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General Medicine

STUDY OF ANEMIA AND IRON STATUS IN CHRONIC KIDNEY DISEASE PATIENTS

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ABSTRACT

Introduction: Anemia is a common feature in Chronic Kidney Disease(CKD) associated with poor outcomes. Anemia in CKD is associated with reduced quality of life and increased cardiovascular disease, hospitalisation, cognitive impairment and mortality1.Thus management and prevention of anemia in CKD patients poses a challenge to clinicians and nephrologist alike.

Aims and Objectives: This study aims to determine the prevalence of anemia and its associated factors among CKD patients, **t**he prevalence and degree of anemia among CKD patients by stages and sex, to determine the prevalence of Iron, Vitamin B12 and Folate deficiency among CKD patients by sex and to describe the morphology of RBC among anemic CKD patients.

Material and Methods: Observational, cross-sectional study was conducted on 100 patients, all were 18 years and above with diagnosis of CKD as per USA NKF- K/DOQI criteria regardless of its primary cause, who are on replacement therapy in the form of Hemodialysis and/or peritoneal dialysis and/or medical line treatment. Patients who were not included in the study were children below 18 yrs of age, pregnant women, all cases of Acute Renal failure, patients with other systemic illness without renal failure, aplastic anemia ,known hematological malignancy causing secondary renal failure, patients with end stage renal disease treated with renal replacement therapy in the form of renal transplant ,history of blood transfusion in the past three months. After getting ethical committee approval, and informed and signed consent from the patients, patients with chronic kidney disease were selected and studied using random sampling methods over a period of one year. The selection was done on the basis of history and thorough clinical examination.

Results-The majority of the study participants belonged to the age group of **41-60yrs.**, male outweigh the no. of female patients. Hypertension and diabetes mellitus were identified as two main medical disease conditions as the underlying cause for CKD ,whereas a majority of patients were of unknown etiology. The majority of patients were in advanced stages of renal disease, stage 5 followed by stage 4.All the study participants had anemia as defined by WHO criteria, of which majority had severe anaemia . There is no statistical association between gender and degree of anaemia. In this study all were anemic and among them, (15.0%) of CKD patients were iron deficient. , the most frequent morphologic features among 100 anemic CKD patients was Normochromic –normocytic. Majority of the patients in the study had normal or high SerumB12 levels and serum folate level indicating these are not an important contributing factor to anemia in this study.

Conclusion-This study points out the need for increase awareness about this disease in general population , importance of early identification, prevention and treatment of risk factors and seeking early relief. This study shows that anemia is prevalent among CKD patients , where severe degree of anemia is most frequent finding. This study highlights the need for early diagnosis and treatment of anemia in CKD patients as anemia leads to CKD progression and cardiovascular disease in these patients

KEYWORDS : Chronic Kidney Disease(CKD), Anemia

INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem[1] affecting millions of people, with high incidence and prevalence and increasing costs. Indeed, the incidence and prevalence of CKD has increased in recent years in both developed and developing countries[2].

Anemia, is a global public health problem affecting both developing and developed countries with major consequences for human health as well as social and economic development. Anemia occurs at all stages of the life cycle, but is more prevalent in pregnant women and young children, majority from developing countries[3].Anaemia, a common observation in CKD, contributes to a poor quality of life.

Anemia, being a major health problem,is also a major co-morbidity of CKD patients and is common in all stages but becomes more pronounced at the latter stages of kidney failure.Anemia in patients with CKD is due to many factors. Erythropoiesis and iron homeostasis are impaired as a result of a complex chain of events, including the relative deficiency of erythropoietin, chronic inflammation, blood loss, decreased iron absorption and utilization, exogenous iron and erythropoietin acquisition via biologically unregulated mechanisms (blood transfusions and medicinal erythropoietin and iron administration). The causes of anemia are multifactorial ranging from erythropoietin deficiency to nutritional anemia due to iron deficiency, vitamin B12 and folate deficiency. However, erythropoietin deficiency is the most significant cause of anemia in CKD and has been demonstrated to occur at later stages of kidney failure. Because in adults, erythropoietin (EPO) is synthesized mainly by interstitial cells in the peritubular capillary bed of the renal cortex, reduction in kidney mass as occurs in progressive CKD often results in impairment of EPO production, resulting in anemia[4].

