Section: Pathology

Original Research Article

CHANGES IN HEMATOLOGICAL PROFILE IN PATIENTS OF CHRONIC KIDNEY DISEASE -- A STUDY IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Background: Chronic kidney disease (CKD) is a dreadful condition with drastic decline in renal function resulting in renal failure, cardiovascular illness and early mortality. Due to increasing risk factors and life style modifications Chronic Kidney Disease has become a major public health problem worldwide. **Aim:** To evaluate the changes in hematological parameters in Chronic Kidney disease patients and to correlate peripheral smear findings with the changes in Renal function tests.

Materials and Methods: The present prospective study was done over a period of 4 years (November 2019 to October 2023) which included clinically diagnosed cases of Chronic Kidney Disease at S.S. Institute of Medical Sciences and Research centre, Davangere. Brief clinical history with associated predisposing factors were also considered and correlated with complete hemogram.

Results: Out of total 220 patients, 70.9% were male and 29.1% were females. Complete hemogram showed Normocytic normochromic anaemia as the most common anemia (65.5%) followed by Normocytic hypochromic anaemia (20%). On Pearson's correlation, there was a significant negative strength of association between serum creatinine and haemoglobin levels in chronic kidney disease patients. Independent T-test showed a significant rise in mean serum urea level among patients with burr cells on peripheral smear as compared to those without burr cells ($p<0.05$).

Conclusion: Normocytic normochromic anaemia is the most common anemia in chronic kidney disease. The serum creatinine level is inversely correlated with the haemoglobin value and directly correlated with severity of anemia. Also presence of burr cells in the peripheral smear were significantly associated with a higher mean serum urea levels.

Keywords: Chronic Kidney Disease, haematological parameters, peripheral smear, burr cells, serum urea, serum creatinine.

INTRODUCTION

Chronic kidney disease (CKD) is one of the growing public health problems worldwide, with unfavourable effects including renal failure, cardiovascular illness, and early mortality.[1] Cardiovascular disease is the leading cause of morbidity and death in chronic renal disease patients at all stages. Advanced cardiovascular problems already exist in 30-45% of CKD patients who progress to End Stage Renal Disease (ESRD).[2]

Diseases of the kidney is ranked 3rd amongst all life-threatening diseases in India after cancer and heart disease.[3] A structural or functional abnormality of kidney with renal damage or a GFR less than 60 ml/min/1.73 m2 of body surface area for more than 3 months is defined as Chronic Kidney Disease.[4] The incidence of new end stage renal disease in India is around 100 per million population per year.[5] The International Society of Nephrology's Kidney Disease Data Center Study reported a prevalence of 17% of CKD in India.[6]

These data invariably point out the ever increasing magnitude of the disease burden of CKD and also fervently appeal the medical fraternity to engross in more research work.

Quality of life of patients living with CKD is adversely impacted due to the hematological alterations. Anaemia is a consistent finding in these patients and contributed towards the morbidity and mortality. Leucocyte and platelet disorders have also been described in cases of renal failure.[5] Therefore, these co-morbid conditions, if managed properly, can improve the cardiac health, cognitive function, functional capacity and overall quality of life of patients with CKD.[7] So, the present study was undertaken to evaluate the changes in hematological parameters in patients of chronic kidney disease.

Aims & Objectives

- To study the type of anaemia and to correlate the hemoglobin values with respect to serum creatinine levels.
- To study the changes in platelet and WBC count and their morphology.
- To study the changes in RBC morphology on peripheral smear with respect to serum urea levels

MATERIAL AND METHODS

All clinically diagnosed cases of CKD (In-patients, out-patients of Nephrology Department and patients on hemodialysis) in SSIMS & RC, Davangere were included in this prospective study that was done over a period of 4 years (November 2019 to October 2023).

Inclusion Criteria

- All clinically diagnosed CKD patients irrespective of the stage of the disease with:
- Age more than 18 years
- Serum Creatinine more than 1.5 mg/dl
- Serum urea more than 45 mg/dl.

Exclusion Criteria

- Genetic disorders
- Cancer
- Bleeding disorders
- Nephrotoxic drugs
- Cytotoxic drugs
- Known case of HIV infection
- Active GI bleeding
- Liver disorders
- Previous history of renal trauma/injury or transplant.

