"CLINICOHEMATOLOGICAL CORRELATION IN PATIENTS WITH CHRONIC RENAL DISEASE"

By

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Dissertation submitted to

SBKS MEDICAL INSTITUTE & RESEARCH CENTRE SUMANDEEP VIDYAPEETH, PIPARIA, VADODARA

In partial fulfillment Of the requirements for the degree of

M.D.

in

PATHOLOGY

Under the Guidance of

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YEAR 2015-2018

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I hereby declare that this dissertation entitled "CLINICOHEMATOLOGICAL CORRELATION IN PATIENTS WITH CHRONIC RENAL DISEASE" is a bonafide and genuine research work carried out by me under the guidance of DR.R.K.TANDON, Professor, Department of Pathology, SBKS Medical Institute & Research Centre, Piparia, Vadodara.

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Dr. Bhavya Saxena

ABSTRACT

Aim and Objectives: The objective of the study was to study the hematological parameters along with there correlations with stages of chronic renal disease.

Methods: Total of 40 chronic kidney disease(CKD) patients referred in Dhiraj hospital , Waghodia , Vadodara were studied which were not on the dialysis, or any treatment were selected, irrespective of their age, sex, history and causative factors. GFR was used for the determination of the stage of CKD. Complete hematological parameters were done.

Results: CKD was seen in almost all the age groups with the mean age of 50.3 years and mostly in males (67.5%). Most number of patients were in stage V CKD (65%) with the commonest cause being diabetes mellitus (52.5%) then was the hypertension and others. The mean hemoglobin was 9.03gm/dl and mean RBC count was $3.4x10^{12}$/L. The reduction in the RBC count and in the hemoglobin shows inverse relationship with the stages of CKD. The absolute reticulocyte count reduces as there is progression of the stage. Mean WBC count and mean platelet count were $11.06x10^{9}$ /L and $300x10^{9}$/L. The peripheral smear finding shows that of normocytic normochromic anemia (47%). Blood group 'O' was commonly seen in CKD patients (47.5%) with the iron profile being normal in the majority.

Conclusion: Chronic kidney disease is seen in almost all the age groups in males mostly. Diabetes is the most common cause in the CKD patients. Anemia of CKD is a normocytic normochromic anemia which is constant as the stage progresses. Fall in the hemoglobin is due to reduced RBC count due to reduced erythropoiesis.

Key words: Chronic kidney disease; hematological correlation, anemia.

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INTRODUCTION

The main concern for public health since many years in the world is Chronic renal disease. Chronic renal disease patients are increasing everyday and will continue to increase till the factors causing it remains unchanged with time[1].

The major factors are Diabetes mellitus and high blood pressure, both together or as a single factor. Some cases are symptomless and show signs when the patient is in end stage.[2]

Even if the chronic renal disease is diagnosed then too the outcomes involves the failure of kidney to perform its function or various other circulatory disturbances. Evidence states that if the patient is alert and shows up at an early stage then its detection with interventions may help in decreased progression of these complications as well as reduced spread of progression to kidney failure.[1]

Various factors affecting chronic renal disease are as follows-[4]

1) Factors of susceptibility – old age adults, relative family history, low birth weight, mental status with low education level.
2) Factors of initiation – diabetes, high blood pressure, autoimmune diseases, renal obstructions, renal stones, various systemic infections, UTI.
3) Factors of progression-increasing the mortality and morbidity which are diabetes, smoking, hypertension, albuminuria.
4) Factors resulting into end stage- late referral for dialysis, reduced dialysis dose (kt/v, where k is urea clearance, t is time and v is volume of distribution of area).

In the present study and also in the initial studies anemia maintains consistency as a complication of the CKD affecting more than 80% of patients. Anemia in cases is caused by reduced renal outflow with other endocrine disturbances. Anemia comes as a constant symptom and also as a complication of the disease. Anemia being slow in onset is detected only by the routine blood evaluations.[5]

Coronary diseases, left ventricular failures, increased risk of cardiovascular disease comes with anemia undiagnosed with chronic kidney disease. The term Renal anemia is trending as a causative agent for abnormal menstrual cycle in females, low immunity, increased fatigue and poor quality of life. Therefore it is important to raise awareness and alert people for early diagnosis and treatment.[5]

OBJECTIVES

1) This study was an attempt towards for identifying aspects which are related with anemia and its relationship with the stages of CKD.

2) To assess the relationship between the other hematological alterations which includes platelets, WBCs, RDW and all included in complete blood count.

REVIEW OF LITERATURE

1) HISTORY:

In the history of kidney diseases the first association between uremia and bleeding was described by Epistola Anatoico Medica XII the Italian anatomist and pathologist Gianbatista Morgagni (1682-1771).[1] They described a women with odor of urine in her breath with epistaxis and hematemesis showing the first association between uremia and bleeding.

Richard Bright was the one who first associated anemia with renal failure by observing pallor in the case of Bright's disease. Anemia stayed constant for 150 years as an important clinical manifestation of progressive renal disease.[2]

Brown and Roth stated correlation between reduced bone marrow production with anemia of chronic nephritis in 1922[2].

Erythropoitic stimulating factor also known as erythropoietin was stated by Erslav in 1953.[2]

Lacking of EPO In bilateral nephrectomised animals was then stated by Jackson and his colleagues in 1957.[2]

Sequencing of amino acids in EPO and helping in identifying and cloning the EPO gene was then made possible by Meyanke and Coworker purified and by Lai et al in 1985.[2]

2) EPIDEMIOLOGY

Since few years chronic kidney disease is a major burden on the economy and health care system by increasing the mortality and morbidity of the patient thereby becoming a global health problem.

Epidemiologically related most of the data is available on end stage renal disease , very little data is available on the prevalence of early stage of chronic kidney disease as it is asymptomatic patients often presents late[3] .

The studies performed shows that evidence from end stage renal disease shows as the tip of the ice berg of CKD whereas the patients with early stage exceeds to that by as much as 50 times[3].

Adults are the ones targeted by CKD the most as the number of CKD patients is increasing everyday.

Because of the high standard of living and good quality of life the number of type 2 diabetes mellitus are increasing making diabetic nephropathy the leading cause of end stage renal disease. CKD ranges approximately to 30%.[3]

In a survey in japan , Australia and Europe states the prevalence of CKD as 6-16% which as in North America it is 11% which is 19 million of the population suffering with CKD .