Anemia is a contributing factor in many of the symptoms associated with reduced kidney function. These include fatigue, depression, reduced exercise tolerance and dyspnoea. In addition, anemia has direct adverse cardiovascular disease (CVD) consequences[5], like left ventricular hypertrophy (LVH), left ventricular systolic dysfunction, coronary artery disease-accelerates progression of CKD to end stage renal disease and stroke[6]. As a result, patients with anemia due to CKD are at increased risk of hospitalization, increased length of hospital stay, reduced quality of life and increased mortality[7-8].As patients with CKD can have anemia for many reasons, it is recommended that in order to improve management of anemia in these patients a thorough evaluation to identify type and causes of anemia is needed other than erythropoietin deficiency which is a primary cause of anemia in CKD. Therefore treatment of renal anemia should not be started until other treatable causes of anemia for instance, iron deficiency, folate and B12 deficiency have been evaluated and treated, with further investigation of the underlying cause[9].

The advent of erythropoiesis stimulating agents (ESA) and various intravenous iron preparations has resulted in a much more effective management of anemia of CKD, allowing us to maintain hemoglobin levels in certain desired ranges and to effectively treat iron deficiency. Among the emerging challenges are the risks associated with administering high ESA and iron doses, leading to elevated hemoglobin levels and iron overload. Recombinant human erythropoietin (rHuEpo) has been available for treatment of renal disease anemia since 1989. However, rHuEpo therapy results in iron deficiency due to insufficient iron stores for the accelerated erythropoiesis. Despite the fact that ESAs has been recognized as the mainstay treatment of anemia in CKD, it has been observed that 10% of patients on ESAs therapy show poor responsive to the drug and the

major factor being iron deficiency[10].Iron deficiency is the main cause of suboptimal response to erythropoietin in dialysis patients. Maintenance iron supplementation is required to successfully treat anemia; intravenous iron compounds are used to treat dialysis patients who become iron deficient. Monitoring erythropoietin treated patient's iron status is important to detect iron deficiency and avoid the adverse effects of iron medication.

Despite all of these advances on understanding of renal anemia and associated treatment challenges, still in our setting the treatment of anemia in CKD is treated presumptively without establishing the type and cause of anemia. This approach of treatment carries the risk of providing inadequate treatment and consequently leading to complications related to anemia in CKD patients such as cardiovascular disease, increased rate of progression to end stage renal disease and decreased quality of life[11-13]

It is important for clinicians to be aware of the magnitude, morphological type and factors contributing to anemia in CKD patients in our set up. Therefore this study will provide data that will influence the provision of comprehensive and effective management of anemia in CKD patients.

It is therefore justifiable to have this study, which describe the prevalence and associated factors of anemia in CKD patients as the information that will be obtained will help in designing the appropriate treatment measures of anemia, so as to reduce complications and morbidity among patients with CKD.

MATERIALAND METHODS

Observational, cross-sectional study was conducted on 100 patients, all were 18 years and above with diagnosis of CKD as per USA NKF-K/DOQI criteria regardless of its primary cause, who are on replacement therapy in the form of Hemodialysis and/or peritoneal dialysis and/or medical line treatment. Patients who were not included in the study were children below 18 yrs of age, pregnant women, all cases of Acute Renal failure, patients with other systemic illness without renal failure, aplastic anemia,known hematological malignancy causing secondary renal failure, patients with end stage renal disease treated with renal replacement therapy in the form of renal transplant, history of blood transfusion in the past three months. After getting ethical committee approval, and informed and signed consent from the patients, patients with chronic kidney disease were selected and studied using random sampling methods over a period of one year. The selection was done on the basis of history and thorough clinical examination. The patients were admitted in terms of History, Blood investigations : complete hemogram including peripheral blood smear, serum levels of iron, ferritin, total iron binding capacity, transferrin, Vitamin B12/folate levels, blood urea, serum creatinine, serum erythropoietin level, routine examination of urine and Imaging study; USG whole abdomen. The validated CKD-EPI equation was used which is expressed as[14]:

$$\mathbf{GFR = 141 \times \min(S_{Cr}/K, 1)^{\alpha} \times \max(S_{Cr}/K, 1)^{-1.209} \times (age)^{-0.203}}$$

Multiply by 1.018 for women
Multiply by 1.159 for African ancestry
Where S_{Cr} is serum creatinine in mg/dl,
K is 0.7 for females , 0.9 for males, α is -0.329 for females, -0.411 for males , min indicates the minimum of SCr/K or 1, max indicates the maximum of SCr/K or 1.

