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A Study on spectrum of Anemia in Chronic kidney disease.

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Abstract:
Background*:Anemia is a very common manifestation among patients of CKD. As the renal dysfunction increases in severity, there is proportional increase in prevalence and severity of haematological impairment. There is increased incidence of cardiovascular dysfunction, cognitive impairment and sleep disturbances in anemic patients with CKD. It is also associated with progression of renal disease and increased mortality. This study was conducted to study the spectrum of Anemia in Chronic Kidney Disease patients at a tertiary care centre in North east India.*
Objectives: *To study the clinicopathological profile of anemia in patients with CKD.*
Materials and Methods*: This prospective observational study was done on 200 patients of CKD taken from Department of Medicine, Agartala Government Medical college & GBP Hospital, Chronic kidney disease (CKD) was defined as per Kidney Disease outcomes Quality Initiative (KDOQI) guideline.*
Results*: The mean age of the study population was 59.59± 10.99 years. Among 200 participants 68.5% were male and 31.5 % were female. The mean Hemoglobin level was 8.98 ± 1.64 g/ dL. 47.5% of the participants had Mild, 28.0% of the participants had Moderate.,14.0% of the participants had severe grade anemia. The mean S. Iron (µg/dL) was 36.75 ± 17.77. 93.5% of the participants had S. Iron: <60 µg/dL. 6.5% of the participants had S. Iron: ≥60 µg/dL. 33.5% of the participants had RBC Morphology of Microcytic Hypochromic, 16.0% of the participants Normocytic Hypochromic. 50.5% of the participants had Normocytic Normochromic. Mean Hemoglobin level were significantly lower in patients with increasing of age and lower eGFR.*
Conclusion: *Anemia is a very common clinical manifestation in patients of Chronic Kidney Disease. Severity of Anemia increases with progressive renal damage. Lower kidney function is strongly associated with a higher prevalence of Anemia.*
Key Word*: Anemia, Erythropoetin, Chronic Kidney Disease, Hemodialysis, GFR, KDIGO*

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I. Introduction

Chronic Kidney Disease is a major health care problem worldwide, with a global prevalence of 8-16%.[1] The US national kidney foundation's kidney dialysis quality initiative (KDOQI) guideline defines CKD as kidney damage or estimated GFR (eGFR <60 ml/min/1.73m2) for more than equal to 3 months.[2] Chronic Kidney Disease leads to a wide range of systemic derangements. Anemia is a very common manifestation among patients of CKD.[3,4] Anemia prevalence worldwide was estimated at 33% in 2010 with iron deficiency being the leading cause in half of the cases[5, 6]. In CKD patients, anemia is a clinically significant burden and it becomes more prevalent with declining GFR [7]. Anemia is associated with reduced quality of life and increased cardiovascular morbidity and mortality[8]. Erythropoietin (EPO) deficiency remains the major cause of anemia in CKD patients due to the decrease in renal EPO production [9]. As the renal dysfunction increases in severity, there is proportional increase in prevalence and severity of haematological impairment. Studies have shown that Anemia begins to manifest when GFR falls below 60ml/min/1.73 m^2 (Stage III).[10] Accordingly, The prevalence of anemia ranges from about 1% in stage 2 of CKD to almost 100% in end stage renal disease (ESRD) patients.[11]

The burden of CKD in India has been recognized as a silent epidemic and a major cause of mortality and morbidity affecting large populations worldwide. The approximate prevalence of CKD is 800 per million population and the incidence of end stage renal disease (ESRD) is 150 – 200 per million population[12]. To reduce the burden and improve the patient outcome CKD should be detected and treated before the onset of kidney

failure through investigations and prompt treatment of CKD. Recent studies show that a substantial number of individuals with CKD are anemic and diagnosis and treatment of anemia is grossly neglected[13].

Anemia is suspected in all CKD patients who are undergoing hemodialysis [14]. A functional or absolute iron deficiency is estimated in 25%–38% of CKD patients with anemia[15]. Despite the administration of recombinant erythropoietin (EPO, a renal hormone that stimulates red blood cell production), less than one-third of hemodialysis patients with CKD achieve target hemoglobin levels of 11 to 12 g/dL [16]. As a result, CKD patients with iron deficiency anemia (IDA) suffer secondary consequences leading to an increased risk of cardiovascular disease [17], cognitive impairments [18], and fatigue and mortality rates. [19]

Iron deficiency is the major contributing factor for anemia in about 23 – 38% of CKD patients but it is unclear to what extent the iron store indices are associated with outcomes in these stages of CKD. Despite the foregoing advances in CKD associated anemia management the unresolved issue is the assessment of iron stores in patients with CKD. Cardiovascular consequences of renal anemia begin relatively early in the course of renal failure, an increase in left ventricular mass index is closely related to the changes in haemoglobin over time[20].

Haemoglobin is a better quantitative measure for monitoring and managing anemia in patients with CKD. Patients with chronic renal disease should have enough iron to achieve and maintain target haemoglobin concentration.

It has also been observed that high serum iron levels may be linked to lower mortality and also with progression of kidney disease in patients with NDD-CKD[21]. Higher haemoglobin targets have been recommended in CKD stages 3 to 4 or individuals without overt cardiovascular disease in order to improve mortality[22]. Death in CKD is principally from cardiovascular diseases rather than development of kidney failure. Hence treatment of earlier stages of chronic kidney disease should not only focus on reducing the rate of progression of CKD but also on treatment of cardiovascular risk factors at early stages of CKD.

