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RESEARCH ARTICLE
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''TO ANALYSES SPECTRUM OF ANEMIA IN PATIENTS WITH CHRONIC KIDNEY DISEASE (CKD) AND TO CORRELATE IT WITH THE STAGE OF THE DISEASE.''

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Abstract-

Background- Chronic kidney disease (CKD) is a major global public healthproblem, estimated to affect more than 10% of the general adult population and up to 50% of some high-risk subpopulations, such as the elderly, those with non-communicable diseases (NCDs), including type 2 diabetes mellitus (T2D) and hypertension, and communicable diseases (CDs), including HIV/AIDS.

Aims- To analyses spectrum of anemia in patients with chronic kidneydisease (CKD) and to correlate it with the stage of the disease.

Materials and methods- This was a prospective study done over one and half year (March 2021-Aug 2022) at NSCB Medical College & hospital, India in 256 CKD patients. The study included adult CKD patients [estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73 m2, who underwent anemia evaluation. The eGFR was calculated from serum creatinine levels using the abbreviated Modification of Diet in Renal Disease equation. Anemia was defined as hemoglobin concentration <13.0 g/dL in males and <12.0 g/dL in females.

The anemia was evaluated by RBC count; MCV; MCHC. Kidney function was evaluated using blood urea, and serum creatinine and GFR. The GFR wasestimated using MDRD study equation.

Results- Out of 256 CKD patients, 46 patients (18%) had microcytic hypochromic anemia while majority of the patients (82%) had normocytic normochromic anemia. Mean age of the patients was 44.83 in patients diagnosed with microcytic anemia while in normochromic anemia mean age was 45.31 with non significance difference statistically. Majority of the patients (64.5%) with CKD were male. Majority of the patients with CKD were associated with profession of private sector employment, farmer, housewife and shopkeeper. The chief complaint in majority of the CKD patients (86%) was weakness followed by fever (14%). By anemic type the complaints in both the groups were not statistically significant ($p>0.05$). Only 3 patients out of 256 CKD patients had positive family history of normocytic normochromic anemia with insignificant difference statistically. In present study those patients with advanced stage of CKD (stage 5) had asignificant association with anemia.

Conclusions- Chronic Kidney Disease is a major health problem worldwide. Chronic Kidney Disease leads to a wide range of systemic derangements. Anemia is a very common manifestation among patients of CKD. As the renal dysfunction increases in severity, there is proportional increase of prevalence and severity ofhaematological impairment. Anemia is a leading cause of morbidity in patients with CKD and it worsens with the stage of the disease. The most common type of anemia is normocytic normochromic anemia due to EPO deficiency and microcytic hypochromic anemia due to iron deficiency. Evaluation of Hb and RBC parameters in patients with CKD helps in classifying the type of anemia and aids in choosing the correct treatment modalities and avoids unnecessary iron overload in the patients.

Keywords- chronic kidney disease, anemia, hemoglobin.

Introduction- Chronic kidney disease (CKD) is a major global public healthproblem,(1) estimated to affect more than 10% of the general adult population and up to 50% of some high-risk subpopulations, such as the elderly,(2) those with non-communicable diseases (NCDs), including type 2 diabetes mellitus (T2D) and hypertension, and communicable diseases (CDs), including HIV/AIDS.(3)
CKD encompasses a wide range of physiological processes altered by the progressive decline in glomerular filtration rate (GFR). (4) The predominant cause of anaemia in CKD is failure of the kidneys to produce enough endogenous erythropoietin, which accompanies the fall in GFR. (7) Untreated, prolonged anaemia is strongly predictive of all-cause and cardiovascular mortality, as well as reduced quality of life and increased morbidity in patients with CKD.(5) Untreated anaemia can also accelerate the decline in renal function by causing renal haemodynamic alterations and tissue hypoxia.(6) Other potentially affected haematological parameters in CKD, of which the association with CKD is not yet fully characterised, include total and differential white blood cell (WBC) counts. Anemia is generally defined as hemoglobin of less than 13.0 g/dL in men and less than 12.0 g/dL in premenopausal women. (10) Anemia of chronickidney disease (CKD) is a form of normocytic normochromic, hypoproliferative anemia. Among other complications of CKD, it is frequently associated with poor outcomes in CKD and increases mortality. The disorder starts to develop when the glomerular filtration rate drops to below 60 mg/ml. The anemia is rare when the GFR is above 80 mg/ml. As the GFR worsens, the anemia gets more severe.(11)

