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ORIGINAL RESEARCH

Serum Iron Profile in Non-Dialysis Chronic Kidney Disease Patients with Anemia

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ABSTRACT

Background: The present study aimed to evaluate the levels of serum iron, total iron binding capacity (TIBC), transferrin saturation and serum ferritin in diagnosed cases of chronic kidney disease due to any aetiology not undergoing dialysis. Study also aimed to determine the correlation between serum creatinine and serum iron levels in chronic kidney disease in this group of patients.

Materials and Methods: The present study was conducted in the city of Dibrugarh and which also included patients belonging to adjoining districts of Upper Assam from 20th October 2018 to 19th October 2019 for a period of 1 year. A clinico-hematological study was undertaken to evaluate the levels of serum iron, total iron binding capacity (TIBC), transferrin saturation and serum ferritin in diagnosed cases of chronic kidney disease (not on dialysis) due to any aetiology. Study included 110 old and newly diagnosed cases of CKD attending the out–patient department not on dialysis. A cut-off off Hemoglobin <13 g/dl in men and <12 g/dl in women was used to make the diagnosis of anemia.

Results: Prevalence of anemia among CKD cases was observed as 74.6% with Hb level <6 gm% was observed in 6.4% cases. Normocytic normochromic picture was observed in 53.6% cases. Decreased level of serum iron, ferritin, TIBC and transferrin saturation was seen in 99.1%, 16.4%, 52.75 and 78.2% cases respectively. Mean levels of haemoglobin, RBC and iron indices (except for TIBC levels) decreased significantly with increase in the CKD stage. A significant positive correlation was observed between eGFR levels with haemoglobin and iron indices (except TIBC) while an inverse correlation was observed with creatinine levels.

Conclusion: Anemia among Pre dialysis-CKD cases is mostly normocytic and moderate in severity. Functional iron deficiency was the predominant form of iron deficiency in these patients. Both hemoglobin and other iron indices worsens with progressive loss of kidney functions.

Keywords: Anemia, Chronic Kidney Disease, Creatinine, Glomerular filtration rate, Iron Deficiency.

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INTRODUCTION

Chronic kidney disease (CKD) is characterized by a decrease in glomerular filtration rate (less than 60 ml /min for three months or longer) and histological evidence of reduction in

nephron population. Multiple causes of kidney injury leads to a final common pathway of End stage renal disease (ESRD), and this syndrome is characterized by hypertension, anemia, renal bone disease, nutritional impairment, neuropathy, impaired quality of life, and reduced life expectancy.[1]CKD is a silent epidemic of the 21st century. Surveys have suggested that as many as 16% of the adult population have CKD. Its occurrence is not confined to developed countries; it is universal. Every year over one lakh people in India are diagnosed with CKD necessitating a kidney transplant or maintenance dialysis.[2]

Anemia is a common complication among patients with CKD, and its prevalence rises as estimated glomerular filtration rate (eGFR) decreases.[3] Anemia in CKD is associated with decreased quality of life and increased risk of cardiovascular disease and mortality.[4–6] Several mechanisms of CKD-related anemia have been implicated,[5] including relative erythropoietin deficiency, decreased red cell life span, abnormal iron metabolism, chronic inflammation, metabolic abnormalities and effects of medications such as renin angiotensin system (RAS) inhibitors.[7-21]

In patients with CKD, anemia is defined when concentration of hemoglobin (Hb) is below 2 times the SD of the mean Hb of the general population, corrected for age and sex.[22] In CKD, anemia may occur at early stages (CKD stages 2 and 3).[23] The Hb levels decreases when the estimated glomerular filtration rate (eGFR) is around 70ml/min/1.73m2 (men) and 50ml/min/1.73m2 (women). However anemia is more common in CKD stage 4 (even earlier in diabetic patients) and worsens as CKD progresses.[24,25] In advanced stages of CKD and in the dialysis population anemia is present in as high as 90% of patients because some amount of blood remains in the dialysis machine leading to greater amount of iron deficiency in dialysis patients.[26,27]

The present study aimed to evaluate the levels of serum iron, total iron binding capacity (TIBC), transferrin saturation and serum ferritin in diagnosed cases of chronic kidney disease due to any aetiology not undergoing dialysis. Study also aimed to determine the correlation between serum creatinine and serum iron levels in chronic kidney disease in this group of patients.