RESULTS

- The majority of the study participants belonged to the age group of **41-60yrs.**
- Male outweigh the no. of female patients in the study.
- Hypertension (31.0%) and diabetes mellitus (21.0%) were identified as two main medical disease conditions as the underlying cause for CKD whereas a majority of patients, about (48.0%) were of unknown etiology.
- The majority of patients were in advanced stages of renal disease, (87.0%) stage 5 and (11.0%) stage 4, both accounting for (98.0%) of the study population. Few patients were in early CKD (stage 1-3) accounted for (2.0%).
- All the study participants (100%) had anemia as defined by WHO criteria, of which majority had severe anaemia (77.0%), followed by moderate anaemia and mild anaemia accounting to about 21.0% and 2.0% respectively
- Majority of the patients, about (87.0%) of them belonged to CKD stage 5 of which (66.0%) had severe anemia. . This indicates that with advancement of stages of CKD, the severity of anaemia increases. But the association observed between CKD stages and degree of anaemia was not statistically significant, p value=0.118(0.05).
- Majority of CKD patients with low EPO production were among CKD patients in stage 5 (85.0%) compared to early CKD stages 1-3 (2.0%) and stage 4(9.0%) respectively. A moderate inverse correlation is observed between the EPO levels and CKD stages which is statistically significant with pvalue □0.01.
- With increasing CKD stages, despite relative EPO deficiency in early course of CKD, physiological response to anemia was somewhat preserved in early stages CKD1-3 and correlation was completely lost in stage 4 and 5.
- In this study all were anemic and among them, (15.0%) of CKD patients were iron deficient, as indicated by serum ferritin <100 ng/ml and transferrin saturation (TSAT) <20% where by (37.0%) had functional iron deficiency as indicated serum ferritin > 100ng/ml and < 20% TSAT. About (45.0%) of the patients had adequate iron stores having serum ferritin >100ng/ml and transferrin saturation TSAT >20%.
- Majority of the patients in the study had normal or high serum B12 and serum folate level indicating these are not an important contributing factor to anemia in this study.
- In this study, the most frequent morphologic features among 100 anemic CKD patients was Normochromic –normocytic . This shows that the anemia in CKD is generally due to EPO deficiency.

CONCLUSIONS

- This study points out the need for increase awareness about this disease in general population , importance of early identification, prevention and treatment of risk factors and seeking early relief.
- This study indicates the importance of proper education and prevention of female negligence.
- In the light of this study, there is a need for clinicians to diagnosis the disease as early as possible followed by early evaluation and treatment of anemia and prevention of CKD progression, thereby decreasing the burden of dialysis and renal transplantation.
- This study highlights the need for early diagnosis and treatment of anemia in CKD patients as anemia leads to CKD progression and cardiovascular disease in these patients.
- This study shows that anemia is prevalent among CKD patients , where severe degree of anemia is most frequent finding in both sexes. Across CKD stages, early stages like CKD 1-3 had mild anaemia and the severity increased with increase in stages, with maximum number of CKD stage 5 patients having severe anaemia.
- In the vast majority of patients this study showed evidence of inadequate endogenous EPO production and defective iron supply for erythropoiesis, whilst vitamin B12 and Folate deficiency were unlikely to be important factor for anemia in CKD patients.
- These observations may have clinical implication as in most instances intravenous iron, combined in selected cases with subcutaneous recombinant human ESAs would represent a rational therapeutic approach to these anemic CKD patients.
- As mainstay treatment of anemia in CKD is ESAs and adequate iron store are necessary to permit an optimal response, therefore it is highly recommended to do iron studies to establish types of iron deficiency as functional iron deficiency will need intravenous iron supplement compared to absolute iron deficiency which needs oral iron.
- This was a hospital based study, therefore the results doesn't reflect true community picture, it is therefore recommended to do similar study using large CKD sample size at the community level which would ascertain all stages of CKD and more factors related to anemia as in this present study with high prevalence of anemia, only few factors were studied and skewed advanced CKD stage.

OBSERVATIONS

Table-1: AGE– WISE distribution of cases under study where total no. of cases are 100 [n=100]

AGE GROUP	FREQUENCY	PERCENTAGE
18-40	**22**	**22%**
41-60	**56**	**56%**
61 and above	**22**	**22%**
TOTAL	**100**	**100%**

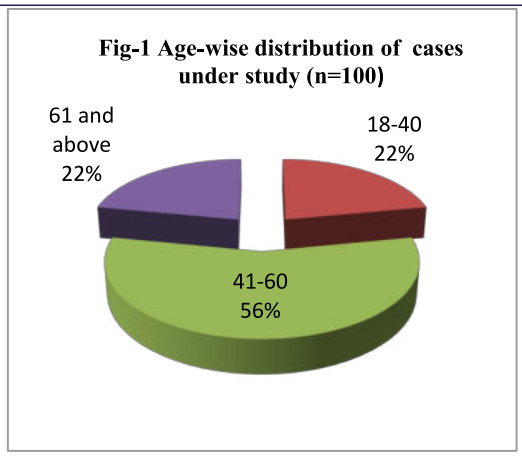


Table-2: Showing SEX– WISE distribution of cases among study participants where total no. of cases are 100 [n=100]