Clinical history was collected from case sheets of enrolled patients with the help of a semi-structured questionnaire/proforma like age, gender, presenting complaints, risk factors, past medical history, physical examination findings and treatment history. Laboratory investigations were extracted from the laboratory reports which included serum creatinine, serum urea, hemoglobin, hematocrit, RBC count, MCV, MCH, MCHC, TLC (Total Leucocyte Count) with differentials, platelet count and Peripheral smear findings.

CKD stages were defined based on eGFR level using the Cockcroft-Gault Formula:

$$\text{Creatinine clearance} = \frac{(140-\text{age}) \times (\text{Weight in kg})}{72 \times \text{Serum Creatinine}}$$

Approximately 4 ml of venous blood was drawn from cubital vein under all aseptic precautions using a 5cc syringe by the phlebotomist in the laboratory or bedside for inpatients and patients on hemodialysis. 2 ml is collected into a tube containing EDTA as anticoagulant and 2 ml is collected in a plain tube without anticoagulant and analyzed within two hours of collection. Erythrocyte indices (RBC count, HGB, HCT, MCV, MCH, MCHC and RDW-CV), TLC and Platelet count was obtained using 6-part Auto Hematology analyzer MINDRAY BC-6200 and serum urea and creatinine levels, serum sodium, potassium and chloride levels were obtained using BECKMAN COULTER AU480. Peripheral smear was studied to look for morphology of RBCs, WBCs and Platelets.

Further, the relationship between these indices to elevated serum creatinine and urea was evaluated and compared wherever possible.

The ethical approval has been obtained from Instituitional Ethical Review Board.

Data were statistically analysed using SPSS version 16. Quantitative data were expressed as mean + SD and as numbers and percentages. Suitable tests of significance are applied where P values of <0.05 was considered statistically significant along with Pearson's correlation.

RESULTS

In the present study, total of 220 patients fulfilling inclusion criteria were included with mean age of 56.009±16.15yrs of age. Among them 70.9% were male and 29.1% were female patients with male preponderance in the study.

Among the 220 patients, 170 cases (77.3%) presented with generalized weakness, 94 (42.7%) presented with pallor, 34 (15.4%) with pedal edema, 22 (10%) had facial edema, 17 (7.7%) presented with easy fatiguability while 3 patients (1.4%) presented with breathlessness.

The various causes attributing to CKD in the present study in decreasing order were Diabetes (74 cases, 33.6%), CKD of unknown etiology (CKDu) (63 cases, 28.6%) followed by Diabetes + Hypertension (42 cases, 19.2%) and Hypertension (30 cases, 13.6%). Other causes noted were Polycystic Kidney Disease (8 cases, 3.6%) and IgA Nephropathy (3 cases, 1.4%).

On assessment of type of anaemia among the patients, 65.5% showed Normocytic normochromic anaemia, followed by 20% Normocytic hypochromic anaemia, 5.5% Microcytic hypochromic anaemia, 3.6% Macrocytic and Dimorphic anaemia- predominantly Normocytic and

1.8% Dimorphic anaemia- predominantly microcytic. Other RBC findings on peripheral smear seen were burr cells (9.1%, 20 cases), few nRBCs (2.3%, 5 cases), Occasional Schistocytes (1.4%, 3 cases) and polychromatophils (1.4%, 3 cases)[Table -1].

The WBC findings on peripheral smear showed predominantly Neutrophilic Leucocytosis (88 cases) probably due to neutrophil activation which commonly occurs in CKD. Leucopenia may be a result of secondary infection or bone marrow suppression.

The platelet findings on peripheral smear were 56.4% (124 cases) showing thrombocytopenia and 1.8% (4 cases) with thrombocytosis and 41.8% (92 cases) having normal platelet count.

On comparison of various types of anaemia with mean serum creatinine levels, there was significantly higher mean creatinine in patients with Normocytic hypochromic anaemia, followed by Dimorphic anaemia- predominantly Normocytic, Normocytic normochromic anaemia and Macrocytic anaemia. [Table 2].