Several studies worldwide have addressed the prevalence of Anemia in CKD patients and there is a great variability regarding the cut-offs used to define iron deficiency. In addition, little is known about the degree and pattern of anemia in CKD patients of Tripura. Hence the study is undertaken to investigate the clinicopathological profile of anemia in CKD patients and also to estimate serum iron profile attending a tertiary care hospital in this geographical area of North-East India.

II. Material And Methods

Study Design: Cross sectional study

Study Location: This prospective observational study was done in Department of Medicine, Agartala Government Medical College & GBP Hospital, Agartala, Tripura

Study Duration: 1and ½ years (October 2018 –May2020)

Sample size: 200

Sample size calculation: To calculate the sample size, the Kish and Leslie formula of 1965 for cross sectional studies was used.

$$N = \frac{Z\alpha^2 \times P(1-P)}{L^2}$$

N = Sample size ;p= Prevelance; q=(1-p); where:-

$Z\alpha^2$ Standard normal deviate at 5% level of significance (95% CI) is 1.96

P = Prevalence of Anemia in CKD patients=86.7% [23]

L = Margin of error at 5%

Sample size(N)=1.96x1.96x0.867[1-0.867]/(0.05)2=177 rounded to 200

Subjects & selection method: This prospective observational study was done in Department of Medicine, Agartala Government Medical College & GBP Hospital, Agartala, Tripura. The study was done over a period of one and half year from October 2018 to May 2020 after approval from the Institutional Ethics Committee. 200 patients of Chronic Kidney Disease presenting to outpatient and indoor facilities in Department of Medicine was included in the study. Chronic kidney disease (CKD) was defined as per Kidney Disease outcome quality Initiative (KDOQI) guideline i.e kidney damage or estimated GFR (eGFR <60 ml/min/1.73m^2) for more than equal to 3 months. According to past 3 year records on & average around 300 patients of CKD attended AGMC &GBPH during one & half year in one unit. Therefore, every 2nd patient was enrolled for the study with a random start till the desired sample size was achieved

Inclusion criteria:

1. Patients with chronic kidney disease with stage I –V disease.
2. Age > 18 years

Exclusion criteria:

1. Patients with other systemic illness other than renal failure
2. Pregnancy
3. Aplastic anemia
4. Any known Haematological malignancy causing secondary renal failure
5. Patients with end stage renal disease treated with renal replacement therapy in the form of renal transplantation.

Procedure methodology

After verification of the inclusion and exclusion criteria, the study design and purpose was explained in detail to all the selected subjects and written informed consent was taken. Detailed history including past and treatment history was elicited. Complete physical examination was performed. The patients were categorized according to their Creatinine Clearance measured by CKD-EPI formula eGFR (ml/min/1.73m^2) = 141 * min(Scr/κ,1)α * max(Scr/κ, 1)-1.209 * 0.993Age * 1.018 [if female] * 1.159 [if black] (140-age x body wt., kg/72 x Creatinine).

Anemia in CKD defined as Hb<13g/dl in adult males and <12g/dl in females according to KDIGO 2012. Further, Anemia was categorized into mild, moderate and severe with Hb% of 9-11 gm%, 7-9 gm% and <7 gm% respectively as per WHO anemia classification. Blood was collected under aseptic precautions for hematological (Complete blood count, peripheral blood smear, Reticulocyte count, serum iron profile) and biochemical (Blood Urea, Serum Creatinine,) investigations. Hematological profile was done on the standard automated analyzer.

Statistical analysis

All data was recorded in the pro forma designed specifically for this study (Appendix I). On completion of the study, data was entered into Microsoft excel spreadsheet for analysis. Data was recorded, entered and analyzed with computer using SPSS version 15.0 and Epi-info-version-7. Descriptive statistics and other statistical tests like Chi square test; kruskal wallis test, binary logistic regression analysis etc were used as per applicability. P value of less than 0.05 was considered as statistically significant.

III. Result

Table no 1 : Summary of All Parameters

All Parameters	Mean ± SD || Median (IQR) || Min-Max || Frequency (%)
CKD Stage	
Stage 3	70 (35.0%)
Stage 4	104 (52.0%)
Stage 5	26 (13.0%)
Age (Years)	59.59 ± 10.99 || 61.00 (53.00-69.00) || 30.00 - 82.00
Age	
30-39 Years	13 (6.5%)
40-49 Years	22 (11.0%)
50-59 Years	48 (24.0%)
60-69 Years	70 (35.0%)
70-79 Years	45 (22.5%)
80-89 Years	2 (1.0%)
Gender	
Male	137 (68.5%)
Female	63 (31.5%)
eGFR (mL/min/1.73m2)	23.71 ± 9.54 || 22.96 (17.49-31.07) || 3.00 - 42.86
eGFR	
<15 mL/min/1.73m2	26 (13.0%)
15-29 mL/min/1.73m2	117 (58.5%)
30-45 mL/min/1.73m2	57 (28.5%)
S. Creatinine (mg/dL)	3.63 ± 2.10 || 3.10 (2.20-4.60) || 1.50 - 14.00

