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HEMATOLOGICAL DYNAMICS IN HEMODIALYSIS: A COMPREHENSIVE EXAMINATION OF PATIENTS WITH CHRONIC RENAL FAILURE IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Background: *Chronic kidney disease (CKD) is a significant health burden in developing countries like India, leading to high morbidity and mortality rates. The study aimed to determine the incidence of anemia among patients with CKD and examine its potential association with other predictive markers.*

Methods: *A cross-sectional observational research was undertaken within a tertiary hospital setting to examine the incidence of hematological abnormalities and explore the association between anemia and its many manifestations in patients with stages 3-5 chronic kidney disease (CKD). The markers for anemia encompassed measurements of hemoglobin percentage (Hb%), mean corpuscular volume (MCV), and examination of peripheral smears. The investigation also examined the correlation between stages of chronic kidney disease (CKD) and red cell distribution width (RDW), thrombocytopenia, leucocyte count, and differential count.*

Result: *The study found that 96.8% of participants displayed symptoms of anemia, characterized by normocytic and normochromic observations on peripheral measures. A significant number of patients (57.3% of them) had a higher total leucocyte count (TLC), but there was no statistically significant link between a higher TLC and the worsening stages of CKD. The mean corpuscular volume (MCV) and platelet levels exhibited a predominantly normal range, with relatively few observed fluctuations. However, there is a positive link between the advancement of CKD and an increase in red cell distribution width (RDW).*

Conclusion: *The study highlights the changes in blood parameters observed in individuals with CKD, with particular attention given to the high occurrence of anemia. The findings underscore the importance of comprehensive iron investigations and the timely identification and intervention of anemia. Adopting a comprehensive strategy that includes regular monitoring of blood parameters, specifically focusing on anemia and iron levels, is crucial for effectively managing and enhancing the overall health of individuals with CKD*

KEY WORDS- *Anemia in CKD, Chronic kidney disease, Iron deficiency anemia*

INTRODUCTION

Chronic kidney disease (CKD) is when the kidneys don't work or look right, and the glomerular filtration rate (GFR) drops to less than 60 ml/min/1.73 m2. This happens for at least three months, no matter what disease is causing it. The condition characterized by a decline in the normal functioning of the kidneys is commonly known as renal insufficiency. The user's text is already academic and does not require any rewriting.

The prevailing risk factors encompass diabetes mellitus, hypertension, glomerulonephritis, polycystic kidney disease, and interstitial fibrosis. According to recent prospective research conducted on a cohort of over 300,000 individuals who underwent screening for the Multiple Risk Factor Intervention Trial (MRFIT), it was projected that around 3% of those diagnosed with diabetes mellitus will experience the development of Stage 5 chronic kidney disease (CKD) throughout the course of their lifetime. Therefore, those diagnosed with diabetes mellitus have a much higher relative risk, approximately 12 times larger, of having stage 5 chronic kidney disease (CKD) compared to those without diabetes.

Glomerular diseases are another vital category of riskfactors for CKD.[2]Other conditions, such as IgA nephropathy, membranous nephropathy, focal segmental glomerulosclerosis, lupus nephritis, and others, are considered causes of CKD.[3,4]

The National kidney foundation's kidney dialysis outcomes and quality initiative (KDOQI) group classifiedCKD based on the presence of structural or functional kidney damage for ≥three months, with or without decreased GFR from average values of ~120 ml/min.[5] CKD is further categorized by the level of kidney function (as defined by GFR) into stages 1 to 5 as follows: stage

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1 with normal or high GFR (GFR >90ml/min), stage 2 mild CKD (GFR=60-89 ml/min),stage 3A moderate CKD (GFR=45-59 ml/min), stage 3B moderate CKD (GFR=30-44ml/min),stage 4severe CKD (GFR=15-29 ml/min), stage 5 end stage CKD (GFR <15 ml/min).