On comparison of mean serum urea levels with various types of anaemia, there was significantly higher mean serum urea noted in patients with Normocytic hypochromic anaemia, followed by Dimorphic anaemia- predominantly Normocytic, Normocytic normochromic anaemia and Macrocytic anaemia which is similarly noted with S. Creatinine levels. [Table 3]

On comparing Serum Sodium, Serum Potassium and Serum Chloride with peripheral smear blood picture showed no significant correlation with type of anaemia among the patients (p= 0.524), (p= 0.714), (p= 0.651) respectively. [Table 4]

Haemoglobin level

Out of 220 cases, 48.5% had Hb less than 5.1 g/dl, 47% had Hb in the range of 5.1-10 g/dl while 4.5% had Hb more than 10 g/dl.

Serum creatinine level

Out of 220 cases, 24.6% had serum creatinine less than 7.1 mg/dl, 63.6% had serum creatinine in the range of 7.1-10 mg/dl while 11.8% had serum creatinine more than 10 mg/dl.

On Pearson's correlation, there was a significant negative strength of correlation between the serum creatinine and haemoglobin. There was higher mean level of serum creatinine with decline in the haemoglobin levels among the patients ($p<0.05$). [Table 5, fig- 1]

On performing independent T-test, a significant association was observed in mean serum urea level in patients having burr cells as compared to those without burr cells. There was higher mean level of serum urea in patients having burr cells in the peripheral smear ($p<0.05$). [Table 6]

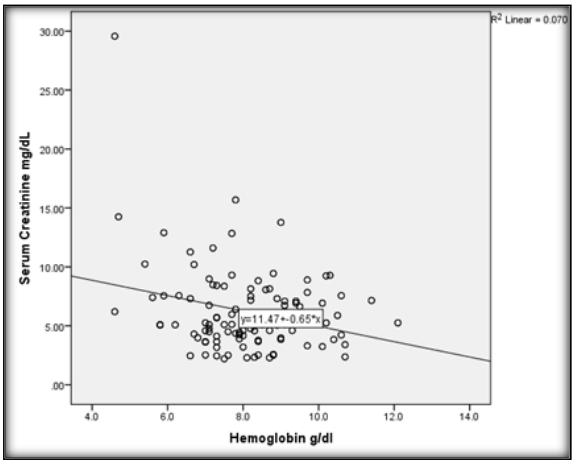

Figure 1: Pearson's correlation of haemoglobin with serum creatinine

PERIPHERAL SMEAR PICTURES

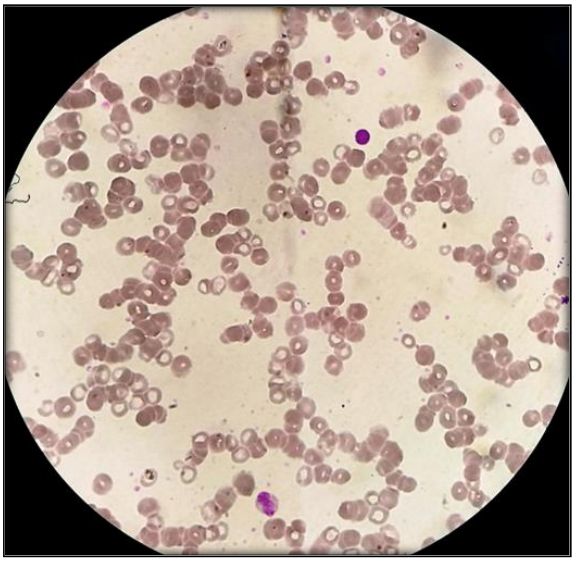

Figure 2: Normocytic normochromic anaemia (100x, Leishman stain)

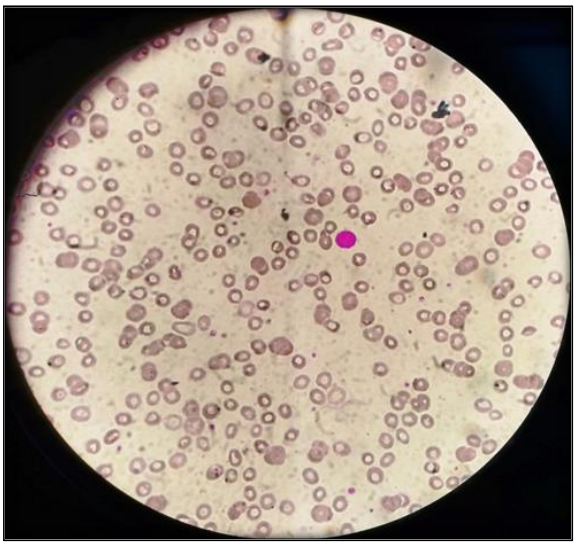

Figure 3: Dimorphic anaemia- predominantly Microcytic (100x, Leishman stain)