All Parameters	Mean ± SD || Median (IQR) || Min-Max || Frequency (%)
Hemoglobin (g/dL)	8.98 ± 1.64 || 9.30 (7.88-10.10) || 4.70 - 12.20
Anemia (Present)	179 (89.5%)
Anemia Grade	
Absent	21 (10.5%)
Mild	95 (47.5%)
Moderate	56 (28.0%)
Severe	28 (14.0%)
S. Iron (µg/dL)	36.75 ± 17.77 || 32.86 (28.00-40.84) || 16.87 - 161.00
S. Iron	
<60 µg/dL	187 (93.5%)
≥60 µg/dL	13 (6.5%)
S. Ferritin (ng/mL)	198.42 ± 159.15 || 157.06 (97.21-281.54) || 58.13 - 1650.00
S. Ferritin	
High	63 (31.5%)
WNL	137 (68.5%)
TIBC (µgm/dL)	232.15 ± 78.82 || 219.95 (164.74-273.64) || 116.41 - 524.13
TIBC	
<250 µgm/dL	130 (65.0%)
≥250 µgm/dL	70 (35.0%)
Transferrin Saturation (%)	16.98 ± 7.71 || 14.88 (11.57-21.22) || 4.90 - 61.75
Transferrin Saturation	
<20%	138 (69.0%)
>20%	62 (31.0%)
RBC Morphology	
Microcytic Hypochromic	67 (33.5%)
Normocytic Hypochromic	32 (16.0%)
Normocytic Normochromic	101 (50.5%)

Table no2: : Distribution of the Participants in Terms of Age (n = 200)

Age	Frequency	Percentage
30-39 Years	13	6.5%
40-49 Years	22	11.0%
50-59 Years	48	24.0%
60-69 Years	70	35.0%
70-79 Years	45	22.5%
80-89 Years	2	1.0%
Total	200	100.0%

6.5% of the participants had Age: 30-39 Years. 11.0% of the participants had Age: 40-49 Years. 24.0% of the participants had Age: 50-59 Years. 35.0% of the participants had Age: 60-69 Years. 22.5% of the participants had Age: 70-79 Years. 1.0% of the participants had Age: 80-89 Years.

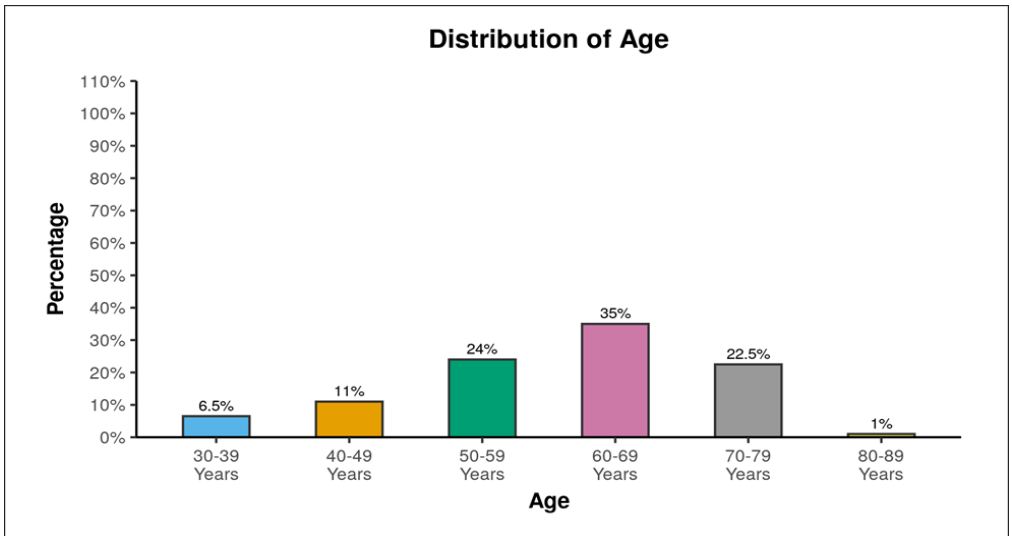

Table no3: : Distribution of the Participants in Terms of eGFR (n = 200)

eGFR	Frequency	Percentage
<15 mL/min/1.73m2	26	13.0%
15-29 mL/min/1.73m2	117	58.5%
30-45 mL/min/1.73m2	57	28.5%
Total	200	100.0%

13.0% of the participants had eGFR: <15 mL/min/1.73m^2. 58.5% of the participants had eGFR: 15-29 mL/min/1.73m^2. 28.5% of the participants had eGFR: 30-45 mL/min/1.73m^2.