Complications of CKD

Progressive CKD is associated with various consequences and complications. These complications contribute to high morbidity and mortality as well as poorquality of life (QOL). A number of these complications (cardiovascular disease, hypertension, anemia, bone disorder, volume overload, electric electrolytes, and acid- base abnormalities) can be easily defined and quantified and require a specific management approach, such as prescribing erythropoietic stimulants to correct anemia. Anorexia, fatigue, pruritus, nausea, and sexual dysfunction are examples of minor, well-definedcomplications with less distinct pathogenesis.[6-8]

Anemia of Chronic Diseases in CKD

Anemia is a common complication of CKD. It has been linked to many adverse clinical outcomes and has a significant impact on the QOL of people with CKD. Patients on dialysis typically required blood transfusions before the availability of recombinant humanerythropoietin (rHuEPO, or epoetin), exposing them tothe hazards of iron overload, viral hepatitis transmission, and sensitization. The introduction of rHuEPO in the late 1980s completely changed the scenario. Even though there is a solid argument for treating anemia in CKDpatients, the best therapeutic options are yet unknown. In addition to ESA therapy, iron replacement is necessaryfor anemia treatment. Importantly, to guarantee an appropriate count of red cell production, CKD patients require target thresholds of iron parameters that differ from those of healthy individuals. The expense of anemiatherapy is substantial; it is thus necessary to assess the risks and benefits rationally and carefully.[9]

The anemia caused by CKD is hypoproliferative. The circulating reticulocyte count is low, and a bone marrow examination usually reveals no increase in progenitor cells, as reported in anemic patients without CKD. There is also a superimposed iron, folate, or vitamin B12 shortage, but red blood cells (RBCs) are usually normochromic and normocytic.[10]

The regulatory hormone erythropoietin, which stimulates the release of RBCs from the bone marrow into the circulation, is the most critical factor governing RBC synthesis in the bone marrow. Although other variables may play a role, the fundamental cause of CKD anemia isa relative deficiency of erythropoietin. Factors involved in the anemia of CKD are represented in (Table 1).

Table 1: Factors involved in the anemia of CKD.

Factors
Most Important/Common Factors
Decreased Erythropoietin Synthesis
Relative Erythropoietin Deficiency
Important, common
Iron Deficiency (Absolute)
Iron Deficiency (Functional)
Chronic blood loss, including from phlebotomy
Infection/inflammation-“anemia of chronic disease”.
Less Critical, Less Common, Or of UncertainSignificance
Vitamin B12 and folate deficiency
“Uremic toxins”
Reduced red blood cell life span
Increased red blood cell fragility
Carnitine deficiency
Aluminum toxicity
Severe hyperparathyroidism
ACEIs/ARBs

Anemia is defined by the world health organization as a hemoglobin level of less than 13.0 g/dl in men and less than 12.0 g/dl in women. The same was adopted in our study. Apart from this, hemoglobin of less than 8.0 g/dl was referred to as severe anemia, as shown in the results section.

Chronic Kidney Disease (CKD) is one of the major health problems worldwide. The morbidity and mortality related to Chronic Kidney Disease is alwaysof great concern in developing nation like India. It is estimated to affect 10% of the general population and affects 50% of the high risk population which comprises of elderly who already suffer from spectrum ofnon communicable diseases like type-2 Diabetes Mellitus and Hypertension [(11)].

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Haematological parameters have shown various changes particularly red blood cell (RBC) indices, are most commonly affected,[12] giving rise to anemia.

MATERIALS AND METHODS

The objective of this study is to identify and analyse haematological abnormalities, including anaemia, thrombocytopenia, and leukocytosis, in patients undergoing hemodialysis. Additionally, the study aims to explore the correlation of these abnormalities with the respective stages of chronic kidney disease (CKD) 130 cases are studied, and all the patients taken in the study have had ESRD for at least the past 3 months and have been seeking hemodialysis at a tertiary care hospital. All age groups are taken into account. Patients' creatinine and urea levels are obtained. Through patients creatinine and other details, eGFR is calculated and they are categorized into CKD stages. Stage1 with GFR of>90ml/min/1.73m^2 and Stage 5 with GFR of<15 ml/min/1.73m^2.

The CBC sample of the patient is run on a 6-part Sysmex XN-1000 haematology analyzer. The haematological parameters that are taken in our study are haemoglobin levels, total count, differential count, platelet count, red cell distribution width (RDW), and mean corpuscular volume (MCV). The peripheral smear examination of the CBC samples was done on ON slides, which are stained with Fields and Leishman stains and observed under the microscope.

RESULTS

The results indicate that among the 130 cases undergoing hemodialysis, the distribution based on the stage of Chronic Kidney Disease (CKD) is as follows: 97 cases (74.4%) were classified in stage 5, 28 cases (21.7%) in stage 4, and 5 cases (3.9%) in stage 3.