Anemia in chronic renal disease is a multifactorial condition, the widely accepted etiology being decreased renal production of erythropoietin, the hormone that is responsible for the stimulation of red blood cells production. Decreased erythropoietin has recently linked with downregulation of hypoxia- inducible factor (HIF), a transcription factor that regulates gene expression of erythropoietin.(12) Other mechanisms include uremia (leading to RBC deformity responsible for hemolysis), folate and vitamin B12 deficiency, iron deficiency, bleeding due to dysfunctional platelets, and rarely blood loss from hemodialysis. RBC fragmentation by injured renovascular endothelium in selected conditions such as glomerulopathy and malignant hypertensionexacerbates the anemia, which explains why anemia can be particularly severe in renal glomerulopathies, including glomerulonephritis, diabetic nephropathy, for the degree of excretory failure.(13) Available population-based determinations of the prevalence of anemia inCKD are becoming dated, with many studies referring back to the National Health and Nutrition Examination Survey (NHANES) III, which ended in 1994. (10,14,15) The most recent studies include NHANES data up to 2006,(14) but one was limited to adults over age 64 with advanced CKD(16) and the other used a GFR classification not directly comparable to that of most other studies.(14) This analysis assessed the prevalence of anemia in CKD in the adult (>18 years of age) during 2007–2010 using the GFR categories specified by the National Kidney Foundation. We therefore aimed to characterize the haematological spectrum of screen-detected CKD participants, and to correlate the complete blood count measures with CKD stages in tertiary care hospital.

Aims- To analyses spectrum of anemia in patients with chronic kidneydisease (CKD) and to correlate it with the stage of the disease.

Materials and methods-
STUDY DESIGN: Prospective observational study

STUDY CENTRE: N.S.C.B. Medical College & Hospital, Jabalpur (M.P.)

1st march **DURATION OF STUDY:** 2021 to 31st august 2022

STUDY AREA AND TARGET POPULATION: Study was done at NSCB medical college hospital and target population was indoor and outdoor patients of CKD.

SOURCES OF DATA; The central lab of pathology and biochemistry department, department of general medicine, department of nephrology, NSCBmedical college.

INCLUSION CRITERIA All patients having chronic kidney disease in adult age group(>14 years of age), indoor and outdoor chronic kidney disease.

EXCLUSION CRITERIA; Patients of pediatric age group (<14 Years), Patients not giving consent

SAMPLE SIZE AND SAMPLE TECHNIQUE
Sample size
Sample size was calculated on the assumptions of reported increased anemia from 1% to 9% in CKD patients with a GFR of 60ml/min/1.73m square to GFR of 30ml/min/1.73m square. Using formula of simple random sampling the minimum required sample size was estimated as 155 at 95% CI, 5% Alpha and 80% power which was further multiplied with 1.5 as design effect to remove the sample clusterization and this accumulated 233. Further 10% more samples were added to adjust the sample losses due to non- response error.Therefore, finally we planned to study on 256 CKD patients.

Formula
n = z square x p (1-p) / l square where n = required sample sizez = 1.96 at 95% CI and 5% alpha p = 0.09
l = 0.045 (precision or margin of error)

Final Sample size: 256 CKD patients.

Methodology
The study was carried out in the central laboratory of NSCB Medical College and Hospital. Two hundred fifty six diagnosed cases of CKD were analyzed.
Two hundred fifty six diagnosed cases of CKD as per the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative criteria regardless of its primary cause were chosen.
All patients with CKD, either outdoor or admitted to NSCB Hospital were analyzed for the following parameters:
- RBC count;
- Hb;
- hematocrit;
- MCV;
- MCH;
- MCHC;

- blood urea,
- Serum creatinine.