In India around 1lakh new patients enter renal replacement programs annually. Due to no such record system the figures in India where on the estimates from the rest of the world along with the tertiary care center and the experience of the nephrologist.

Diabetes and high blood pressure are adding on to the burden of chronic kidney disease. Approximately 20-40% of the patients are believed to develop chronic kidney disease in India. Old age along with these chronic diseases are likely to result in chronic kidney diseases.[4]

A very small proportion of the pediatric age group constitute the ESRD population though the information is very little about that age group.

Less than 2% Is accounted in north America. Males are affected more than the females which is due to high incidence of congenital anomalies of kidney and urinary tract in males which includes prone belly syndrome, obstructive uropathy, renal dysplasia and hypoplasia. Due to no screening guidelines in children with CKD along with the limited data about them results into reduced medical attention.[7]

In study children with renal failure are 54% through the exact incidence is still unknown due to the weak record system.

3) DEFINATION

CKD is a combination of different types of pathophysiologic process related to abnormal functioning of the kidneys and a decline in GFR.

National Kidney foundation narrated clinical practical guidelines on chronic kidney disease.[5]

National Kidney Foundation defination of CKD

"Damage of the kidney for 3 months or more than 3months , with the structural and functional abnormalities of the kidney, with or without reduced glomerular filtration rate ,showing pathologic abnormalities or kidney damage markers ,which includes aberration in the composition of the blood or urine or aberration in imaging.

OR

When Glomerular filtration rate is less than 60 mL per minute per 1.73 m^2 for 3 months or more than 3 months , with or without kidney damage"

The term *chronic renal failure* (CRF) applies to the process of continuing significant irreversible reduction in nephron number, and typically corresponds to CKD stages 3 to 5.

The term *chronic renal insufficiency* (CRI) is defined as a reduced glomerular filtration rate (GFR) not requiring renal replacement therapy.

The term e*nd-stage renal disease* (ESRD) represents a stage of CKD where the accumulation of fluids, toxins and electrolytes which are normally excreted by the kidneys results in the uremic syndrome. It corresponds to stage V CKD.[5]

4) STAGING OF CKD

Main aim of CKD classification is to give us the information regarding the disease progression and its development.

NKF Classification of Chronic Kidney Disease[1]: based on estimated Glomerular filtration rate (eGFR).

Table 1: Staging of CKD[1]

Stage	Description	eGFR (mL per minute per 1.73m^2)
	At increased risk for chronic kidney disease	> 60 (with risk factors for chronic kidney disease)
1	Kidney damage with normal or elevated GFR	≥ 90
2	Kidney damage with mildly decreased GFR	60-89
3	Moderately decreased GFR	30 to 59
4	Severely decreased GFR	15 to 29
5	Kidney failure	< 15 (or dialysis)

5) ESTIMATION OF KIDNEY FUNCTION

A. GLOMERULAR FILTRATION RATE:

Overall kidney function is best measured by glomerular filteration rate. According to the NKF guideline serum creatinine concentration alone is not helpful for the assessment of the kidney function[21]. GFR normally changes according to patient sex, age, and weight. In youngs, the GFR is approximately 120 to 130 mL per minute per 1.73 m^2 which decreases with age. GFR level less than 60 mL per minute per 1.73 m^2 shows loss of one and a half or more of the adult level of normal function of the kidneys.

Direct measure of the GFR is not done. Range of markers are used to determine GFR. Inulin is considered to be the gold standard, but technetium- labelled diethylene

triamine penta acetic acid (99mTc-DTPA) , iohexol and ethylene diamine tetra acetic acid (EDTA) gives similar results. Though all are expensive and time consuming and requires correct measurements which ultimately leads to the measure of GFR by the use of serum creatinine.

Clinically, GFR is measured by creatinine clearance (CCr) which is calculated by:[10]

1. 24-hour urine for CCr: CCr calculated by the equation, where Ucr is urine creatinine and Scr is serum creatinine,
    a. CCr = Ucr x urine volume (mL) Scr (mg/dl) x 1, 440 (min)
2. Equation from the Modification of Diet in Renal Disease study:
    a. e GFR (mL/min per 1.73 m^2) = 1.86 x $(P_{Cr})^{1.154}$ x $(age)^{0.203}$

       Multiply by 0.742 for women and multiply by 1.21 for African Americans
3. Cockcroft-Gault equation estimates CCr:
    a. CCr = (140-age) x weight(kgs) 72 x Pcr (mg/dl)

       (multiply by 0.85 for women)

       where Pcr is plasma creatinine
4. In children-
    a. Schwartz formula

       eGFR= *k* x Height (cm) Pcr (mg/dl)

Where Pcr is plasma creatinine and *k* is a constant which depends on muscle mass, which varies with child's age: for pre-term babies, *k*=0.33 and for full-term infants, *k* =0.45.

For infants and children of age 1 to 12 years, k =0.55

b. Counahan formula

eGFR= 0.43 x Height (cm) Pcr (mg/dl)

where Pcr is plasma creatinine.

B.CYSTATIN C:

1. Cystatin C is a low-molecular-weight protein which is produced by all human nucleated cells
2. Marker of kidney insufficiency
3. Studies have shown estimation of GFR by cystatin C in transplant patients, and cirrhotics and in children[18]
4. In the established nephropathy which are stages 3 and 4 , the plasma cystatin C estimates of GFR are superior to creatinine based estimates.
5. Cystatin C is a new superior estimator of GFR, at higher GFR levels[23].