Age and Sex

In terms of age, the cases examined spanned from 18 to 86 years. The distribution of Chronic Kidney Disease (CKD) showed a higher prevalence among males; out of the 130 cases, 94 (71.8%) were males, while 36 (28.2%) were females. This suggests a greater susceptibility to CKD among the male gender in the studied population.

Anemia

Anemia emerges as the most prevalent complication of Chronic Kidney Disease (CKD). In alignment with the KIDGO 2012 guidelines, the diagnosis of anemia in adults and children under 15 years with CKD is established when the Hemoglobin (Hb) concentration falls below 13.0 g/dl (130 g/l) in males and 12.0 g/dl (120 g/l) in females.

In the current study, an overwhelming 96.8% of patients exhibited anemia. The severity of anemia was assessed in relation to the stages of CKD, with a categorization based on Hemoglobin levels: 7 gm% was considered severe, 7-11 gm% was classified as moderate, and levels exceeding 11 gm% were indicative of mild anemia (refer to Table-2). This comprehensive evaluation sheds light on the significant prevalence and varying degrees of anemia among CKD patients in the study cohort.

Table-2 Distribution of Hemoglobin

Hb(gm%)	CKD Stage 3	CKD Stage 4	CKD Stage5
< 7	2 (40%)	16 (57.14%)	61 (62.11%)
7-11	2 (40%)	11 (39.29%)	32 (33.68%)
>11/<13	0	0	1 (1.05%)
>13	1 (20%)	1 (3.57%)	3 (3.16%)

The study findings reveal a substantial prevalence of severe anemia among CKD patients, particularly in Stage-5, where 62.1% of patients were identified with severe anemia. In Stage 4 CKD, 57.1% of patients exhibited severe anemia, while in Stage 3, a lower proportion of 3.16% was observed. These results underscore the escalating severity of anemia with the progression of CKD, emphasizing the need for targeted interventions, especially in advanced stages of the disease.

Among Stage 4 patients, 3.57% exhibited Hemoglobin levels exceeding 11 gm%. The mean Hemoglobin (Hb) value across all CKD patients was 7.49. Notably, the mean Hb was highest in Stage 3, suggesting a positive relationship between the degree of anemia and the stage of Chronic Kidney Disease (CKD). The probability value (p value) for the presence of anemia in CKD patients was found to be <0.5%, indicating a statistically significant positive correlation. These statistical insights strengthen the understanding of the association between anemia and the advancing stages of CKD in the study cohort.

The analysis of Stage 5 Chronic Kidney Disease (CKD) patients revealed a statistically significant association with anemia, particularly with Hemoglobin levels less than 9 gm% ($p<0.05$), as indicated in Table-3. This finding emphasizes the clinical significance of anemia in the advanced stage of CKD, underlining the need for targeted interventions and vigilant management strategies in this specific patient population.

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Table-3 –Mean and Standard of deviation of Hemoglobin

Stage	Mean(Hb-gm%)	Standard of Deviation
III	8.98	3.62
IV	7.27	2.05
V	7.48	6.05

Peripheral Smear Examination

Peripheral examination was conducted for all patients, and anemia typing was performed for individuals with Hemoglobin levels less than 13 g/dl. The results revealed that Normocytic Normochromic Anemia was prevalent in 91.1% of the patients, with a notable 76% of these cases found in Stage-5 CKD. Microcytic Anemia was identified in 5.6% of the patients, while Macrocytic and Dimorphic anemias were each present in only 1.56% of cases, as outlined in Table-4. These findings offer valuable insights into the specific types of anemia associated with different stages of Chronic Kidney Disease in the study population.

Table-4: RBC morphology in Anemias - Stagewise

Morphology	Stage-3	Stage-4	Stage-5	Total
Normocytic Normochromic	4	23	85	112
Microcytic Hypochromic	0	1	6	7
Macrocytic	0	1	1	2
Dimorphic	0	2	0	2

Total Leucocyte count

The study encompassed 130 patients, with 57.3% (75 patients) displaying a normal Total Leucocyte Count (TLC), 27.1% (35 patients) exhibiting Leucocytosis, and 15.5% (20 patients) presenting with Leucopenia. Notably, a significant majority of Stage-5 CKD patients demonstrated High TLC, with almost all of them (95.9%) exhibiting this pattern, except for three cases, as detailed in Table-5. These findings underscore the prevalence of leucocytic abnormalities, particularly elevated TLC, in the context of advanced CKD.