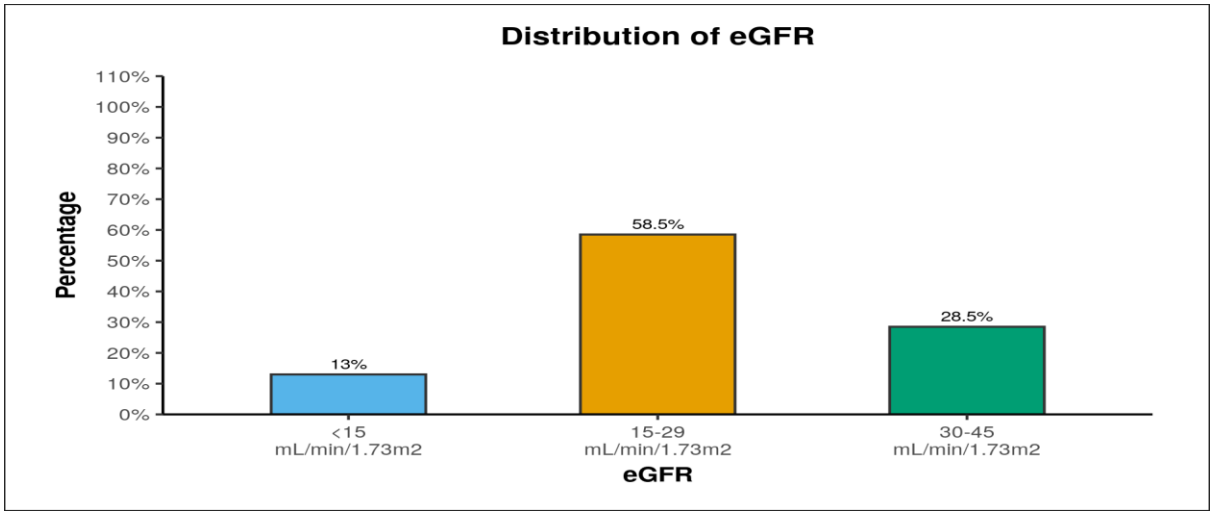

Table no4 : Distribution of the Participants in Terms of Hemoglobin (g/dL) (n = 200**)**

Hemoglobin (g/dL)	
Mean (SD)	8.98 (1.64)
Median (IQR)	9.3 (7.88-10.1)
Range	4.7 - 12.2

The variable Hemoglobin (g/dL) was not normally distributed (Shapiro-Wilk Test: p = <0.001).

The mean (SD) of Hemoglobin (g/dL) was 8.98 (1.64). The median (IQR) of Hemoglobin (g/dL) was 9.30 (7.88-10.1). The Hemoglobin (g/dL) ranged from 4.7 - 12.2.

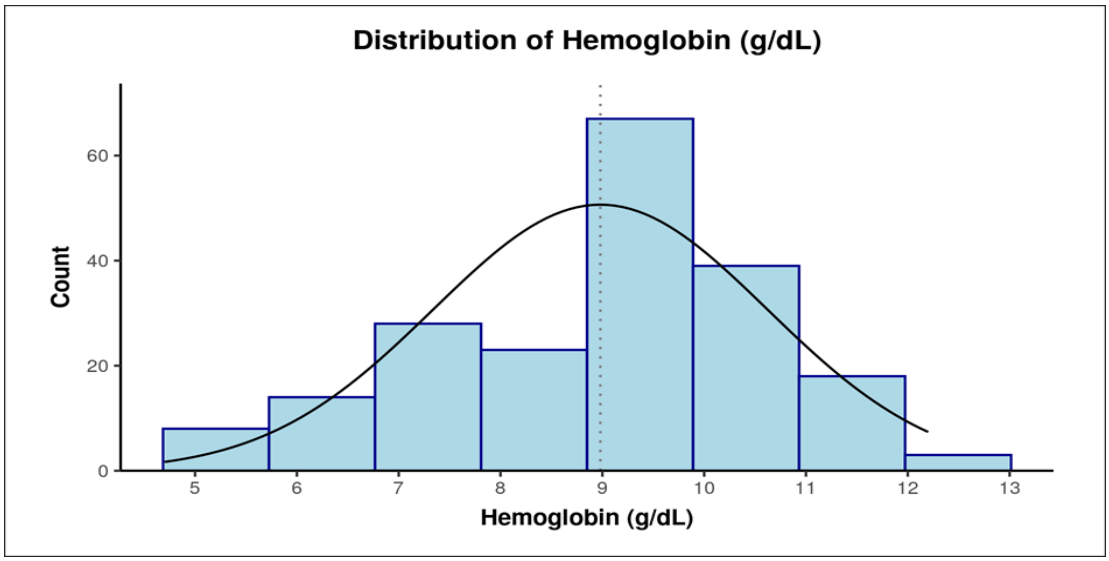

Table no 5 : : Distribution of the Participants in Terms of Anemia Grade (n = 200)

Anemia Grade	Frequency	Percentage
Absent	21	10.5%
Mild	95	47.5%
Moderate	56	28.0%
Severe	28	14.0%
Total	200	100.0%

10.5% of the participants had Anemia Grade: Absent. 47.5% of the participants had Anemia Grade: Mild. 28.0% of the participants had Anemia Grade: Moderate. 14.0% of the participants had Anemia Grade: Severe.