Table 2: Comparison of estimates of GFR as markers of progression of nephropathy[23]

Estimates of GFR as markers of progression of nephropathy[23]			
Method	**Advantage**	**Disadvantage**	**Comments**
Creatinine clearance	24-h urinary creatinine excretion allows check on completeness of urinary collection	1.Underestimates hyperfiltration, overestimates GFR at CKD stages 3 and 4 2.Time consuming and training required for patients to perform accurate urine collections	Underestimates GFR progression
Cockcroft-Gault	Requires weight for calculating eGFR	Underestimates GFR at CKD stages 1 and 2	Underestimates GFR progression at CKD stages 1 and 2
MDRD-4	1.Suitable for automated reporting 2.Accurate at CKD stages 3 and 4	1.Influenced by body weight, muscle mass 2.Underestimates GFR progression at CKD stages 1 and 2	Underestimates GFR at CKD stages 1 and 2
Cystatin C	Independent of weight or muscle mass	1.More expensive than creatinine 2.False low GFR with inflammation, steroid therapy, hyperthyroidism	Accurate marker of GFR progression at CKD stage 1 and 2

C. ASSESSMENT OF PROTEINURIA

Proteinuria, was considered as a marker for non functioning of the kidneys, which is itself pathogenic and disease progression was best defined by this[24]. Underlying glomerular disease, renal tubular dysfunction and progressive kidney injury was diagnosed by proteinuria. Urinary proteins exposure to the renal tubules causes inflammation of the interstitium and simultaneously fibrosis, along with apoptosis in proximal tubular cells.

Definition of urinary albumin or protein excretion:

1) Normal albumin excretion: <30 mg/24 hours

2) Microalbuminuria: 20-200 μg/min or 30-300 mg/ 24 hour or

a) in males—urine albumin(mg)/creatinine(mmol) = 2.5-25

b) in females— urine albumin(mg)/creatinine(mmol) = 3.5-35

3) Macroalbuminuria (overt proteinuria): >300 mg/ 24 hours

4) Nephrotic range proteinuria: >3 g/24 hour

Small amount of proteins are normally in the urine. Though, a constant increase in protein excretion is a good sign of kidney damage. Type of protein, like low- molecular-weight albumin or globulins, is dependent on the type of kidney disease. Increasing excretion of low-molecular-weight globulins is a sensitive marker of some kinds of tubule interstitial disease. Increased excretion of albumin is a sensitive marker of chronic kidney disease from glomerular disease, diabetes mellitus and hypertension.

Albumin excretion rate (AER) is a marker of reduced GFR.

Most of the times, random urine samples should be used to detect and to monitor proteinuria but first-morning urine specimens are preferred for the best diagnosis. Urine

dipstick tests were acceptable to detect proteinuria. Adults with CKD, proteinuria should be measured with the albumin-to-creatinine ratio (ACR). Use of the total protein-to-creatinine ratio (PCR) is accepted if the albumin-to-creatinine ratio is high (500 to 1,000 mg of albumin to 1g of creatinine). Microalbuminuria assessment by the help of albumin creatinine ratio (ACR) is a constant essential component of diabetes care which is an indicator of the development of diabetic nephropathy and the progression of chronic kidney disease. Amount of proteinuria is a marker of progression of CRF in a non-diabetic patient.[11]

D. OTHER MARKERS OF CKD

1) Abnormalities in Urinary sediment

Urinary sediment examination, along with the protoenuria estimates, is useful in identifying chronic kidney disease and its type.

Fresh morning sample is best preferred to determine the Casts forming in the tubules from Tamm-Horsfall protein trap material which includes cells, debris, crystals, fat along with the filtered proteins. Slide is prepared for carefull examination of the urine sedements under the microscope, repeated examinated is necessary if in doubt. The presence and nature of formed elements possibly directs us to some glomerular, tubulointerstitial or vascular pathology[28]., Broad casts , hyaline cast and granular casts are the most frequent casts seen in the urine of patients with chronic kidney disease[29].

2) Abnormal findings on imaging studies

Imaging studies are recommended in patients with chronic kidney disease as any abnormal imaging studies suggests us the cause of CKD[21].

The echo-consistency of the renal cortex is decreased as compared to medulla and the collecting system. In adults, the loss of this 'cortico-medullary differentiation' (CMD) is a sensitive marker but is non-specific marker of CKD. Other than the renal size and CMD, other noticeable abnormalities reported by ultrasound include the presence of cysts which may be simple or complex, any solid lesions, and urinary obstruction[30]. Hydronephrosis may be a finding in patients with urinary tract obstruction or with vesico-ureteric reflux. Radionuclide imaging appears necessary for identifying renal scars and urinary reflux and renal scars[28].

3) Renal biopsy

Used only in unexplained chronic renal failure[28].

4) New markers

Markers of development of diabetic nephropathy are cytokines, which includes transforming growth factor β (TGFβ) and connective tissue growth factor (CTGF). Studies shows that the urinary excretion of CTGF is co-related to albuminuria and to GFR in type 1 diabetic patients with diabetic nephropathy[23].

Proinflammatory chemokines which includes interleukin-8 (IL-8), interferon-gamma-inducible protein (IP-10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1δ (MIP-1δ) and proinflammatory cytokines, interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) are excreted out in urine and are also associated with the development of renal failure[31]. Excretion I urine of retinal binding protein but not albumin increases with the kidney scarring in reflux nephropathy in children. Excretion of the retinol-binding-protein in urine, urinary N-acetyl-b-glucosaminidase (NAG) is present in the absence of albuminuria in diabetes[28].

6) ETIOLOGY

The etiology of CKD are classified by that segment of the renal anatomy which is most affected by the disorder[32].

The most common cause of CKD is diabetic nephropathy, mostly secondary to type 2 DM. In adults Hypertensive nephropathy is a common cause of CKD, in whom chronic renal ischemia as a result of small and large vessel renovascular disease may not known. About 7-10% of cases are grouped under chronic kidney disease of unknown etiology.

Table 3: Etiological classification of CKD

Pathology	Etiology
Primary glomerular diseases	Focal segmental glomerulosclerosis Membranous nephropathy Membranoproliferative glomerulonephritis IgA Nephropathy Idiopathic Crescentric glomerulonephritis Others
Secondary glomerular diseases	Diabetic nephropathy Amyloidosis Post-infectious glomerulonephritis Heroin abuse nephropathy Collagen vascular diseases Sickle cell glomerulopathy
Tubulointestitial renal disease	Nephrotoxic drugs: e.g., Antibiotics, NSAIDs, heavy metals Reflux nephritis Chronic pyelonephritis Renal Tuberulosis Myeloma kidney Lymphoma / leukemia Multisystem disorder: e.g., sarcoidosis
Hereditary diseases	Polycystic kidney diseases Alport's syndrome Medullary cystic disease Fabry's disease
Vascular diseases	Renal artery stenosis Hypertensive nephrosclerosis Chronic radiation nephritis
Obstructive nephropathy	Nephrolithiasis Prostatic disease Retroperitoneal fibrosis Tumor

IN CHILDREN-

Congenital causes account for approximately 60 percent of cases of CKD[15].