Table-5: Stage wise Total Leucocyte Distribution.

WBC count	Stage-3	Stage-4	Stage-5	Total
Leucocytosis	3	7	25	35
Normal Count	2	19	54	75
Leucocpenia	0	2	18	20
Total	5	28	96	130
Mean	17522	11104	9803	10389
Standard Deviation	**9941.2**	**7985.61**	**7437.68**	**7745.15**

Mean Corpuscular Volume

The mean Mean Corpuscular Volume (MCV) for CKD patients was calculated to be 87.50. The p-value associated with MCV concerning the stage of Chronic Kidney Disease (CKD) was found to be >0.05, indicating that the relationship between MCV and CKD stage was not statistically significant, as outlined in Table-6. This suggests that there may not be a substantial association between MCV values and the progression of CKD in the studied patient population.

Table-6: Stage wise MCV Distribution.

MCV	Stage-3	Stage-4	Stage-5
<83	0	4 (14.29%)	24(24.11%)
83-100	4(80%)	23(82.14%)	67(70.53%)
>100	1(20%)	1(3.57%)	6(5.26%)
Mean	92.44	86.84	87.43
Std Deviation	9.86	9.45	9.79

Platelets

The study determined that the mean platelet count for the 130 Chronic Kidney Disease (CKD) patients was 1.87 Lakhs/cumm. This falls within the normal range for platelet count, which is typically between 1.5 and 4.5 Lakhs/cumm, as indicated in Table-7. These results suggest that, on average, the platelet counts in the CKD patient population studied were within the expected and healthy range.

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Table-7: Stage wise Mean Platelet Distribution.

Platelet	Stage-3	Stage-4	Stage-5
Mean	1.74	2.20	1.78
Std Dev	0.60	2.06	1.06

Table-8: Stage wise RDW Distribution

RDW	Stage-3	Stage-4	Stage-5
<15	80%	78.5%	60%
>=15	20%	21.5%	40%
Mean	16.22	17.33	16.09
Std.Dev	2.04	4.72	2.02

DISCUSSION

The discussion highlights key findings from the hospital-based study focusing on hematological parameters in Chronic Kidney Disease (CKD) patients with a low glomerular filtration rate (GFR) of less than 60 ml/min/m². The majority of CKD patients in the study were male, consistent with findings from other studies by Pandurang et al[13], Chakravarti et al[14], and Arun et al[15]. The mean age of the CKD patients was not provided in the excerpt.

One noteworthy observation was the high prevalence of anemia among CKD patients, with 96.8% of the study population exhibiting this complication. This aligns with similar findings in studies conducted by Chinwuba et al[16], Islam et al[17], and Bhattacharjee et al[18]. The distribution of hemoglobin levels was categorized into mild, moderate, and severe anemia, revealing statistically significant anemia in Stage 5 CKD patients with hemoglobin levels below 9 gm%, consistent with studies by Chakravarti et al[14] and Dewan et al[19] .

The discussion delves into the potential causes of anemia in CKD patients, attributing it to the lack of erythropoietin (EPO) synthesis in damaged or injured peritubular cells in the kidneys. This results in low EPO levels, contributing to anemia. The nuanced discussion on the types of anemia observed in CKD patients, such as normocytic and normochromic types due to low EPO levels, as well as microcytic hypochromic, macrocytic, or dimorphic anemias resulting from declining nutritional status due to repeated dialysis and inadequate intake, provides a comprehensive understanding of the multifactorial nature of anemia in CKD.

The study references the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines, which recommend maintaining hemoglobin concentrations ≥10 g/dL in CKD-5D patients. Individualized therapy is suggested for patients with Hb <10 g/dL, taking into account factors such as the rate of fall in Hb concentration, response to iron therapy, transfusion risk, risks associated with erythropoietic stimulating agent (ESA) therapy, and the presence of symptoms.

Overall, the discussion provides a thorough analysis of the study's findings, contextualizing them within existing literature and clinical guidelines. It effectively highlights the significance of anemia in CKD patients, emphasizing the need for individualized management strategies in accordance with established guidelines.