We want to do this study because Iron deficiency anaemia is very common in CKD patients and timely diagnosing Iron deficiency anaemia and supplementing it with Iron therapy can significantly reduce the morbidity and mortality in CKD patients.

MATERIALS & METHODS

Present Hospital based observational study was conducted in the city of Dibrugarh and which also included patients belonging to Adjoining districts of upper Assam from 20th October 2018 to 19thOctober 2019 for a period of 1 year on 110 CKD Patients (not on dialysis). Patients who were on dialysis, haematinics, erythropoietin, blood transfusion therapy (within 3 months) were excluded. Other excluded cases were: patients with acute infections, burn, or patients on drugs (like cephalosporins, dapsone, levodopa, levofloxacin, methyldopa, nitrofurantoin, NSAIDs, etc.), pregnancy, haemoglobinopathies and children below 13 years of age.

We screened the patients and case selection of chronic kidney disease was done according to the Kidney Disease Improving Global outcome (KDIGO) workgroup 2012 definition[23]. Under aseptic and antiseptic precaution, 5 ml of blood was collected from each subject from a suitable vein (preferably from antecubital vein) with a sterilized syringe. The serum was separated and used for iron estimation test in the same day and haemolysed sample were discarded. The following threshold values for Hemoglobin was used for diagnosis of anemia: Hb <13 g/dl in men and Hb <12 g/dl in women.[24]

Normal laboratory Values:

- Serum Iron: 70—200 □ g/dl.
- Total Iron Binding Capacity (TIBC): 250—435 □ g/dl.
- Transferrin Saturation: 20—45%
- Serum Creatinine: Males: 0.9—1.5 mg/dl and; Females: 0.8—1.3 mg/dl.
- Serum Ferritin: Males: 12-300ng/ml and; Females: 12-200ng/ml

Result

Mean age of the study participants was 58.62 years with 64.5% males to 35.5% females. Out of the 110 cases, 1.8% were in CKD stage 2 while 27.3% and 70.9% were in CKD stage 3 and 4 respectively. Hemoglobin level below 6 gm% was observed in 6.4% cases while it was between 6-10 gm% in 68.2% cases. On peripheral smear, microcytic hypochromic picture was observed in 19.1% cases while normocytic hypochromic picture was seen in 27.3% cases. Normocytic normochromic picture was observed in 53.6% cases. Decreased level of serum iron, ferritin, TIBC and transferrin saturation was seen in 99.1%, 16.4%, 52.75 and 78.2% cases respectively. Mean levels of haemoglobin, RBC and iron indices (S. Iron, ferritin and Transferrin saturation) decreased significantly with increase in the CKD stage. Mean values of all the above parameters were significantly lower in CKD stage 4 as compared to stage 3 and stage 2 respectively except for TIBC levels, where mean values were greater in stage 4 as compared to stage 3 ($p<0.05$; [Table1]). A significant positive correlation was observed between eGFR levels with haemoglobin and iron indices (except TIBC) i.e. with decrease in eGFR (i.e. increased severity of CKD) leads to decrease in all these parameters while S. TIBC increases with decrease in eGFR [Table 2]. A significant inverse correlation was observed between creatinine levels with haemoglobin and iron indices (except TIBC) while S. TIBC increases with increase in creatinine levels [Table 3].