The following distribution of causes is based upon the NAPRTCS CRI database of over 7000 patients who were registered from 1994 to 2008.

Table 4: Causes of CKD in children[15]

CAUSE	PERCENTAGE
1. Congenital renal anomalies • Obstructive uropathy (21%) • Renal aplasia/hypoplasia/dysplasia (18%) • Reflux nephropathy (8%) • Polycystic kidney disease (4%)	57 percent of cases
2. Glomerular disease • FSGS (9%)	17 percent of cases
3. Other causes • Primary diagnosis not identified (15%) • Primary diagnosis unknown (3%) • hemolytic-uremic syndrome • genetic disorders (Alport's syndrome) • interstitial nephritis	26 percent of cases

Diabetic nephropathy and hypertension are rare causes of CKD in children which is not the same in adults[15].

7) PATHOPHYSIOLOGY OF CKD

The pathophysiology of CKD involves two mechanisms of damage:

a) First is the initiating mechanism which is specific to the involved etiology (for e.g., immune complexes and the mediators of inflammation in few types of glomerulonephritis, or toxin exposure in various diseases of the interstitium and the renal tubules); and

b) Second is the progressive mechanisms, which involves hypertrophy and hyperfiltration of the remaining functioning nephrons.

When there is reduction in the nephrons vasoactive hormones, growth hormones and cytokines come into play Eventually, these short-term adaptations of hypertrophy and hyperfiltration become adaptive as the increased pressure and flow predisposes to sclerosis and dropout of the remaining nephrons. Increase in the intrarenal activity of the renin-angiotensin system chose to contribute both to the initial adaptive hyperfiltration and then in the maladaptive hypertrophy and sclerosis, resulting in the stimulation of transforming growth factor β (TGF-β). This process defines a reduction in renal mass from an stimulator leads to a increasing decline in renal function over years[3].

CKD resulting in to ESRD occurs through a common pathway among diabetes and non diabetes-associated kidney diseases. Processes involved are epithelial mesenchymal transition, inflammation with fibrosis which leads to the scarring of the glomerulus and tubulointerstitium, resulting in decrease in the kidney mass and reduced kidney function. These pathways accounts for the changes in the progression to ESRD among different ethnic groups[33].

In 2008, two independent studies utilizing the MALD (Mapping by admixture linkage disequilibrium), a novel genetic analysis method to identify genes for ESRD and FSGS, successfully identified MYH9 as a susceptibility gene for kidney disease. Further studies are required in these areas[33, 34].

8) CLINICAL FEATURES

The clinical presentation in CKD is mainly as a result of elevation of nitrogenous and ammonium products and complications of CKD

9) COMPLICATIONS:

A] CKD-associated Mineral and Bone Disorders

The term "CKD-associated mineral and bone disorders" involves abnormalities in the bone and mineral metabolism which also includes extraskeletal calcification which is secondary to CKD pathophysiology as a result of aberrant calcium and phosphorus metabolism in the body.

Renal osteodystrophy (ROD) is the amalgamation of histological changes, which occur in bone architecture of patients with CKD[2].

Changes in bone architecture can be caused by either a high or low bone turnover status. Four types of renal osteodystrophy can be diagnosed in Chronic kidney disease patients:), osteomalacia (low bone turnover and inadequate mineralization, primarily related to diminished vitamin D synthesis), osteitis fibrosa cystica (high bone turnover with secondary hyperparathyroidism), mixed osteodystrophy (with elements of both high and low bone turnover), and adynamic bone disorder (low bone turnover from excessive suppression of the parathyroid glands) [2].

Children with CKD are at risk for aberrant bone development from renal osteodystrophy and related vitamin D deficiency[2].

B] Cardiovascular Abnormalities

Cardiovascular disease is the leading cause of mortality and morbidity at all the stages of CKD[3]., arteriosclerosis, aortic stiffness, Left ventricular hypertrophy (LVH), congestive heart failure (CHF) ,coronary artery disease (CAD), and uremic pericarditis is seen in patients with Chronic kidney disease[2]. Hypertension, anemia, metabolic bone disease, inflammation, dyslipidemia and proteinuria seen in CKD are related with increased risk for cardiovascular disease with early cardiovascular mortality[2].

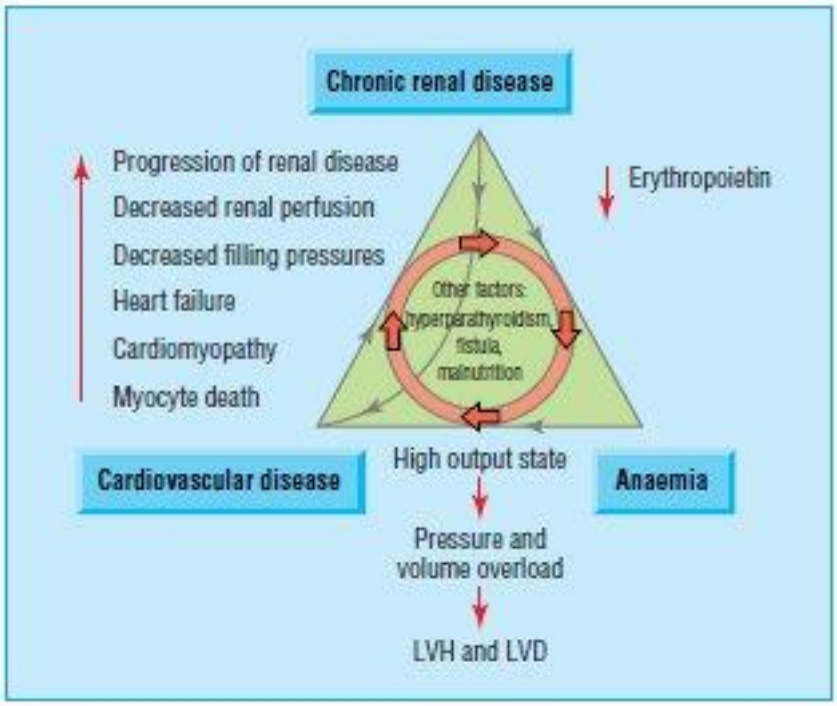


Figure 1: Perpetuating triad of chronic kidney disease, anemia and cardiovascular disease[24]

C] Dyslipidemia

Dyslipidemia is common in patients with chronic kidney disease[1]. Alterations in lipid metabolism with, triglyceride-rich particles, low high-density lipoprotein cholesterol, and increased triglyceride levels occur with CKD and aging, which have significant atherogenic status. The occurence of hyperlipidemia increases as renal function reduces, with the degree of hypertriglyceridemia and elevation of LDL cholesterol being proportional to the severity of non functioning kidneys.