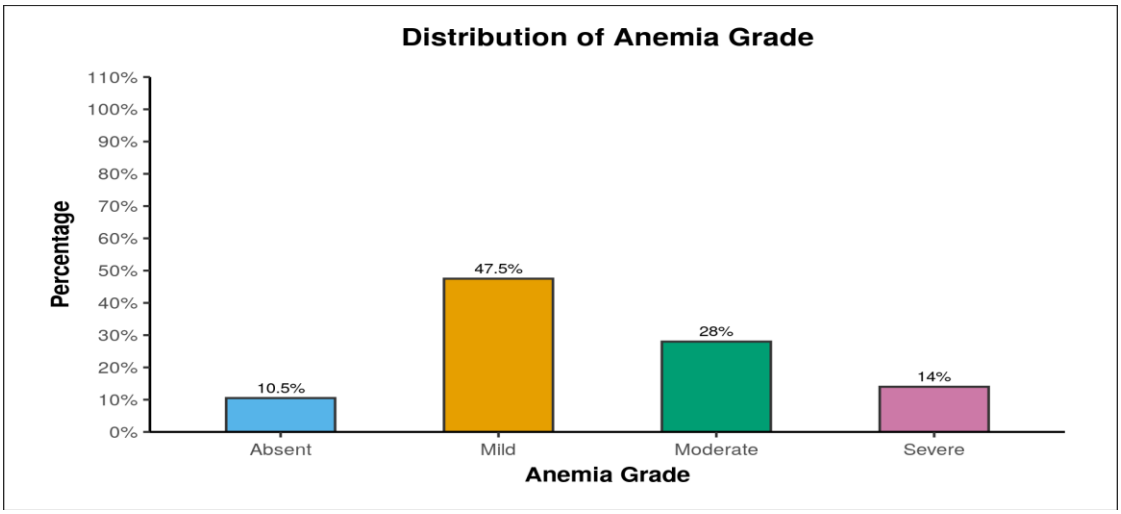

Table no 6 : Distribution of the Participants in Terms of RBC Morphology (n = 200)

RBC Morphology	Frequency	Percentage
Microcytic Hypochromic	67	33.5%

RBC Morphology	Frequency	Percentage
Normocytic Hypochromic	32	16.0%
Normocytic Normochromic	101	50.5%
Total	200	100.0%

33.5% of the participants had RBC Morphology: Microcytic Hypochromic. 16.0% of the participants had RBC Morphology: Normocytic Hypochromic. 50.5% of the participants had RBC Morphology: Normocytic Normochromic.

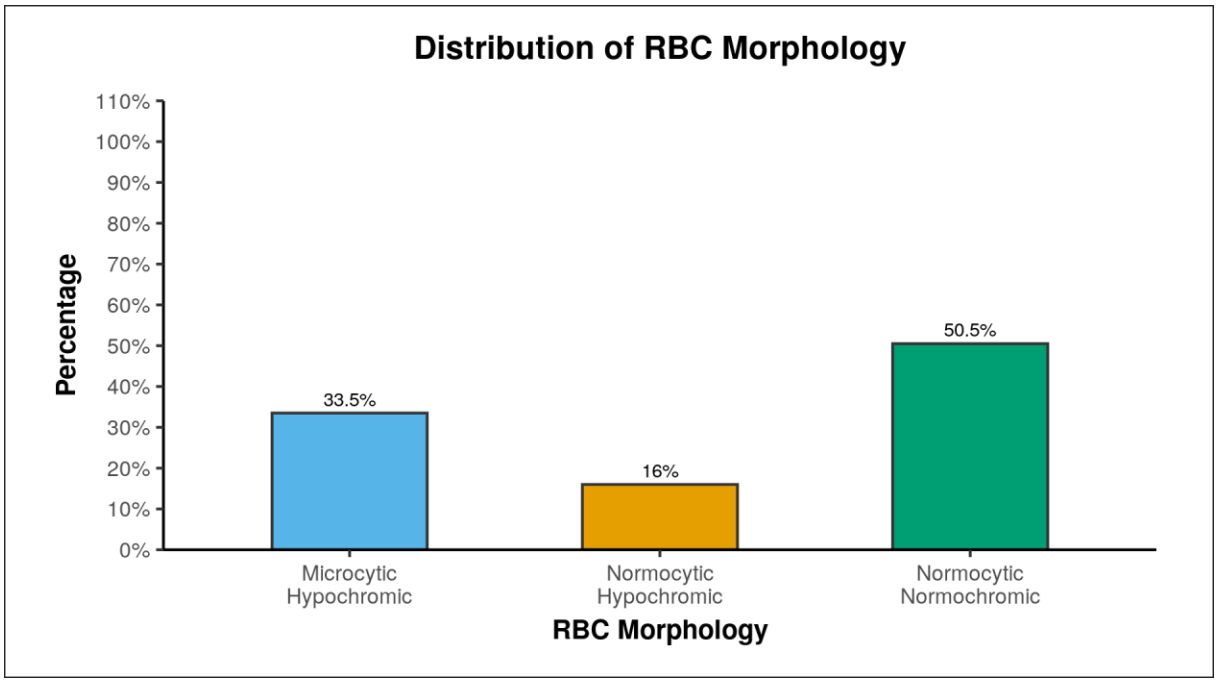

Table no 7: Association Between CKD Stage and Anemia Grade (n = 200)

Anemia Grade	CKD Stage				Chi-Squared Test	
	Stage 3	Stage 4	Stage 5	Total	$\chi 2$	P Value
Absent	21 (30.0%)	0 (0.0%)	0 (0.0%)	21 (10.5%)	67.891	<0.001
Mild	36 (51.4%)	55 (52.9%)	4 (15.4%)	95 (47.5%)		
Moderate	9 (12.9%)	34 (32.7%)	13 (50.0%)	56 (28.0%)		
Severe	4 (5.7%)	15 (14.4%)	9 (34.6%)	28 (14.0%)		
Total	70 (100.0%)	104 (100.0%)	26 (100.0%)	200 (100.0%)		