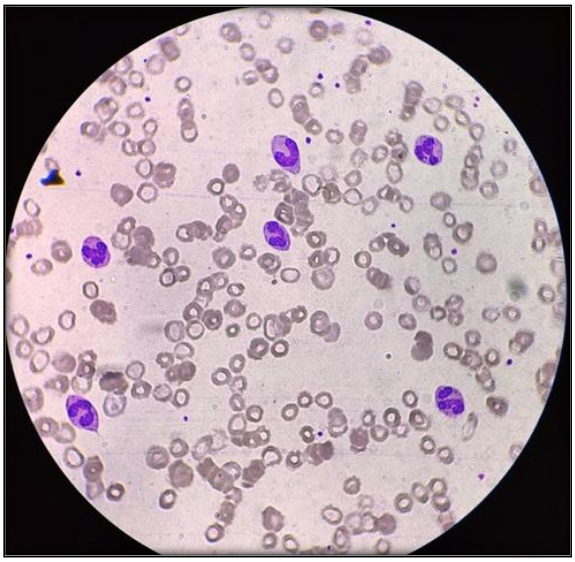

Figure 4: Normocytic hypochromic anemia with Neutrophilic leucocytosis (100x, Leishman stain)

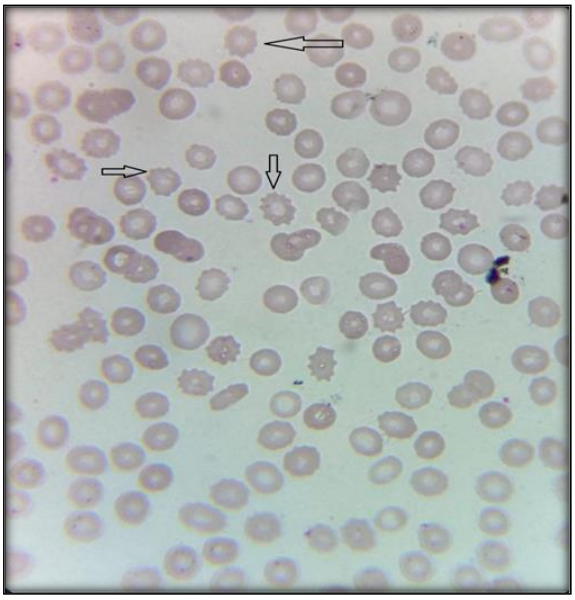

Figure 5: Burr Cells (100x, Leishman stain)

Table 1: Distribution of Peripheral Smear blood picture among CKD patients

		Number	Percentage (%)
Peripheral Smear blood picture	Dimorphic anaemia- predominantly microcytic	4	1.8
	Dimorphic anaemia- predominantly normocytic	8	3.6
	Macrocytic anaemia	8	3.6
	Microcytic hypochromic anaemia	12	5.5
	Normocytic hypochromic anaemia	44	20.0
	Normocytic normochromic anaemia	144	65.5
	Total	220	100.0

Table 2: Comparison of serum creatinine with peripheral smear blood picture

		Serum Creatinine (mg/dl)		
		Mean	SD	p-value
Peripheral Smear blood picture	Dimorphic anaemia-predominantly microcytic	3.98	0.37	0.01*
	Dimorphic anaemia- predominantly Normocytic	7.41	2.57	
	Macrocytic anaemia	5.50	1.31	
	Microcytic hypochromic anaemia	3.89	1.85	
	Normocytic hypochromic anaemia	7.66	5.86	
	Normocytic normochromic anaemia	5.94	2.63	

*** Statistically significant**

Table 3: Comparison of serum urea with peripheral smear blood picture

		Serum Urea (mg/dl)		
		Mean	SD	p-value
Peripheral Smear blood picture	Dimorphic anaemia- predominantly microcytic	73.9	13.7	0.01*
	Dimorphic anaemia- predominantly Normocytic	108.9	55.7	
	Macrocytic anaemia	99.1	68.3	
	Microcytic hypochromic anaemia	81.4	30.6	
	Normocytic hypochromic anaemia	128.8	90.9	
	Normocytic normochromic anaemia	105.3	59.5	