Table 1: Mean values of Iron indices as per CKD stage

Variables	CKD Stage	N	Mean	SD	p- value
Hemoglobin	II	2	13.60	0.57	<0.01
	III	30	10.01	1.48	
	IV	78	8.60	1.45	
	Total	110	9.07	1.69	
S. Iron	II	2	39.46	3.92	<0.05
	III	30	35.09	9.76	
	IV	78	32.19	10.53	
	Total	110	33.11	10.31	
S. TIBC	II	2	366.60	100.90	<0.05
	III	30	261.53	90.75	
	IV	78	237.24	86.50	
	Total	110	256.82	90.81	
S. Ferritin	II	2	156.92	136.51	<0.01
	III	30	238.77	104.13	
	IV	78	143.02	75.12	
	Total	110	169.38	94.16	
S. Transferrin Saturation	II	2	11.34	4.19	<0.05
	III	30	16.57	6.82	
	IV	78	13.52	5.61	
	Total	110	14.31	6.07	

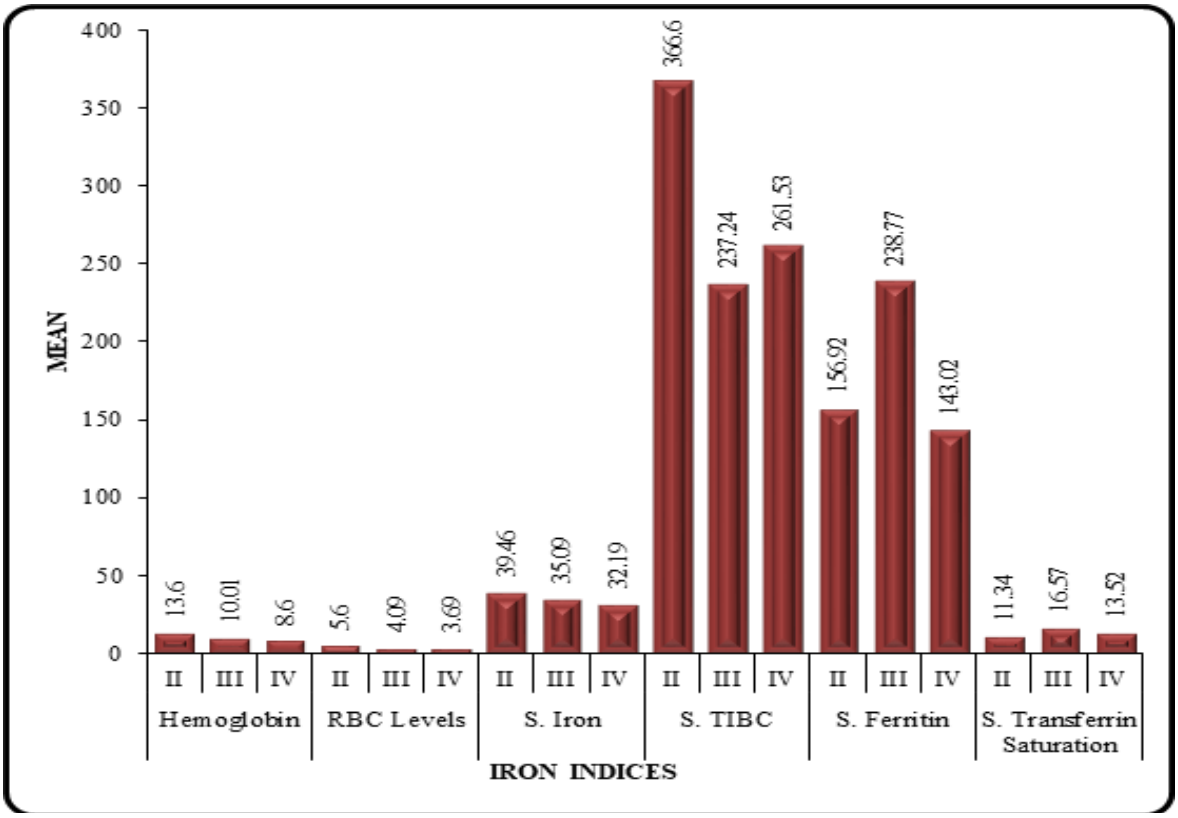

Figure 1: Bar diagram showing mean values of Iron indices as per CKD stage

Table 2: Correlation of GFR with Iron indices

Pearson co-relation		
eGFR	**r-value**	**p- value**
Hemoglobin	0.50	<0.01
S. Iron	0.27	<0.01
S. TIBC	-0.19	0.045
Transferrin	0.33	<0.01
S. Ferritin	0.37	<0.01