SEX	FREQUENCY	PERCENTAGE
MALE	**68**	**68%**
FEMALE	**32**	**32%**
TOTAL	**100**	**100%**

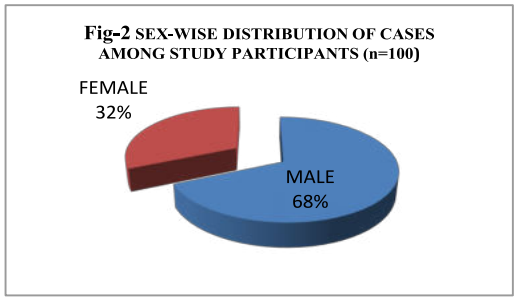


Table 3:-Risk factors for CKD in study population

[n= 100]

RISK FACTOR FOR CKD	FREQUENCY	PERCENTAGE
DIABETES	**21**	**21%**
HYPERTENSION	**31**	**31%**
UNKNOWN	**48**	**48%**
TOTAL	**100**	**100**

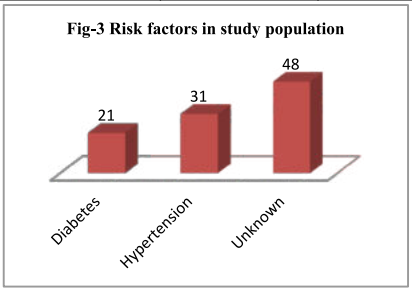


Table 4-Distribution of CKD stages among study population (n=100)

CKD STAGE	FREQUENCY	PERCENTAGE
CKD STAGE 1-3	**02**	**2.0%**
CKD STAGE 4	**11**	**11%**
CKD STAGE 5	**87**	**87%**
TOTAL	**100**	**100%**

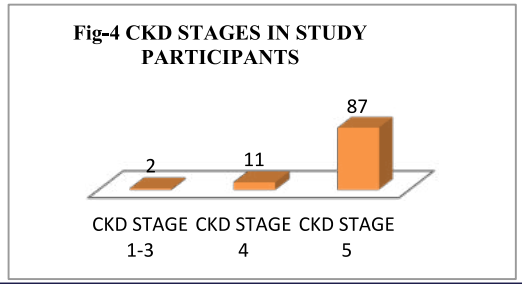


Table 5-Degree of Anaemia in study participants [n=100]

DEGREE OF ANAEMIA	FREQUENCY	PERCENTAGE
MILD ANAEMIA	**02**	**2.0%**
MODERATE	**21**	**21%**
SEVERE ANAEMIA	**77**	**77%**
TOTAL	**100**	**100%**

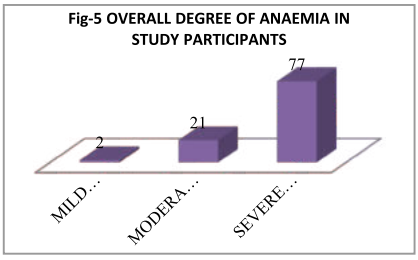


Table-6: Relationship between Degree of anaemia and CKD stages

DEGREE OF ANAEMIA	CKD STAGE 1-3	CKD STAGE 4	CKD STAGE 5	TOTAL
MILD ANAEMIA	**02**	**00**	**00**	**02**
MODERATE ANAEMIA	**00**	**00**	**21**	**21**
SEVERE ANAEMIA	**00**	**11**	**66**	**77**
TOTAL	**02**	**11**	**87**	**100**

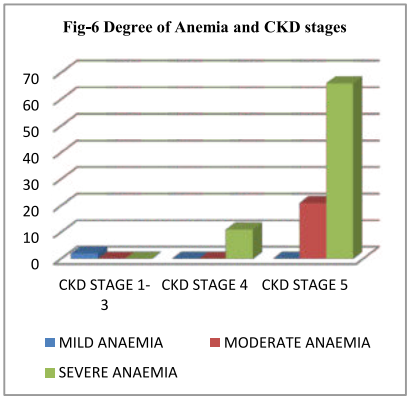
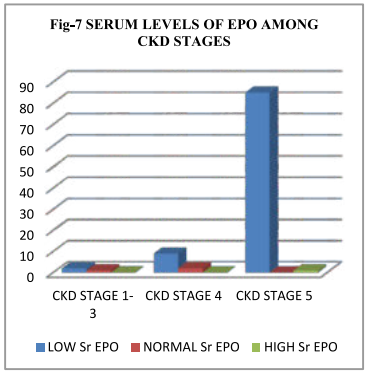