*** Statistically significant**

Table 4: Hematological and biochemical mean variables in the study

	Minimum	Maximum	Mean	SD
Hemoglobin g/dl	4.6	12.1	8.131	1.44
RBC Count 10^6/microL	1.5	4.6	2.934	.55
PCV %	13.8	36.6	24.681	4.57
MCV fL	64.7	108.2	85.358	7.12
MCH pg	19.7	35.1	27.945	2.62
MCHC g/dL	30.0	37.0	32.715	1.18
RDW CV	12.5	26.1	15.754	2.57

TLC 10^3/microL	1360.0	47090.0	11865.000	7933.23
Platelet Count 10^3/microL	0.15	7.20	1.6710	1.214
Serum Urea mg/dL	15.6	373.6	108.035	66.22
Serum Creatinine mg/dL	2.20	29.57	6.1725	3.55
Serum Na mmol/L	106.1	143.0	132.803	6.03
Serum K mmol/L	2.71	7.75	4.6995	.91
Serum Cl mmol/L	70.97	113.20	100.1945	6.39

Table 5: Pearson's correlation of haemoglobin with serum creatinine

Correlations		Serum Creatinine mg/dL
Haemoglobin g/dl	Pearson's Correlation	-.265**
	Sig. (2-tailed)	.000
**. Correlation is significant at the 0.01 level (2-tailed).		

Table 6: Correlation of mean serum urea with respect to presence of Burr cells in peripheral smear

Burr cells	N0.	Mean	Std. Deviation
Present	200	232.140	113.79
Absent	20	96.825	41.77
T=5.28		p=0.000(sig)	

(Independent t-test)

DISCUSSION

"Chronic kidney disease (CKD) is defined by the presence of kidney damage or decreased kidney function for three or more months, irrespective of the cause." The hematological profile has a major impact on the quality of life of patients with CKD. Anaemia is seen consistently in these patients contributing towards the morbidity and mortality. Leucocyte and platelet disorders have also been described in cases of renal failure. Therefore, these co-morbid conditions, if managed properly, can improve the cardiac health, cognitive function, functional capacity and overall quality of life in patients with CKD.[5,7]

In present study total of 220 patients fulfilling inclusion criteria were included with mean age of 56.009±16.15yrs of age. Among them 70.9% was male and 29.1% were female patients with a male to female ratio of 2.44:1. Similar to present study Bhattacharjee K et al had series containing 100 instances, with 37% of the patients being between the ages of 51 and 60 yrs. Male predominance was seen, with men accounting for 65% of the population and females accounting for 35%.[4] Sigdel MR et al[18]., Behera BP et al,[21] also observed similar mean age with male preponderance (Male: female ratio- 2:1).

In our study, the most common etiology of CKD was attributed to Diabetes Mellitus (33.6%) followed by a combination of diabetes mellitus and hypertension (19.2%). Other causes of CKD included hypertension (13.6%), polycystic kidney disease (3.6%) and IgA nephropathy (1.4%) while remaining cases (28.6%) were of unknown etiology (CKDu). In other study the three most prevalent recognised causes of CKD were chronic glomerulonephritis (CGN) (36.2%; n=145), diabetes mellitus (31.9%; n= 128), and hypertension (21.7%; n=87)[18]. Similar to present study, Bhattacharjee K et al., observed that the most common etiological factor was diabetes followed by hypertension, other diagnosed causes being chronic glomerulonephritis, polycystic kidney disease and obstructive nephropathy.[4] Dewan P et al., similarly noted that diabetes was the most common etiology of CKD followed by obstructive uropathy, hypertension, renal TB and NSAID use.[5] Singh S et al., studied that diabetes and hypertension were the leading causes of chronic renal disease in 38.46% of cases followed by hypertension alone in 30.76%.[12]

In our study, most of the patients presented with generalised weakness (77.3%). Other clinical findings were pallor (42.7%), pedal edema (15.4%), facial puffiness (10%), easy fatiguability (7.7%) and breathlessness (1.4%). Similar findings were observed in the study by Bhattacharjee K et al., where the most common symptom was generalised weakness.[4]