D] Neuromuscular Abnormalities

Central nervous system (CNS) which includes the autonomic and peripheral neuropathy along with the abnormalities in muscle structure with function are well-developed risk factors of CKD. Retained nitrogenous metabolites and middle molecules, including Parathyroid hormones contribute to its development. Manifestations in the early stage of CNS complications involves disturbances in the memory and concentration along with the sleep disturbances. Neuromuscular irritability which includes hiccups and twitching of muscles, becomes evident at not so early stages. In advanced untreated CKD, asterixis, myoclonus, seizures, and coma are also seen.[3]

E] Gastrointestinal Abnormalities

A urine-like odor on the breath also known as uremic fetor, peptic disease, gastritis and mucosal ulcerations at any level of the gastrointestinal tract occur in CKD patients. The retention of toxins also leads to anorexia, nausea along with vomiting and constipation[3]

F] Nutritional Abnormalities

As the patient progresses the stages of CKD, altered nutritional requirements and altered protein metabolism , water, salt, potassium, and phosphorous are hampered .

These changes lead to not so efficient energy generation ven though there is adequate intake of protein and carbohydrate. In more extreme manifestations uremic malnutrition occurs which is a syndrome that is caused from malnutrition caused by inadequate nutrient intake. Both inadequate nutrient intake and abnormal nutrient metabolism contributes to nutritional disorders in CKD patients[3].

G] Endocrine-Metabolic Disturbances

Glucose metabolism is hampered due to glucose intolerance because of the reduced renal degradation of insulin in chronic kidney disease.

Women with CKD, estrogen levels are reduced , abnormal menstruation and pregnancy abortions are common. Men with CKD have reduced plasma testosterone levels, sexual disability. Delayed sexual maturation in adolescent children with CKD[3].

H] Dermatologic Abnormalities

Abnormalities of the skin is seen in progressive CKD involving pruritus to *nephrogenic fibrosing dermopathy;* a skin condition in which progressive subcutaneous induration occurs mostly on the arms and legs[3].

I] Fluid, Electrolyte and Acid-Base Disorders

Fluid retention and fluid overload along with metabolic acidosis, hyperkalemia, hyponatremia, hypernatremia, hypokalemia are common disturbance seen in progressed CKD.

10). ANEMIA IN CKD

Anemia is *'decrease in one or more of the red blood cell size; hemoglobin concentration, hematocrit, or count'*[2].

The World Health Organization defines anemia as *'hemoglobin level less than 13 g/dL in males and post-menopausal women, and less than 12 g/dL in young and adolescent women'*[36].

The NKF defines anemia as *'hemoglobin of less than 13.5 g/dL in males and less than 12.0 g/dL in females'*[37].

Anaemia of chronic renal disease is when the glomerular filtration rate reduces to 30-35% of normal[24].

Normochromic, normocytic anemia accompanies the progressive CKD, and the prevalence of chronic kidney disease-associated anemia is approximately 45%-50%. Though anemia can be diagnosed in patients at any stage of CKD, hence there is a correlation between the severity of CKD. One fourth of stage 1 patients, one half of CKD stages 2, 3, and 4 and three fourth of CKD patients starting dialysis suffers from anemia[2].

Though renal anemia develops independent of the etiology, there are still some exceptions .Patients with diabetes, anemia can occur at much lower degrees of renal failure, though, the degree of anemia in patients with CKD caused by autosomal dominant polycystic kidney disease is generally less serious[38]. Patients with already progressed renal failure are not anemic which relate to IGF-1 sensitivity[39].

The anemia of CKD increases the morbidity and mortality of the patient from the cardiovascular complications which leads to further hampering of the renal function and the formation of a vicious cycle termed as the "cardiorenal anemia syndrome".

a. Evaluation of anemia in CKD:[40]

Complete blood count (CBC)

Hemoglobin concentration

Total and differential white blood cell count

Red blood indices- MCV, MCH, MCHC

Platelet count

Absolute reticulocyte count (ARC)

Serum ferritin to assess iron stores

Serum transferrin saturation (TSAT)

Causes of Anemia in CKD can be broadly categorized as follows:[3]

- Deficiency of erythropoietin
- Decreased red blood cell survival
- Bleeding
- Deficiency of iron stores
- Hyperparathyroidism
- Inflammation which is chronic
- Deficiency of Folate or vitamin B12
- Hemoglobinopathy
- Comorbid conditions: HIV-associated disease, hypo/hyperthyroidism, autoimmune disease, pregnancy, immunosuppressive drugs Severity of anemia is assessed best by measurement of the hemoglobin concentration than the hematocrit because hemoglobin is measured directly, and not influenced by differences in instrumentation[40]. The RBC's are usually normocytic

normochromic. Occasionally, 'burr' cells or acanthocytes are observed along with some schistocytes, helmet-shaped, or fragmented cells[41]. The reticulocyte count is reduced according to for the degree of anemia[38]. Burr cell is a red cell, measuring about 7.5μm, or less in diameter, and having large spiny projections along its periphery which is mostly seen in azotaemia[42]. The amount of erythropoiesis is decreased relative to that expected for the degree of anemia.