GFR was estimated using MDRD study equation.
Estimated glomerular filtration rate = 175 × standardized Scr−1.154 × age−0.203 Multiply by 0.742 for women.
Clinical details was collected from the medical record department, and hematological and biochemical data has retrieved from central lab NSCB Medical College, Jabalpur.

Stages of CKD of all types

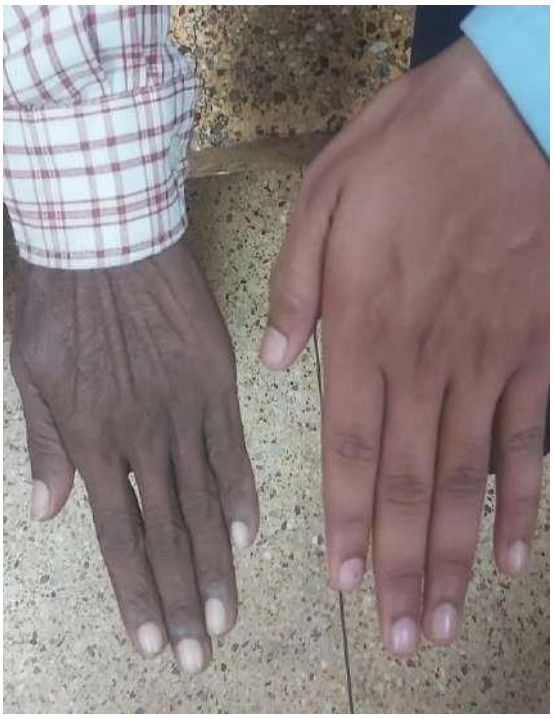
Stage	Qualitative Description	GFR (mL/min/1.73 m²)
1	Kidney damage – normal GFR	> 90*
2	Kidney damage – mild ↓ GFR	60-89*
3a	Moderate ↓ GFR	45-59
3b	Moderate ↓ GFR	30-44
4	Severe ↓ GFR	15-29
5	End-stage renal disease	<15

*A GFR >60 mL/min/1.73 m² in isolation is not CKD, unless other evidence of kidney damage is present

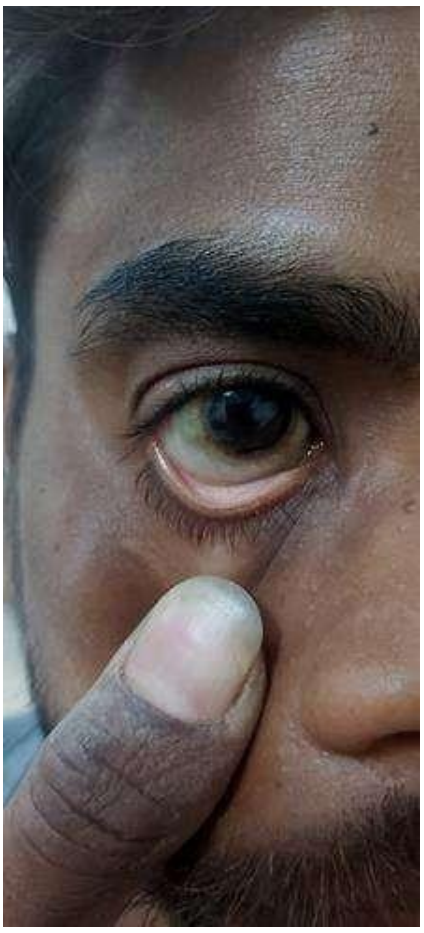
CKD, chronic kidney disease; *GFR*, glomerular filtration rate

Statistical analysis

Data was recorded in Microsoft Excel programme and statistical analysis was performed by the SPSS program for Windows, version 25 (SPSS, Chicago, Illinois). Continuous variables were presented as mean ±SD, and categorical variables were presented as absolute numbers and percentage. Data was checked for normality before statistical analysis. Descriptive analysis was performed to obtain general characteristic of the study population.
Categorical variables was analysed using either the chi square test or Fisher's exact test. Continuous variables were assessed using ANOVA or independent sample t-test. Pearson correlation (r) was performed to establish the correlation between different parameters. $P<0.05$ was considered statistically significant.



