, and available oral and intravenous iron options. It also discusses the risks of liberal iron supplementation and the IV vs. oral iron supplementation debate in CKD (20).

Notably, in non-dialysis-dependent CKD patients, the real-world management of Anemia often falls short of optimal standards. Treatment initiation appears to be influenced by hemoglobin trajectory and a history of heart failure (21).

Lastly, a study explored the impact of iron deficiency on mortality and cardiovascular events in non-dialysis CKD patients, regardless of Anemia. It suggests the necessity for innovative iron deficiency management strategies in CKD, extending beyond anemia treatment for potential improvements in patient outcomes. This study observed that iron deficiency is prevalent in non-dialysis CKD patients and highlights the need for further interventional studies to optimize iron administration strategies (22).

Acknowledging that iron deficiency anemia (IDA) is a common concern in CKD, the article also addresses the challenges posed by conventional oral iron agents and their limited effectiveness and side effects. It provides insights into current treatment guidelines for Anemia in CKD. It presents clinical trial data on existing and novel oral iron therapies, such as ferric citrate, which shows promise in non-dialysis-dependent CKD patients, and emerging options like ferric maltol and microsomal iron that are under development for CKD-associated IDA (23).

## **Conclusion**

In the studied CKD patient population, Functional and Absolute Iron Deficiency Anemia were equally prevalent. We recommend integrating comprehensive iron studies (serum ferritin, serum iron, TIBC, and TSAT) into routine assessments to optimize anemia management. This approach helps prevent overuse of iron therapy in functional Anemia and under-treatment in absolute anemia cases.

Patients with inadequate responses to iron supplementation should be investigated for functional iron deficiency.

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