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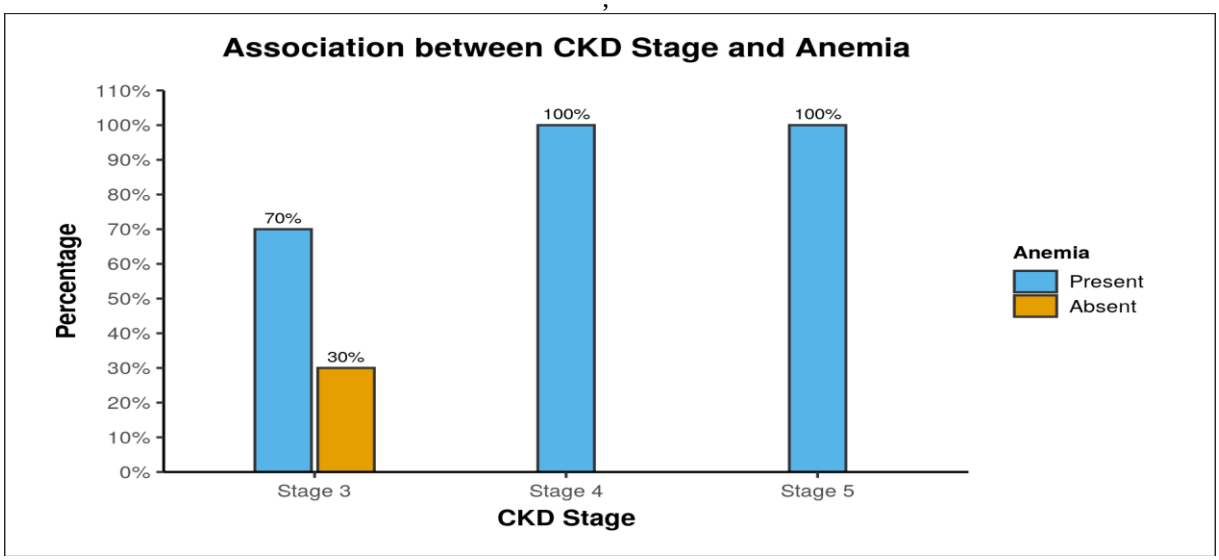


30.0% of the participants in the group [CKD Stage: Stage 3] had [Anemia Grade: Absent]. 51.4% of the participants in the group [CKD Stage: Stage 3] had [Anemia Grade: Mild]. 12.9% of the participants in the group [CKD Stage: Stage 3] had [Anemia Grade: Moderate]. 5.7% of the participants in the group [CKD Stage: Stage 3] had [Anemia Grade: Severe]. 0.0% of the participants in the group [CKD Stage: Stage 4] had [Anemia Grade: Absent]. 52.9% of the participants in the group [CKD Stage: Stage 4] had [Anemia Grade: Mild]. 32.7% of the participants in the group [CKD Stage: Stage 4] had [Anemia Grade: Moderate]. 14.4% of the participants in the group [CKD Stage: Stage 4] had [Anemia Grade: Severe]. 0.0% of the participants in the group [CKD Stage: Stage 5] had [Anemia Grade: Absent]. 15.4% of the participants in the group [CKD Stage: Stage 5] had [Anemia Grade: Mild]. 50.0% of the participants in the group [CKD Stage: Stage 5] had [Anemia Grade: Moderate]. 34.6% of the participants in the group [CKD Stage: Stage 5] had [Anemia Grade: Severe].

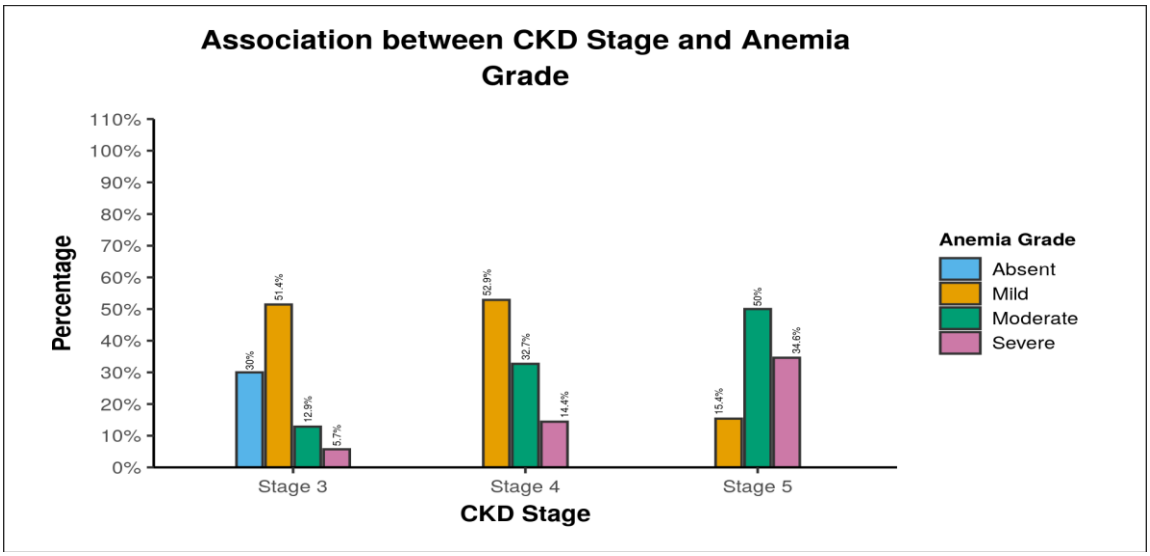


Table no 8: Association Between CKD Stage and S. Ferritin (n = 200)