COMPARISON OF ANEMIA WITH NORMAL SUBJECTS



CONJUNCTIVAL PALLOR IN ANEMIA

CHRONIC KIDNEYDISEASE PATIENT

CHRONIC KIDNEYDISEASE PATIENT

OBSERVATIONS & RESULTS

TABLE NO. – 1: MORPHOLOGIC DISTRIBUTION OF ANEMIA IN CKDPATIENTS

Anemia type	Frequency	Percent
Microcytic Hypochromic	46	18.0
Normocytic Normochromic	210	82.0
Total	256	100.0

-Out of 256 CKD patients, 46 patients (18%) had microcytic hypochromic anemia while majority of the patients (82%) had normocytic normochromic anemia.

TABLE NO. – 2: MEAN AGE DISTRIBUTION OF ANEMIA TYPES IN CKDPATIENTS

Anemia typing	Mean	Std. Deviation	P value
Microcytic Hypochromic	44.83	16.869	
Normocytic Normochromic	45.31	14.446	
Total	45.22	14.875	0.842

-Mean age of the patients was 44.83 in patients diagnosed withmicrocytic anemia while in normochromic anemia mean age was 45.31 with non- significance difference statistically (p>0.05).

TABLE NO. – 3: SEX DISTRIBUTION OF ANEMIA TYPES INCKD PATIENTS

			Anemia typing		Total	P value
			Microcytic hypochromic	Normocytic Normochromic		
Sex	F	Count	19	72	91	0.368
		%	41.3%	34.3%	35.5%	
	M	Count	27	138	165	
		%	58.7%	65.7%	64.5%	

-Majority of the patients (64.5%) with CKD were male by sex. By anemic type the difference is sex distribution was not statistically significant. (p>0.05).