On assessment of type of anaemia among the patients, 65.5% were having Normocytic normochromic anaemia, followed by 20% showing Normocytic hypochromic anaemia, 5.5% Microcytic hypochromic anaemia, 3.6% Macrocytic and Dimorphic anaemia- predominantly Normocytic and 1.8% Dimorphic anaemia- predominantly Microcytic. Other RBC findings seen on peripheral smear were 9.1% cases showing burr cells, 18.2% cases having microcytes and 8.2% showing macrocytes. The mean RBC count was 3.29 ±0.79 millions/cumm with a considerable drop with increase in the stage of CKD. Also observed were presence of occasional nRBCs, Schistocytes and polychromatophils. The WBC findings on peripheral smear showed 40% cases with Neutrophilic Leucocytosis, 22.7% Neutrophilia, 5.5% leucopenia and 2.7% Leucocytosis. The platelet findings on peripheral smear observed are 56.4% thrombocytopenia, and 1.8% with thrombocytosis. Similarly, Dewan P e t al., found that patients with chronic renal failure show abnormal hematological parameters, commonest being anaemia and thrombocytopenia.[5]

As observed by most of the studies like Bhattacharjee K et al,[4] Arun S et al,[13] Krishnan Y et al,[15] and Chakravarti A et al,[16] the most

prevalent hematological manifestation and most frequently noted on peripheral smear is anaemia i.e., Normocytic Normochromic anaemia which is the anemia of chronic disorder. In the study by Arun S et al., although the majority of the anaemia was normocytic, roughly a third of the patients showed microcytic hypochromic and mixed anaemia.[13]

The RBCs are usually normocytic and normochromic in CKD primarily due to EPO deficiency. Absolute iron deficiency was found to be significantly related to chronic renal failure.[4] However, microcytic hypochromic anaemia can be seen due to blood loss because of bleeding from the GI tract, haematuria or even from blood retention in the tubing of the hemodialysis apparatus.[15] Macrocytic anaemia can also occur due to folate and Vit B12 deficiency.[10] It is critical to recognise and treat subclinical iron shortage in CKD patients as well as to avoid over-investigating slight hematological variations.

On comparison of various types of anaemia with serum creatinine and urea levels, we found that there was significantly higher mean serum creatinine and mean urea in patients with Normocytic hypochromic anaemia followed by Dimorphic anaemia-predominantly Normocytic, Normocytic normochromic anaemia and Macrocytic anaemia. Singh S et al., stated that serum urea and creatinine levels were raised and was statistically significant when compared to controls ($p<0.05$).[12] Chronic renal disease patients have abnormal biochemical and hematological markers. The routine assessment of these markers is beneficial in the care of these individuals.

CKD patients are more prone for infections due to immunocompromised state leading to leucocytosis. However, leucocytosis was not always connected with infections. Similar to present study, Krishnan Y et al. documented leucocytosis most of which was neutrophilic leucocytosis.[15] Neutrophilic leucocytosis was also seen in the study by Dewan P et al,[5] and Iyawe OI et al.[17] In many cases of ESRD (End stage Renal Disease), there is neutrophil activation, release of neutrophil content like neutrophil elastase (NE) and stimulation of inflammatory cytokines. This might explain the rise in neutrophil proportion in some cases of CKD.[11]

A large majority of individuals had aberrant cells in their peripheral blood, such as burr cells, schistocytes and pencil cells, suggesting that there were additional reasons contributing to the anaemia in the study by Chakravarti A et al.[16] Female patients had a substantially higher prevalence of increased red cell distribution width (>15%) than men ($p = 0.001$) and a lower frequency of normocytic normochromic anaemia ($p = 0.009$). White blood cell counts and platelet counts were all within normal ranges, with no statistically significant correlation with hemodialysis duration, serum creatinine or serum blood urea nitrogen which was observed in the present study. The study concludes that anaemia is a substantial comorbidity in patients with end-stage renal failure with numerous causes leading to it and that careful workup and appropriate treatment of anaemia are required in this group of patients.