The discussion further emphasizes the importance of establishing an adequate hemoglobin (Hb) target in the management of anemia, emphasizing its positive impact on physiological and clinical parameters, as well as the overall quality of life. The text highlights the crucial role of adequate iron stores in optimizing the effects of erythropoiesis-stimulating agents (ESA), such as recombinant human erythropoietin (EPO) or darbepoetin alfa. Notably, decreased iron stores or reduced iron availability is identified as a common cause of resistance to the effects of these agents.

The discussion underscores the significance of two key tests, serum ferritin and transferrin saturation (TSAT), in assessing iron status. These parameters are crucial for guiding and monitoring ESA therapy, ensuring that patients receive optimal treatment. Peripheral smear analysis revealed that the predominant morphology of anemia in the studied population was Normocytic Normochromic (91.1%). This finding aligns with the observations of other studies, including those by Chakravarti A et al[14] , Mudiyammanarava NR et al[20], Dewan P et al[21], Reza et al[22] , Arun S et al[15]. Additionally, macrocytosis has been associated with increased mortality in hemodialysis CKD patients, as demonstrated by Tennakore KK et al[23]. Neutrophilic leukocytosis has been linked to an elevated risk of mortality, according to the study by Redden et al[24]

The Mean Corpuscular Volume (MCV) is long being used diagnostic approach of anemia in clinical practise. The mean MCV was 87.3 and it was within the normal range. 5.25% of Stage 5 Patients showed MCV >100.

The discussion appropriately highlights the elevated mean Red Cell Distribution Width (RDW) observed in the study, noting its statistical significance. RDW is emphasized as a quantitative marker reflecting the variability in the size of erythrocytes. An increased RDW is explained as indicative of heightened size variations in red blood cells, suggesting altered erythrocyte life span or dysfunction.

The text introduces a critical hypothesis proposed by various authors, linking the size variations of erythrocytes to functional iron status and bone marrow functions. This insight underscores the potential clinical significance of RDW as a marker not only for erythrocyte abnormalities but also as a reflection of broader

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aspects of hematological health, including iron status and bone marrow functionality[25-26].

The discussion extends to explore additional factors associated with Chronic Kidney Disease (CKD), including endothelial dysfunction, microalbuminuria (a marker of cardiovascular risk), inflammation, and increased oxidative stress, all of which have been suggested as potential contributors to increased mortality[27]. It is acknowledged that these mechanisms are still controversial, indicating a need for further research and clarification.

The text proposes the undertaking of prospective multicentric studies to delve deeper into the underlying pathophysiology of the elevated Red Cell Distribution Width (RDW) in CKD patients. This recommendation highlights the complexity of factors influencing RDW in CKD and emphasizes the necessity for comprehensive, multicenter investigations to elucidate the intricate relationships between RDW and various physiological and pathological processes in these patients.

CONCLUSION

The conclusion of the study succinctly summarizes key findings and implications:

Prevalence of Anemia: The study reveals a high prevalence of anemia, affecting 96.8% of the cases. The suspected cause is low erythropoietin levels, although specific data on this aspect is not available in the current study.

Statistical Significance of Low Hemoglobin: Hemoglobin levels less than 9 gm% were found to be statistically significant in Chronic Kidney Disease (CKD) patients, highlighting the clinical importance of monitoring and addressing anemia in this population.

Morphology of Anemia: Normocytic normochromic morphology was predominant in the majority of anemia cases, providing insights into the types of anemia observed in the study population.

Leucocytosis and Infective Etiology: Neutrophilic leucocytosis was observed in 27.3% of cases, suggesting a potential underlying infective etiology in these CKD patients. This emphasizes the importance of considering infectious factors in the clinical management of CKD.

Platelet Count: Approximately 43.7% of cases exhibited a lower platelet count, indicating a potential need for further platelet function and coagulation studies to understand the underlying cause.

MCV within Normal Limits: Mean Corpuscular Volume (MCV) was found to be within normal limits, providing insight into the size of red blood cells in the study population.

Raised RDW and Further Workup: Red Cell Distribution Width (RDW) was elevated and statistically significant, suggesting the need for further investigations to understand the underlying pathophysiology associated with this finding.

The conclusion emphasizes the clinical relevance of the study's hematological parameters in hemodialysis patients, highlighting their potential impact on prognosis and subsequent management. Additionally, the need for further research and understanding of underlying mechanisms is emphasized, pointing towards the importance of ongoing investigation and prospective studies in this patient population.

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