GRAPH NO. – 1 SEX DISTRIBUTION OF ANEMIA TYPES IN CKD PATIENTS

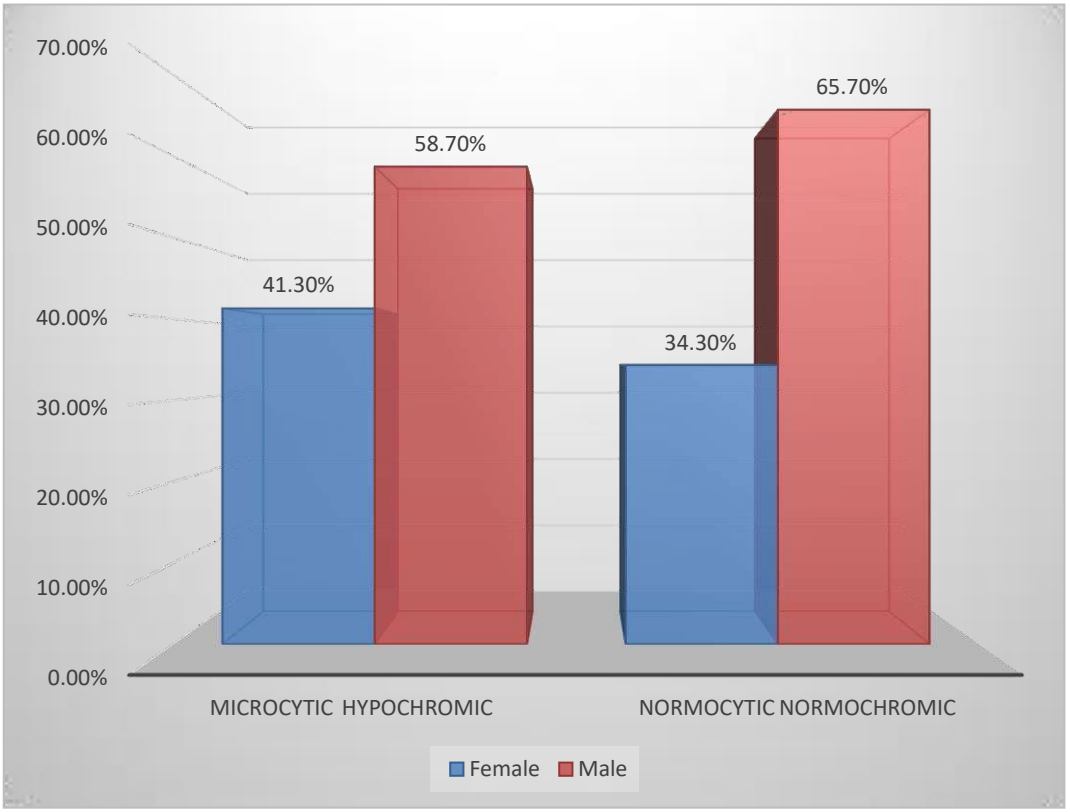


TABLE NO. – 4 OCCUPATION WISE DISTRIBUTION OF ANEMIATYPES IN CKD

PATIENTS

			Anemia typing		Total	P value
			Microcytic Hypochromic	Normocytic Normochromic		
Occupation	Clerk	Count	0	1	1	0.032
		%	0.0%	0.5%	0.4%	
	Farmer	Count	11	34	45	
		%	23.9%	16.2%	17.6%	
	Govt.Job	Count	1	22	23	
		%	2.2%	10.5%	9.0%	
	Housewife	Count	8	45	53	
		%	17.4%	21.4%	20.7%	
	Labour	Count	3	21	24	
		%	6.5%	10.0%	9.4%	
	OtherJobs	Count	13	31	44	
		%	28.3%	14.8%	17.2%	
	Retired	Count	1	0	1	
		%	2.2%	0.0%	0.4%	
	Shop keeper	Count	3	38	41	
		%	6.5%	18.1%	16.0%	
	Student	Count	6	15	21	
		%	13.0%	7.1%	8.2%	
	Teacher	Count	0	3	3	
		%	0.0%	1.4%	1.2%	

-Majority of the patients with CKD were associated with profession of private sector employment, farmer, housewife and shopkeeper. The difference was statistically significant but nullifies the impact of occupation on type of anemia in CKD patients.

TABLE NO. – 5: CHIEF COMPLAINTS WISE DISTRIBUTION OF ANEMIATYPES IN CKD PATIENTS

			Anemia typing		Total	P value
			Microcytic Hypochromic	Normocytic Normochromic		
Chief Complaints	Fever	Count	8	28	36	0.473
		%	17.4%	13.3%	14.1%	
	Weakness	Count	38	182	220	
		%	82.6%	86.7%	85.9%	

-The chief complaint in majority of the CKD patients (86%) was weakness followed by fever (14%). By anemic type the complaints in both the groups were not 2279toically significant (p>0.05).