In our study, the mean levels of Hb, RBC count and PCV were reduced with levels of 8.131 g/dl, $2.934x10^6$/microL and 24.681% respectively. The mean levels of MCV, MCH and MCHC were in the normal range with levels of 85.358 fL, 27.945 pg and 32.715 g/dl respectively. The mean RDW-CV value was raised in our study and was 15.754. This observation was similar to the results obtained by Suresh M et al., where hemoglobin concentration, RBC count and PCV were decreased.[3] In the study by Naeem et al., the MCV, MCH and MCHC values were normal similar to our study where MCV, MCHC, and MCH had mean values of 76.05, 31.06 and 27.67 respectively. In individuals with chronic renal failure, MCV and MCHC levels were lower than the standard ranges (80-90 fL and 33.3-35.5 g/dL, respectively), whereas MCH values were within the guideline range (27-33 pg).[14] In the study by Behera BP et al., hemoglobin, RBC count and PCV levels were decreased while RDW-CV was raised when compared to the control group[21]. Singh S et al., documented Chronic renal disease patients had lower haemoglobin, hematocrit, red blood cell count, total leukocyte count and platelet count when compared to controls ($p<0.05$).[12] Hence anaemia in CKD patients should be identified and treated as early as possible.

Out of 220 cases, 48.5% had Hb less than 5.1 g/dl, 47% had Hb in the range of 5.1-10 g/dl while 4.5% had Hb more than 10 g/dl. Also 24.6% of cases had serum creatinine less than 7.1 mg/dl, 63.6% had serum creatinine in the range of 7.1-10 mg/dl while 11.8% had serum creatinine more than 10 mg/dl. Similarly, Sowmya Eshwari V also noted in their study that majority of the patients had serum creatinine levels between 5.1 and 10 mg/dl and half of them had haemoglobin levels between 7.1 and 10 mg/dl.[19]

On Pearson's correlation, there is a significant negative strength of correlation between the serum creatinine and haemoglobin among the patients. There is higher mean level of serum creatinine with decline in the haemoglobin levels in the present study ($p<0.05$). Suresh et al., observed that patients with chronic renal failure have poorer hematological indices due to decreased erythropoietin production and other variables such as increased hemolysis, inhibition of bone marrow erythropoiesis, hematuria, and gastrointestinal blood loss. All hematological markers have a negative correlation with serum creatinine levels. And the extent of the modifications is determined by the severity of the renal failure[3]. Similar to present study Chakravarti A et al., documented significant negative correlation ($r = -0.74$) between hemoglobin and serum creatinine.[16] Also in the study by Bhattacharjee K et al., the concentration of hemoglobin had a statistically significant negative correlation with

serum creatinine.[4] Thus, monitoring hematological parameters may aid in determining the erythropoietin stimulating agent dose, avoiding potential problems and as a result, lowering the mortality/morbidity rate in ESRD (End Stage Renal Disease) patients on hemodialysis.

On performing independent T-test in our study, it has been observed that patients having burr cells in their peripheral smear had a significant higher mean level of serum urea as compared to those who had no burr cells in the peripheral smear ($p<0.05$). Due to scarcity of literature regarding the cause of this observation however, the hypothesis put forward by Desforges JF, is that due to uremia in the blood, there may be changes in the lipid membrane of the RBCs leading to abnormalities in the RBC membranes.[23]

Limitations of The Study

There is a high prevalence of anaemia in this part of South India. So, various other causes of anaemia have to be ruled out before considering anaemia of CKD. Even after excluding many causes of anaemia in the study, still there can be an overlap of other causes of anaemia with that of anemia of chronic disease. Serum iron, Vit.B12 and red cell folate levels of these CKD patients were not done routinely and hence subclassification of anaemia was not possible.

CONCLUSION

CKD is a global menace as far as morbidity and mortality is concerned. Anaemia is a common phenomenon in a CKD patient. Determining the type of anaemia in the patient helps in choosing appropriate treatment modality in a timely manner so that the progression of anaemia can be halted. In our study, anaemia was predominantly Normocytic normochromic followed by Normocytic hypochromic. The serum creatinine showed a significant negative correlation with the haemoglobin levels suggesting that the severity of anaemia increases with increase in the serum creatinine levels. Also, patients with burr cells in their peripheral smear had a higher level of mean serum urea pointing towards a possible role of uremia in altering RBC morphology.

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