Table 3: Correlation of Creatinine with Iron indices

Pearson co-relation		
Creatinine	**r-value**	**p- value**
Hemoglobin	-0.37	<0.01
S. Iron	-0.26	<0.01
S. TIBC	0.34	0.045
Transferrin	-0.41	<0.01
S. Ferritin	-0.18	0.064

Table 4: Distribution of study cases as per findings on peripheral blood smear irrespective of sex

PBS	**Number of cases**	**Percentage (%)**
Microcytic Hypochromic	21	19.1%
Normocytic Hypochromic	30	27.3%
Normocytic Normochromic	59	53.6%
Total	110	100.0%

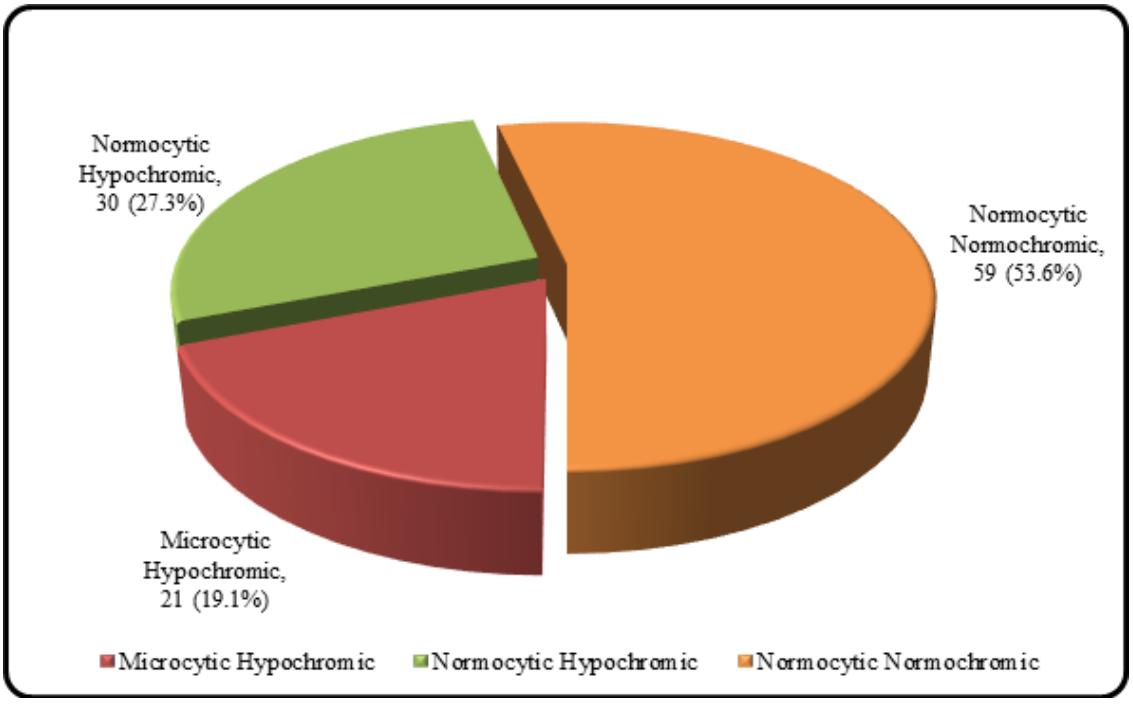

Figure 2: Bar diagram showing distribution of study cases as per findings on peripheral blood smear irrespective of sex.

Table 5: Distribution of study cases as per haemoglobin levels irrespective of sex

Hemoglobin levels (gm%)	Number of cases	Percentage (%)
<6 gm%	7	6.4%
6–10 gm%	75	68.2%
> 10 gm%	28	25.5%
Total	110	100.0%