The RBCs from uremic patients are normal, because cross- transfusion studies shows that RBCs from normal subjects have a shortened half- life after transfusion into patients, whereas RBCs from uremic patients have a normal survival after transfusion into nonuremic subjects.[8]

A related factor in reducing the RBC life is the lipid peroxidation of the cell membrane, which depends on the defective antioxidant activity of uremia or on the aging of circulating erythrocytes, as the membranes of the imatures or young RBCs contain more antioxidant enzymes.[8]

b. Role of erythtopoietin in anemia of CKD:

Erythropoietin is the glycoprotein which is secreted by the renal interstitial fibroblasts of the cortex and is important for the growth and differentiation of RBCs in the marrow[2]. In the bone marrow, Erythropoietin acts on both the burst forming unit erythroid (BFU-E) and also as the colony forming unit erythroid (CFU-E) [42]. Whereas in anemia in CKD results from the number of mechanisms where there is decreased erythropoietin synthesis and specific etiology causing CKD-associated anemia[2].

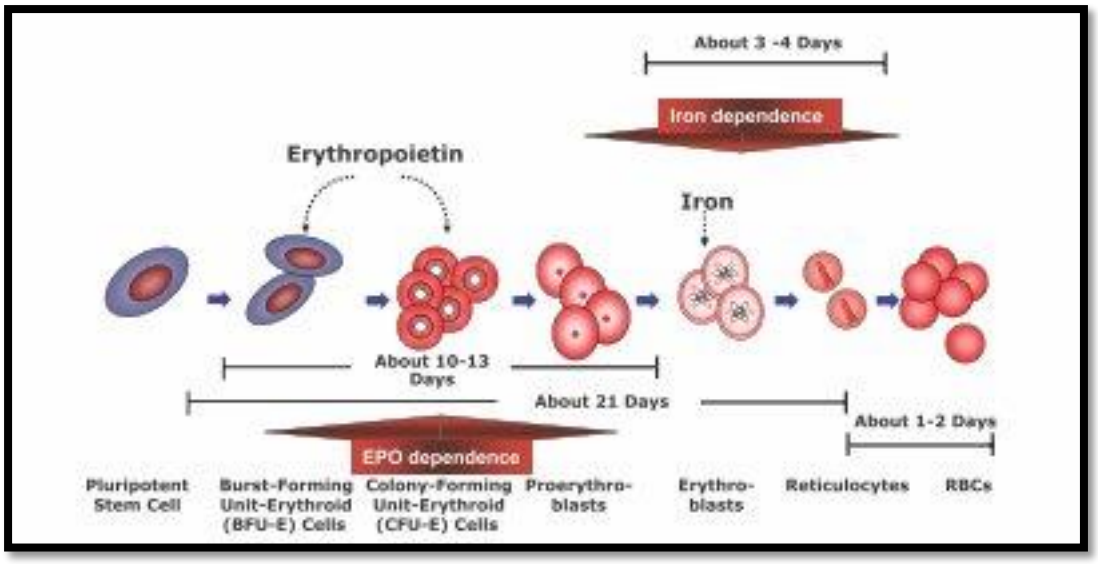


Figure 2: Role of erythropoietin (EPO) and iron erythropoiesis[44]

c. Role of inflammation in anemia of CKD:

CKD is an chronic inflammatory disease, with increase in the number of reactive oxygen species (ROS) and improper balance of ROS and the antioxidant defence mechanism[45]. Chronic infections and inflammations have been related with anemia. The mechanism is then mediated by the inflammatory cytokines related with erythropoietin and thereby not allowing its action at the cellular level[38].

d. Role of hepcidin in anemia of CKD:

Hepcidin also known as hepatic bactericidal protein[47] is an acute phase reactant which is generated, processed, and secreted majorly by hepatocytes[46]. Today the main function of hepcidin this homeostatic regulation of iron metabolism and mediation of the inflammation host defense [46]. It manages intestinal iron absorption and the release of it from macrophages and liver stores[47]. Hepcidin is occurs in circulation by iron loading and by inflammation and is reduced by erythropoitin[47]. Production of hepcidin

causes iron deficiency anemia as a result of the individual's inability to absorb iron, even when there is normal intake of iron-enriched diet[47].

High levels of hepcidin (prohepcidin) is found in patients with chronic renal failure and anemia[45]. In CKD, both inflammation and the reduced clearance of hepcidin by both the kidneys, and could raise blood hepcidin concentrations which leads to iron-restricted erythropoiesis. In some cases, iron restriction could become manifest only when erythropoietic activity and iron demand increase as a result of treatment with recombinant erythropoietin. In these cases, iron restriction leads to erythropoietin resistance along with partial reversibility by parenteral iron therapy[45].