S. Ferritin	CKD Stage				Chi-Squared Test	
	Stage 3	Stage 4	Stage 5	Total	$\chi 2$	P Value
High	43 (61.4%)	0 (0.0%)	20 (76.9%)	63 (31.5%)	101.744	<0.001
WNL	27 (38.6%)	104 (100.0%)	6 (23.1%)	137 (68.5%)		
Total	70 (100.0%)	104 (100.0%)	26 (100.0%)	200 (100.0%)		

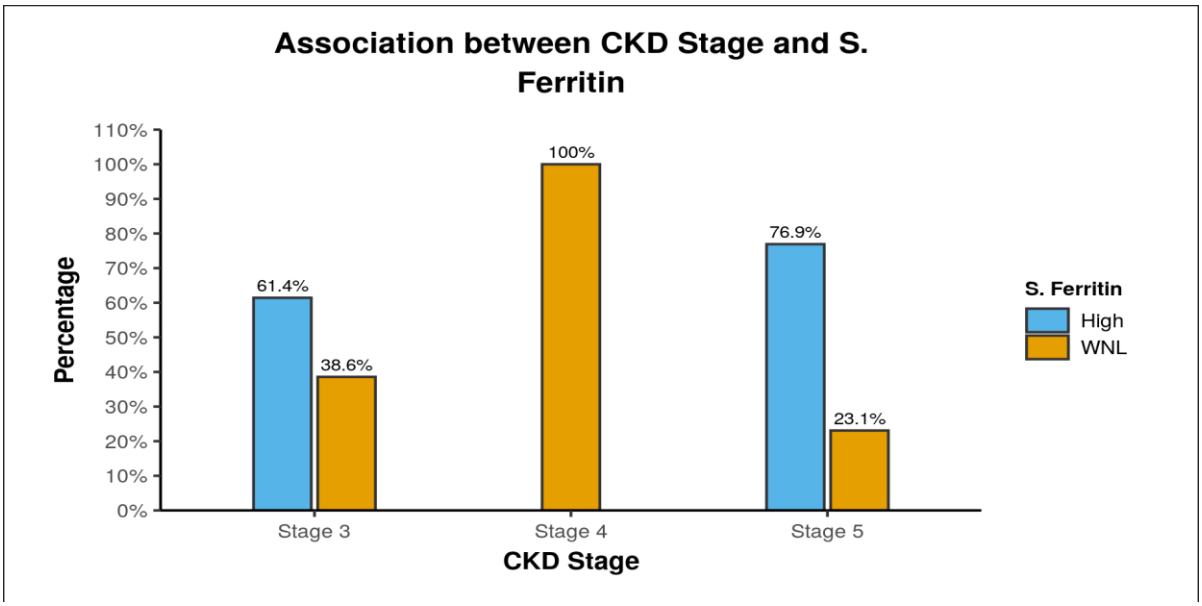
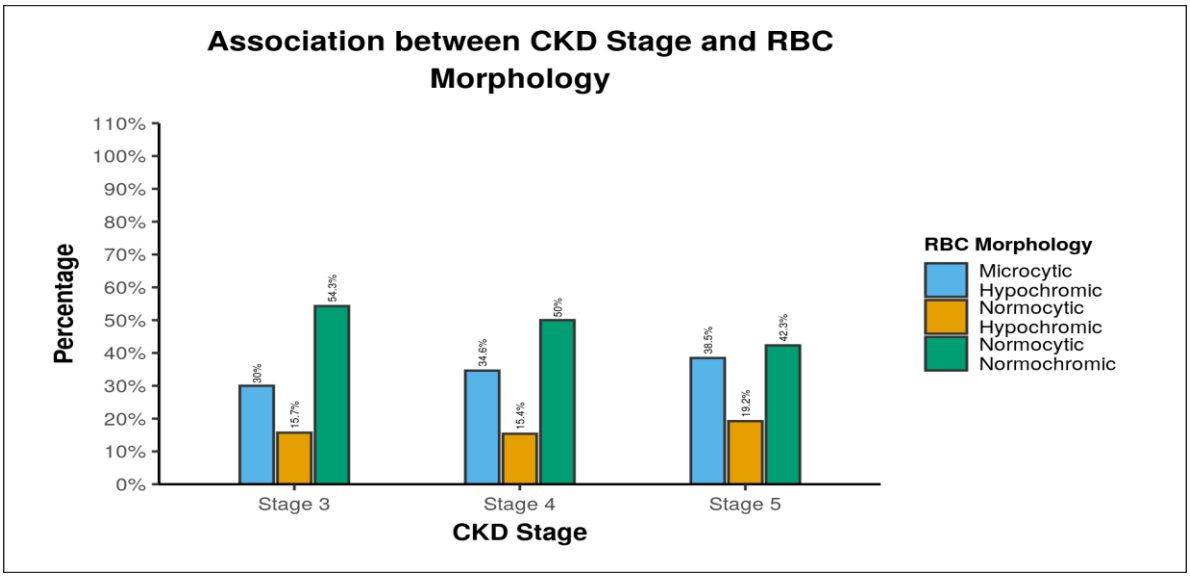