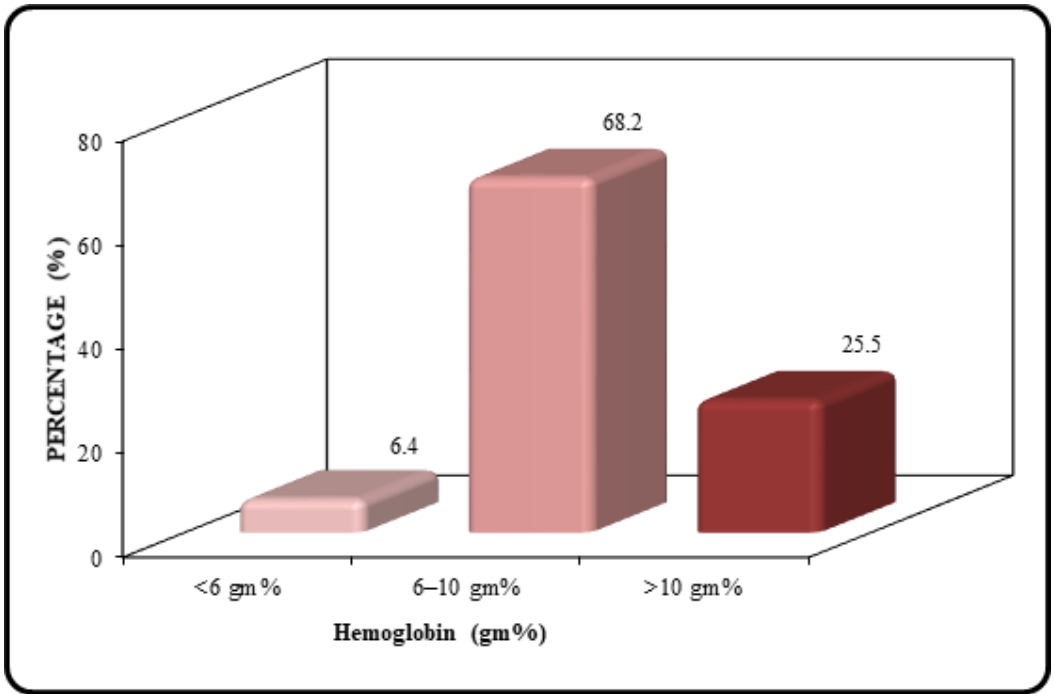

Figure 3: Bar diagram showing distribution of study cases as per Hemoglobin levels irrespective of sex

Table 6: Association of CKD stage with haemoglobin levels

Hemoglobin	CKD Stage			Total
	II	III	IV	
<6 gm%	0	1	6	7
	0.0%	3.3%	7.7%	6.4%
6–10 gm%	0	12	63	75
	0.0%	40.0%	80.8%	68.2%
> 10 gm%	2	17	9	28
	100.0%	56.7%	11.5%	25.5%
Total	2	30	78	110
	100.0%	100.0%	100.0%	100.0%
p value <0.01				