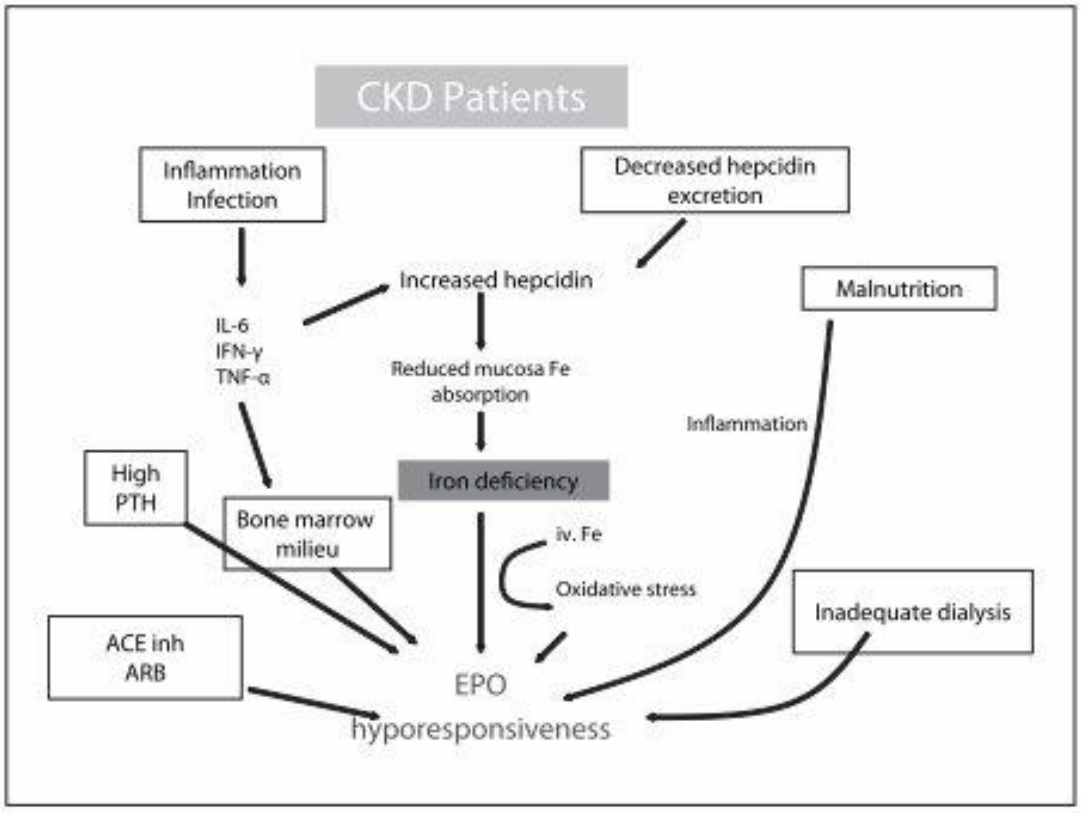


Figure 3: Anemia in chronic kidney disease and the possible role of hepcidin[47]

e. Iron balance in CKD:

Along with *'true iron deficiency'*, it is now shown that a *'functional iron deficiency'* exists among patients with renal failure; this is defined by the presence of adequate iron stores as defined by conventional criteria's, but with the inability to sufficiently mobilize this iron to adequate support of erythropoiesis with the use of erythropoietin[47].

Disturbance of iron homeostasis occurs with increase in the uptake and store of the iron within the cells of the reticuloendothelial system. This results into a diversion of iron from the circulation into storage sites of reticuloendothelial system, limitation of the presence of iron for erythroid progenitor cells and iron-restricted erythropoiesis[47]. An inadequate amount of iron is released from the hepatocytes and other storage sites. In these patients, the serum ferritin level is normal or elevated, but the Transferrin saturation (TSAT) falls to about 20% or lower than that. Clinically important to distinguish functional iron deficiency, which normally responds to iron therapy, from '*inflammatory iron block'*, which does not respond. The inflammatory iron block occurs among CKD patients with anemia largely due to an overlapping inflammatory state. But, with both functional deficiency and inflammation factors, the TSAT is less than 20% and the ferritin level is elevated (between 100 to 800 ng/ml). In patients with functional deficiency, but not with inflammatory iron block, ferritin levels decreases with erythropoietin administration in to the CKD patient. Inflammatory block is likely present if the administration of intravenous iron is associated with a progressive increase in ferritin concentration than the increase in erythropoiesis[49].

The main role of transferrin, both in the absorption of iron and in its delivery in tissues, possess a problem for patients with CKD, especially in those who are on dialysis.

Because transferrin is a negative acute-phase reactant, its concentration is very low in CKD patients[44]. Serum ferritin alone has a low specificity and sensitivity in diagnosis of iron status[52].

Table 5: Attributes of the three iron diagnostic tests[42]

	Serum Ferritin	TSAT	CHr
Accuracy	Poor	Moderate	High
Variability	High	High	Low
Ease of use	Good	Good	Good
Cost	Moderate	Moderate	Low
Availability	Excellent	Excellent	Low

Iron deficiency results in the production of hypochromic RBCs[33]. The amount of hypochromic red blood cells (RBC), is recognised as those with a cellular hemoglobin of less than 28 g/dl has been suggested to be a sensitive and specific marker of functional iron deficiency[34]. The level of Hemoglobin in patients with CKD has changed as different studies have reported. Normal levels of hemoglobin levels is no longer considered the aim of therapy since these target levels have been associated with higher risk of mortality[2]. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend target hemoglobin levels in the range 11 to 12 g/dl, whereas hemoglobin >13 g/dl should not be there[35].

f. Anemia in children with CKD:

KDOQI guidelines says anemia in a child with CKD should be identified and evaluated at a time that the child's Hemoglobin level reduces to less than the fifth percentile for their sex and age[36].

Staples et al shows that anemia was related with an increased risk of hospitalization in non dialysis dependent children with Chronic kidney disease[37].

g. Reticulocyte parameters in CKD:

The anemia of chronic kidney disease is a hypo-proliferative: erythropoietic activity is reduced which is consistent with insufficient erythropoietin activation[40]. An approximate estimate of the reticulocytes present in the blood is helpful for evaluating the erythropoietic activity of bone marrow[38]. Proliferative activity is determined by determination of the absolute reticulocyte count (ARC), the reticulocyte index (RI), and the reticulocyte production index (RPI) [40].

Though there is significance between-patient variability in absolute reticulocyte count (ARC), the test is useful to serve its targeted purpose as a semi-quantitative marker of erythropoietic stimulation. The specific use of the reticulocyte production index (RPI) for the diagnosis and management of anemia in patients with CKD is not evaluated so far[30]. Direct measurement of the reticulocyte hemoglobin provides us useful information for the diagnosis and treatment of iron-deficiencies[39].

h. Diabetes Mellitus, Albuminuria, CKD and Anemia:

Diabetes mellitus is a risk factor for chronic kidney diseases[40]. Diabetic chronic kidney disease (CKD) is the leading cause of kidney failure in the world and is also related with increased cardiovascular morbidity and mortality[41].

Estimates suggest us that diabetic nephropathy occurs in 35–40% of patients with Type 1 or Type 2 diabetes within 15–25 years of disease onset[42].

National Kidney Foundation: KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease now states the term "diabetic kidney disease" (DKD) as a nonproteinuric designation of CKD in type 1 or type 2 diabetic patients. DKD will occur in 25–40% of patients with diabetes[43].

Bad glycemic control and hypertension are the two most important risk factors in the begening and development of diabetic nephropathy[44].

Glomerulopathy is known to be the major contributor in the pathogenesis of DN, however, a evidences suggests that tubulointerstitial injury through an inflammation process also contribute majorly to the development of DN and its progression[31].

In stage V CKD, morbidity and mortality is 2–3 times higher than for non-diabetic patients with end-stage renal failure due to the high incidence of cardiovascular disease in this group[45].