Table no 9: Association Between CKD Stage and RBC Morphology (n = 200)

RBC Morphology	CKD Stage				Chi-Squared Test	
	Stage 3	Stage 4	Stage 5	Total	$\chi 2$	P Value
Microcytic Hypochromic	21 (30.0%)	36 (34.6%)	10 (38.5%)	67 (33.5%)	1.233	0.873
Normocytic Hypochromic	11 (15.7%)	16 (15.4%)	5 (19.2%)	32 (16.0%)		
Normocytic Normochromic	38 (54.3%)	52 (50.0%)	11 (42.3%)	101 (50.5%)		
Total	70 (100.0%)	104 (100.0%)	26 (100.0%)	200 (100.0%)		



IV. Discussion

CKD is one of the worldwide public health issues and anemia is the most common complication of advanced CKD [24]. The prevalence of CKD in India in different communities is about 0.16% and other renal disorders is about 0.7%[25]. The recent population-based study assessed the incidence at 150-200 cases per million population per year in India [26].

The anemia in CKD is mainly caused by insufficient production of erythropoietin by diseased kidneys. Iron deficiency, chronic inflammation, hyperparathyroidism, and blood loss may also contribute to anemia in these patients. Recombinant human erythropoietin (rHuEPO) has been used in the treatment of the anemia of

CKD since 1986 [27]. Our study evaluated the clinicopathological profile of Anemia in patients of Chronic Kidney Disease presenting at a tertiary care center.

In our study the proportion of patients having Anemia among CKD patients in this study was found to be 89.5%. This is similar to the results obtained in the study conducted by Sang-Ryol Ryu, et al[23] was found to be (86.7%).

The proportion of anemia increases with increasing age, highest with 60-69 years 70(35.0%) in comparison to 30-39 years which is 13(6.5%)

Our study had 137 Male patients and 63 Female patients. Out of them 119 male and 60 female developed anemia however no statistical significance was seen.

Anemia was seen to be present in 49(70%) patients in stage 3. 104(100%) in stage 4 and 79(100%) patients in stage 5.

This is in concurrence with the findings in previous studies which have shown a high prevalence of anemia in CKD patients[28,29,30]. One of the reason of this high prevalence in our study could be that majority of our patients were in advanced stage of CKD.

In our study 51.4% had mild ,12.9% patient's had moderate anemia, and 5.7% had severe anemia in stage 3. 52.9% had mild ,32.7% patient's moderate anemia, and 14.4% had severe anemia in stage 4 and 15.4% had mild ,50% patients' moderate anemia, and 34.6% had severe anemia in stage 5. It has been shown in previous studies that grade of Anemia is usually proportional to the severity of CKD[31]. This association was also seen in our study. Large majority of patients (>95%) having severe Anemia (Hb <7g/dL) belonged to Stage 4 or 5 of Chronic Kidney Disease.

Most of the patients in our study had normocytic normochromic anemia (50.8%) on peripheral blood smear examination, followed by microcytic hypochromic anemia (32%) and normocytic hypochromic anemia was seen in (16.8%).

The predominantly normocytic normochromic picture on PBF is because of the absolute deficiency of Erythropoetin (Epo) with progressive renal dysfunction. Majority of the previous studies have shown similar findings with regards to morphological picture of Anemia.

S.Arun et.al showed in their study that all though most of the anemia was of the normocytic type, nearly a third of the patients had microcytic hypochromic and a mixed type of anemia. Those with a microcytic hypochromic picture correlated with a severe degree of anemia.[32,33,34]

Akinsola A et.al[34]. showed in his study that Red cell morphology was variable but the majority of patients showed a normocytic, normochromic blood film.

V. Conclusion

Chronic Kidney Disease is a major health care problem worldwide, with a global prevalence of 8-16%.[35] The US national kidney foundation's kidney dialysis quality initiative (KDOQI) guideline defines CKD as kidney damage or estimated GFR (eGFR <60 ml/min/1.73m^2) for more than equal to 3 months.[36] Chronic Kidney Disease leads to a wide range of systemic derangements. Anemia is a very common manifestation among patients of CKD[37,38]. As the renal dysfunction increases in severity, there is proportional increase in prevalence and severity of haematological impairment.

Among 200 subject 89.5% were found to have Anemia. People between the age of 60 - 69 years are mostly affected with anemia, although there is no significant association with sex seen.

70 (35.0%) of the participants had CKD Stage: Stage 3. 104 (52.0%) of the participants had CKD Stage: Stage 4. 26 (13.0%) of the participants had CKD Stage: Stage 5.

The mean Hemoglobin (g/dL) was 8.98 ± 1.64.

47.5% of the participants had Mild, 28.0%of the participants had Moderate.,14.0% of the participants had severe grade anemia.

33.5% of the participants had RBC Morphology of Microcytic Hypochromic, 16.0% of the participants Normocytic Hypochromic. 50.5% of the participants had Normocytic Normochromic.

Evaluating the anemia and iron status is very important, as treating the anemia in early stage would prevent considerable morbidity and mortality associated with this anemia in CKD.

We also observed that a substantial number of patients with CKD do not have sufficient iron stores to support erythropoiesis as judged by NKF-K/DOQI targets. Estimation of serum ferritin and haemoglobin in patients with CKD can be used as a specific iron deficiency marker.

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