Table-7 Correlation between serum levels of EPO among CKD stages in study population (n=100)

Sr.EPO LEVEL	CKD STAGE 1-3	CKD STAGE 4	CKD STAGE 5	TOTAL
LOW	**02**	**09**	**85**	**96**
NORMAL	**01**	**02**	**00**	**03**
HIGH	**00**	**00**	**01**	**01**
TOTAL	**03**	**11**	**86**	**100**



-Spearman's rho correlation test to calculate statistical significance of correlation between serum levels of EPO among CKD stages in study participants: The test of association applied between Serum erythropoietin and CKD stages is Spearman's rho correlation test. The correlation coefficient is -.361 and p value <0.001 which shows that there is mild to moderate inverse correlation between Serum erythropoietin and CKD stages which is significant.

Table-8: Relationship between Iron Status and CKD patients by sex (n=100)

IRON STATUS	MALE	FEMALE	TOTAL
NORMAL IRON STATUS	**32**	**13**	**45**
ABSOLUTE IRON DEFICIENCY	**09**	**06**	**15**
FUNCTIONAL IRON DEFICIENCY	**26**	**11**	**37**
IRON OVERLOAD	**02**	**01**	**03**
TOTAL	**69**	**31**	**100**

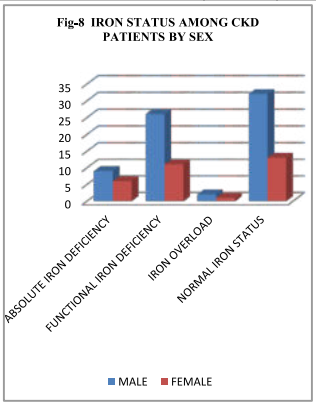


Table-9: Serum B12 levels among CKD patients (n=100)

Sr.Vit B12 LEVEL	FREQUENCY	PERCENTAGE
BELOW	**01**	**1%**
NORMAL	**59**	**59%**
HIGH	**40**	**40%**
TOTAL	**100**	**100%**

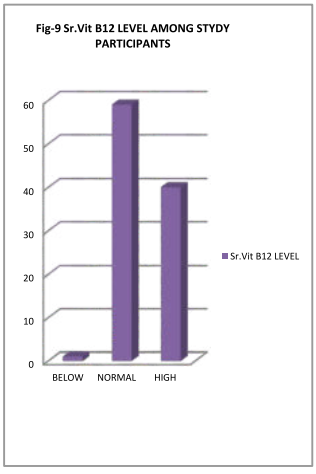


Table-10: Serum folate levels among CKD patients (n=100)

Sr.FOLATE LEVEL	FREQUENCY	PERCENTAGE
BELOW	**01**	**1.0%**
NORMAL	**70**	**70%**
HIGH	**29**	**29%**
TOTAL	**100**	**100%**

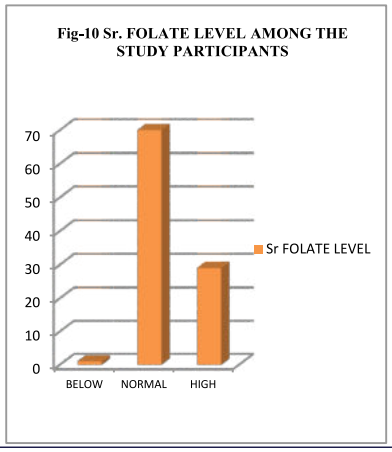
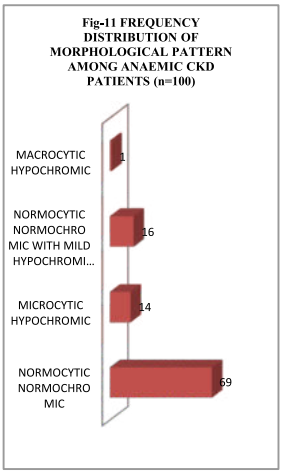


Table-11: Frequency distribution of morphological pattern among anemic CKD patients (n=100)

PBS-RBC	FREQUENCY	PERCENTAGE
NORMOCYTIC NORMOCHROMIC	**69**	**69%**
MICROCYTIC HYPOCHROMIC	**14**	**14%**
NORMOCYTIC NORMOCHROMIC WITH MILD HYPOCHROMIA AND FEW MICROCYTES	**16**	**16%**
MACROCYTIC HYPOCHROMIC	**01**	**1.0%**



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