GRAPH NO. – 2 CHIEF COMPLAINTS WISE DISTRIBUTION OF ANEMIATYPES IN CKD PATIENTS

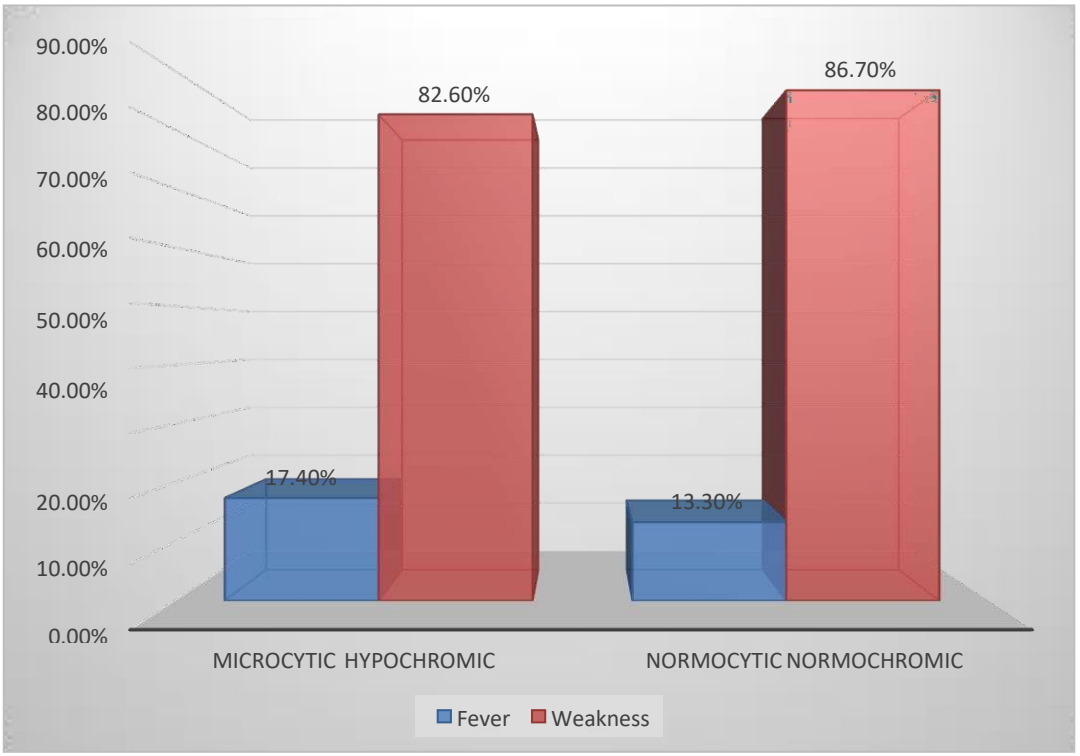


TABLE NO. – 6: FAMILY HISTORY WISE DISTRIBUTION BETWEEN ANEMIATYPE IN CKD PATIENTS

			Anemia typing		Total	P value
			Microcytic Hypochromic	Normocytic Normochromic		
FamilyHistory	No	Count	46	207	253	0.415
		%	100.0%	98.6%	98.8%	
	Yes	Count	0	3	3	
		%	0.0%	1.4%	1.2%	

-Only 3 patients out of 256 CKD patients had positive family history of normocytic normochromic anemia with insignificant difference statistically. This nullifies the impact of positive family history upon occurrence of particular type anemia in CKD patients.