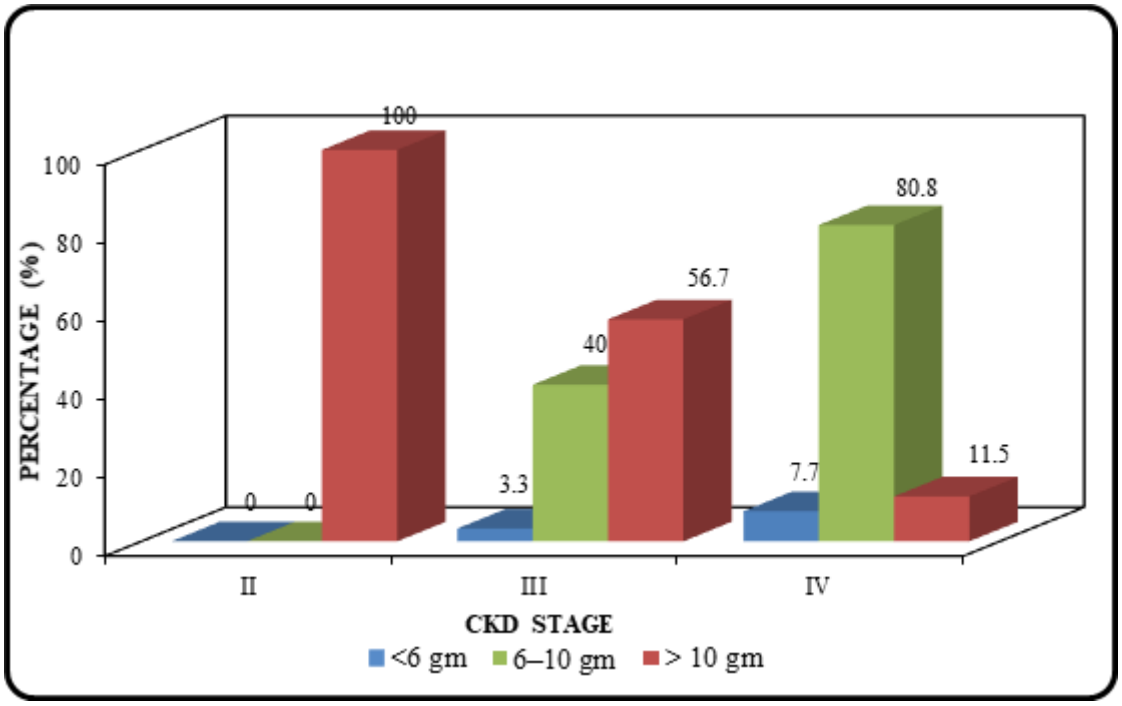

Figure 4: Bar diagram showing association of CKD stage with Hemoglobin levels

DISCUSSION

Present study included 110 old and newly diagnosed cases of CKD cases (not on dialysis). Out of the 110 cases, 1.8% were in CKD stage 2 while 27.3% and 70.9% were in CKD stage 3 and 4 respectively.

We observed prevalence of anemia as 74.6% among CKD cases with Hb level below 6 gm% in 6.4% cases. We observed a significant fall in hemoglobin as the CKD stage progresses. This fall in hemoglobin is statistically significant and correlated well with the stage of CKD. Mean hemoglobin levels among CKD cases was 9.07 gm% while mean hemoglobin in stage 2 was 13.6 g/dl, in stage 3 was 10.0 g/dl while in stage 4 was 8.6 g/dl.

Talwar et al,[28] and Singh et al,[29] observed lower hemoglobin similar to present study i.e. 7.1 gm% and 6.93 gm% among CKD cases. Vikrant S et al,[30] observed mean hemoglobin as 9.2 ± 2.2 g/dL. There was a progressive fall in hemoglobin with increasing severity of CKD and in CKD Stage 3, 4, and 5 the mean hemoglobin was 10 ± 2.2, 9.4 ± 2.1, and 8.4 ± 1.9 g/dL, respectively (P = 0.001). Khanam et al,[31] in their study observed mean hemoglobin levels 12.7 gm% in stage I & II, 10.8 gm% in stage III, 9.1 gm% in stage IV and 7.4 gm% in

stage V. Stauffer ME et al,[32] observed that prevalence of anemia increased with stage of CKD, from 8.4% at stage 1 to 53.4% at stage 5.

Anemia in CKD is usually normocytic normochromic which is mainly hypoproliferative anemia due to EPO deficiency leading to bone marrow suppression and peripheral destruction. Sometimes, it can be microcytic hypochromic due to superimposed iron deficiency anemia and hypoproliferative due to reduced EPO activity in the bone marrow.[33] Patients may also show macrocytic anemia due to Vitamin B12/folate deficiency, dialysis-induced changes in red cell volume, and bone marrow suppression.[34] Hematocrit is reduced in these patients due to hemodilution.[35]

In the present study, normocytic normochromic picture (53.6%) was the predominant finding in the peripheral smear and the most common anemia was also being normocytic normochromic type in the majority. Microcytic anemia was seen in 19.1% cases. Lack of macrocytic anemia cases in the present study is because of the low frequency of occurrence of Vitamin B12 deficiency in CKD as vitamin B12 levels are increase in renal failure as a result of decreased clearance by the failed kidneys.

Sundhir N et al,[35] in their study also observed most common profile seen on peripheral blood smear as normocytic normochromic anemia (76%), followed by microcytic hypochromic picture seen 22% patients. The results of the present study are also similar to the study by Singh, et al,[29] and Sundhir, et al.[35] The differences in the smear findings between different studies are due to the variation in the sample size and difference in the study population.

Decreased level of serum iron, ferritin, TIBC and transferrin saturation was seen in 99.1%, 16.4%, 52.75 and 78.2% cases respectively. Mean levels of iron indices (S. Iron, ferritin and Transferrin saturation) decreased significantly with increase in the CKD stage. Mean values of all the above parameters were significantly lower in CKD stage 4 as compared to stage 3 and stage 2 respectively except for TIBC levels, where mean values were greater in stage 4 as compared to stage 3 ($p<0.05$).

Vikrant S et al. 30 observed 307 (52.6%) patients having transferrin saturation (TSAT) <20% (functional iron deficiency), 162 (27.7%) patients had serum ferritin <100 ng/mL (absolute iron deficiency). Wong MM et al,[36] studied a total of 6766 participants with CKD Stages 3a–5ND from nephrology clinics in Brazil, France, Germany and the USA. The proportion of anemic patients with ferritin <100 ng/mL or TSAT <20% ranged from 42% in Brazil to 53% in France and Germany. In a study done by Iyawe, et al,[37] in Nigeria included 100 pre-dialysis CKD patients mean serum ferritin was 223.23 ng/ml which is within normal range and similarly in the present study mean serum ferritin was 169.38 ng/ml which is also within the normal range indicating absence of functional iron deficiency among CKD patients in the present study.

The assessment of iron status is easy if the Transferrin saturation and serum ferritin are both high and low in the evaluated patients. In present study, 18 patients (16.4%) had low serum ferritin (<100 ng/ml) with low TSAT (<20%) indicating absolute iron deficiency. Another study done in India by Veena A et al,[38] percentage of absolute iron deficiency in CKD patient was 20.8% which is somewhat similar to present study. Iyawe IO et al,[37] in their study observed that among CKD patients with ID, 11 (85.7%) had functional iron deficiency while three (14.3%) had absolute iron deficiency which was also comparable to present study (78.2% and 16.4%).

In present study, a significant inverse correlation was observed between creatinine levels with haemoglobin, RBC and iron indices (except TIBC). Increase in creatinine levels (i.e. deterioration of kidney functions) leads to decrease in all these parameters except S. TIBC, which increases with increase in creatinine levels.

Branten AJ et al,[39] in their study observed that in univariate analysis, serum ferritin correlated significantly with creatinine (r = −0.19, P = 0.02). Kovesdy CP et al,[40] in their study of Patients with Non-dialysis-Dependent Chronic Kidney Disease observed a significant correlation between iron indices with serum creatinine levels ($p<0.05$). Fishbane S et al,[41] in their study observed thatlow levels of iron tests [either serum ferritin < 100 ng/ml or transferrin saturation (TSAT) < 20%] were present in most patients with increased creatinine levels. Reddy GC et al. 42 studied correlation between the indices of iron status in CKD patients and found significant correlation between creatinine and ferritin (r-0.242; $p<0.05$) and hemoglobin levels (r -0.23; $p<0.05$).

To summarize, anemia among Pre dialysis-CKD cases is mostly normocytic and moderate in severity. Management of anemia in these patients requires recognizing that not only decreased EPO production but also decreased iron availability, can lead to anemia. Functional iron deficiency was the predominant form of iron deficiency in pre-dialysis CKD patients. Bothe hemoglobin and other iron indices worsens with progressive loss of kidney functions i.e. decrease in eGFR levels and increase in serum creatinine levels. Thus, physicians managing pre dialysis-CKD patients should conduct a full anemia workup to determine its etiology and guide appropriate treatment decisions.

CONCLUSION

Anemia among Pre dialysis-CKD cases is mostly normocytic and moderate in severity. Functional iron deficiency was the predominant form of iron deficiency in these patients. Bothe hemoglobin and other iron indices worsens with progressive loss of kidney functions i.e. decrease in eGFR levels and increase in serum creatinine levels. Thus, physicians managing pre dialysis-CKD patients should conduct a full anemia workup to determine its etiology and guide appropriate treatment decisions.

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