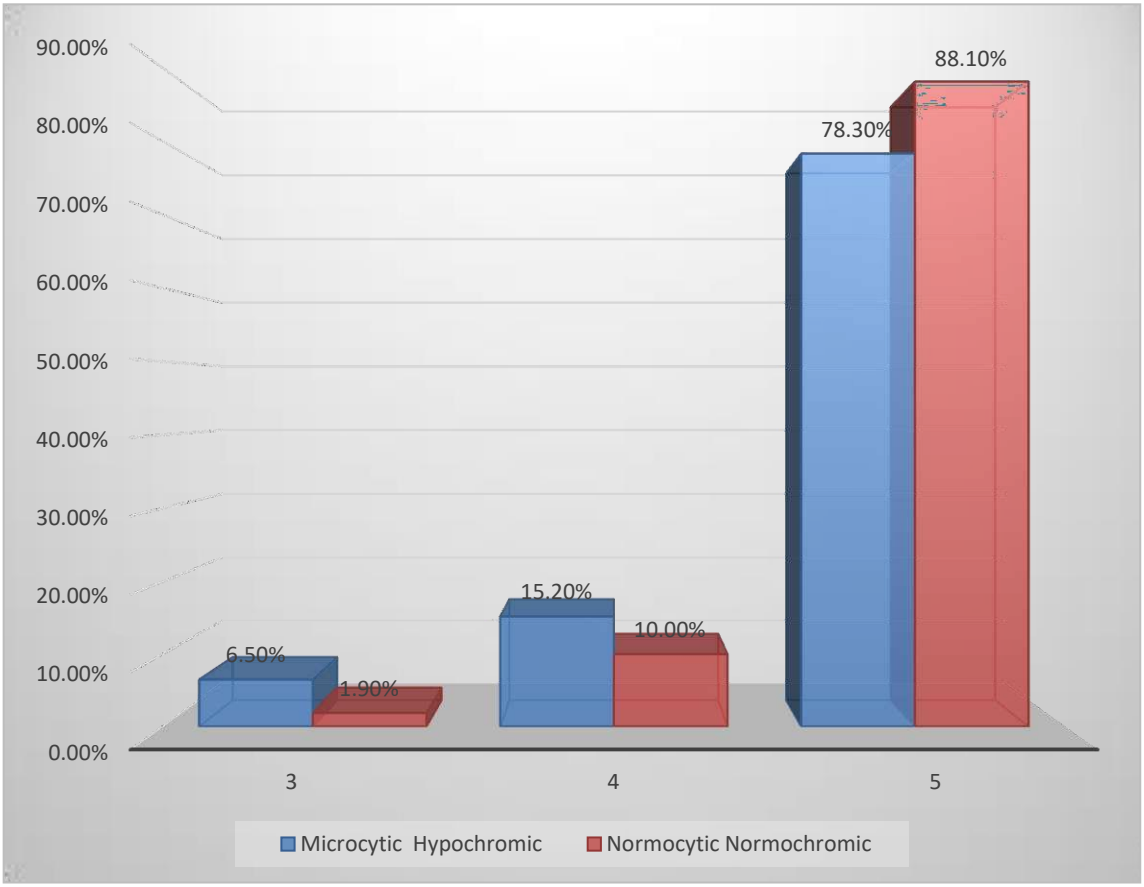
TABLE NO. – 7: DISTRIBUTION OF ANEMIA TYPES WITH STAGES OF CKD IN PATIENTS

			Anemia typing		Total	P value
			Microcytic Hypochromic	Normocytic Normochromic		
	3	Count	3	4	7	
		%	6.5%	1.9%	2.7%	
		Count	7	21	28	

StageofCKD	4	%	15.2%	10.0%	10.9%	0.116
	5	Count	36	185	221	
		%	78.3%	88.1%	86.3%	

-Most of the patients (86%) had been complicated by anemia in fifthstage of CKD. The type of anemia had not significant difference in any stage of CKD in both the groups (p>0.05).

GRAPH NO. – 3 DISTRIBUTION OF ANEMIA TYPES WITH STAGES OF CKD IN PATIENTS



DISCUSSION

Chronic kidney disease is one of the worldwide public health issue and anemia is the most common complication of chronic kidney Disease. (21) The prevalence of CKD in India's about 0.16% and other renal disorders are about 0.7%**.** (22). The recent population-based study showed the incidence of 150-200 cases per million population per year in India. (23)

The anemia in CKD is mainly caused by insufficient production of erythropoietin by diseased kidneys. Iron deficiency, chronic inflammation, secondary hyperparathyroidism (due to defect in activation of vitamin D at kidney level), 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 (24). Our study evaluated the spectrum profileof anemia in the patients of Chronic Kidney Disease presenting at the tertiary care centre.

In our study out of 256 CKD patients, 46 patients (18%) had microcytic hypochromic anemia while majority of the patients (82%) had normocytic normochromic anemia. Most of the patients in our study had normocytic normochromic anemia (82%) on **peripheral blood smear examination**, followed by microcytic hypochromic anemia (18%).

Previous studies have shown similar findings with regards to morphological picture of Anemia. Arun et al. (25) showed in their study that all though most of anemia type was of the

normocytic normochromic type, nearly one third of the patients had microcytic hypochromic and a mixed type ofanemia. (26) Akinsola et.al. Showed in his study that red cell morphology was variable but the majority of patients showed a normocytic, normochromic bloodfilm.

Talwar et al. (27) showed a higher incidence of microcytic hypochromic anemia compared to our study population. In the study by Arun et al., (25) only 25% of cases showed microcytic hypochromic anemia, but iron deficiency was associated with only subset of cases. Remaining 75% of cases were of normocytic normochromic population. A study by Vikrant et al. (28) found that the anemia was normocytic normochromic in 65.4%, microcytic hypochromic in 14.2%, and macrocytic picture in 20.4%.

In our study mean age of the patients was 44.83 years in patients diagnosed with microcytic hypochromic anemia while in normocytic normochromic anemia mean age was 45.31 with non significance difference statistically ($p>0.05$). According to the meta- analysis by Shiferaw et al (29), the pooled effects of four studies indicated that those over 50 years of age were 62% more likely to develop anemia compared to those less than 50 years old, although this association was not statistically significant. Another study by Vikrant et al. (28) reported around 55% patients were male and 45% were female. Mean age of the patients was 55.5 years in this study (28). A study by Shastry et al. (30) found that the mean age of presentation was 52 ± 14 years with male-to-female ratio was 4.3:1.

Epidemiological data by the National Health and Nutrition Examination Survey 3 and the Kidney Early Evaluation Program show an increase in the prevalence of anemia in individuals aged >61 years in Stage 3 CKD patients or in higher stages. According to the World Health Organization (WHO), anemia is present in 43% of the population in patients affected with CKD. (36)

In our study majority of the male patients (64.5%) with CKD developed anemias while remaining fraction of 35.5% patients were females affected by CKD. By anemic type the difference in sex distribution among CKD patients was not statistically significant.($p>0.05$). The results are different from the systemic review by Shiferaw et al. (29) in 2020, females were more likely to develop anemia in patients with CKD than male patients. The predominant impact of anemiain female sex CKD patients is supported by previous studies conducted in Korea- Yi SW, Moon SJ, Yi JJ et al.(31), Australia- Ng YH, Myers O, Shore X, Pankratz VS, Norris KC, Vassalotti JA, et al. (32), London- Al-Khoury S, Afzali B, Shah N, Covic A, Thomas S, Goldsmith D et al. (33), and New York- McFarlane SI, Chen SC, Whaley-Connell AT, Sowers JR, Vassalotti JA, Salifu MO, et al (34).This would suggest that female patients had lower Hb concentrations than male patients, which likely explains why females had greater risk of developing anemia- McClellan WM, Flanders WD et. al (35).

The chief complaint in majority of the CKD patients (36%) was weakness followed by fever (14%). By anemic type the complaints in both the groups were not statistically significant ($p>0.05$).

Majority of the patients with CKD were associated with profession of private sector employment, farmer, housewife and shopkeeper. Only 3 out of 256 CKD patients had positive family history of normocytic normochromic anemia with insignificant differencestatistically. This nullifies the impact of positive family history and occupation upon occurrence of particular type anemia in CKD patients. Non significant impact of occupation in our study is supported by Hussain et al. (37) found no significant difference between the anemic andnonanemic patients regarding sex, marital status, family history education, occupation, substance use, family income, and co-morbidities.

In our study those patients with advanced stage of CKD (stage 5) had a significant association with anemia, which has been previously reported in study conducted in Australia- by Ng YH, Myers et al. (82)**,** Korea- AI-Khoury, (33).

Shiferaw et al. (29) evaluated the pooled effects of seven studies showed that stage 5 CKD patients' were 13 times more likely to develop anemia than patients with stage 1 CKD. This implies that anemia is gradually progressive with deterioration of renal function according to serum creatinine and GFR. In general stage 5 CKD, being male were found to be significantly associated with anemia of chronic kidney disease. Therefore, situation- based interventions and country context-specific preventive

strategies should be developed to reduce the risk factors of anemia in this patient group. In addition, this study may help policymakers and program managers design evidence-based interventions on preventing the occurrence of anemia with CKD patient populations.

CONCLUSION

Chronic Kidney Disease is a major health problem worldwide. Chronic Kidney Disease leads to a wide range of systemic derangements. Anemia is a very common manifestation among patients of CKD. As the renal dysfunction increases in severity, there is proportional increase of prevalence and severity ofhaematological impairment. Anemia is a leading cause of morbidity in patients with CKD and it worsens with the stage of the disease. The most common type of anemia is normocytic normochromic anemia due to EPO deficiency and microcytic hypochromic anemia due to iron deficiency. Evaluation of Hb and RBC parameters in patients with CKD helps in classifying the type of anemia and aids in choosing the correct treatment modalities and avoids unnecessary iron overload in the patients.

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