Albuminuria: The earliest clinical manifestation of diabetic CKD has been the presence of persistent microalbuminuria. Studies suggested that the finding of microalbuminuria shows an increase in urinary albumin excretion rate (AER) and has been equated with incipient nephropathy. Low Glomerular filtration rate (GFR) starts when AER reaches the macroalbuminuric (dip-stick positive proteinuria) range. Albuminuria, while being a sensitive and specific index of altered renal management of proteins, which lacks specificity as a marker for diabetic nephropathy[23].

High degree of microalbuminuria in diabetics have been related to the universal use of renin–angiotensin system (RAS) blockers in patients with microalbuminuria. Wider use of methods of accurate estimation of GFR, such as use of *cystatin C*, required in order to find out non-albuminuric patients [41].

There are stages of progression of GFR and AER may occur simultaneously and which can be independent from each other. Which has given rise to the concept of albuminuric and normoalbuminuric pathways to renal impairment[23].

a) Normoalbuminuric chronic kidney disease in diabetes

Approximately 25% of people with type 2 diabetes develop at stage 3 CKD while remaining normoalbuminuric. It been suggested that premature senescence of the diabetic kidney, ischaemic vascular disease or cholesterol microemboli , interstitial fibrosis, as opposed to classical diabetic glomerulosclerosis contributes to the development of normoalbuminuric renal impairment in type 2 diabetes[41].

The natural history of normoalbuminuric diabetic CKD is poorly defined, it is more to be benign than impaired kidney function related with increased AER. Normal ageing most likely attributes to the high reported prevalence of normoalbuminuric CKD in diabetes, especially in type 2 diabetes.

b) Albuminuric chronic kidney disease in diabetes

The history of the albuminuric pathway is related with a reduced GFR, majorly in type 1 diabetes, has several well-characterized stages. Mogensen suggested 'The five- stage classification',

1. The main features in the first stage are hyperfiltration along with renal hypertrophy.
2. The second stage, lasts for many years and consists of a 'silent phase' related with normal AER or intermittent episodes of microalbuminuria.
3. The third stage states by persistent microalbuminuria.
4. Normaly GFR is preserved till the onset of hypertension and macrovascular disease.

5. The fourth stage, states *'diabetic nephropathy'*, which is characterized clinically by detectable proteinuria, high blood pressure and declining GFR. In the absence of antihypertensive treatment, GFR may decrease by 10–15ml/min per year in this stage.

6. The final fifth stage happens when patients progress to end-stage renal failure[41].

   High blood pressure is twice as common in patients with diabetes melitus in comparison to the normal population[46]. The causation of hypertension in diabetic nephropathy is not well understood; and shows excess retention of sodium, activates the sympathetic nervous system (SNS) and endothelial cell dysfunction (ECD), the renin- angiotensin-aldosterone system (RAAS), and increased oxidative stress[46].

Lesions in diabetic nephropathy:

i. Glomerular : The structural changes in the glomeruli include (a) thickening of Capillary basement membrane , (b) Mesangial sclerosis(diffuse), and (c) nodular glomerulosclerosis (**Kimmelstiel-Wilson disease**)

ii. Arteriolar : hyalinizing arteriolar sclerosis is seen often.

iii. Tubular: Diabetes causes a variety of tubular lesions including increased susceptibility to the development of pyelonephritis and papillary necrosis[47].

Anemia:

Patients showing up with diabetic nephropathy mostly have a larger degree of anemia for their degree of renal impairment than those presenting with other etiology of renal

failure. Anemia develops early in these patients than in those patients with renal impairment from other causes[45].

Anemia occurs in diabetes without hidden chronic renal disease. [5]. Inflammation related with the diabetic state contributes to EPO no responses before the occurrence of nephropathy by increase in the production of cytokines, such as, interleukin-1, or interferon-γ, tumor necrosis factor-α which may suppress the erythrocyte stem cell proliferation[45].

In diabetes, advanced glycosylation end products (AGEs) accumulates on the erythrocyte membrane, resulting in the enhancement of the interactions between the erythrocytes and the endothelial cells which reduces the survival of the RBC. In type 1 diabetics a number of autoimmune antibodies may be present which indirectly affects the erythropoesis[9]. EPO production is seriously is impaired in the patients with severe diabetic autonomic neuropathy[38].

Majority factors are suggested as the reason for the early onset of anemia in patients with diabetes, which includes impaired function of EPO-producing fibroblasts related with the interstitial fibrosis and a defect of "anemia-sensing" mechanisms related with severe symptomatic autonomic neuropathy, resulting into efferent sympathetic denervation of the kidney and loss of the appropriate erythropoietin (EPO) production; damage to which leads to renal interstitium damage; inhibition of EPO release and systemic inflammation; [45].

Early Epo deficiency anemia happens in both the type 1 and type 2 diabetes, though the prevalence might be higher in type 1 diabetes [45].

When inflammation is there, proteinuria or both are present, DKD patients are highly susceptible to the anemia of chronic kidney disease[33]. Recent studies shows that the higher levels of hepcidin in the diabetic patients is due to the increase in the ferritin and IL-6 levels, which may have adaptive response through the along with down- regulated erythropiesis with down-regulated iron metabolism and play an important role in pathogenesis of anemia in Type 2.

11). WHITE BLOOD CELLS

In myeloid lineage, a decrease in the capacity of the bone marrow to produce new granulocytes has been shown in the renal failure, there is proofs for increased leucocyte apoptosis.[7] Uremic toxicity has an important role in granulocytes apoptosis[39]. Substances gathering in uraemia, includes *granulocyte inhibitory proteins*, which leads to decreased chemotaxis, intracellular killing of bacteria, oxidative activity, and impaired glucose consumption by leucocytes.[7]

The larger frequency of bactericidal infections in end stage renal disease (ESRD) patients shows that PMN non functioning may be involved in the immune deficiency which is observed in this general public. The factors which are associated to PMN dysfunction are complex and have been related to malnutrition, uraemic toxins, iron overload, , elevated levels of intracellular calcium, zinc deficiency and dialysis therapy per se[39].

Monocyte importance has been associated as impaired in dialysis patients, with many evidences illustriating abnormal antigen presentation, a reduction in the chemotactic response, and a reduction in the phagocytic activity.[7]

Uraemia is related with an acquired immune deficiency which includes both the cellular and humoral immunity[39]. Which is thus, impaired granulocyte, lymphocyte and the monocyte, functions attribute to the chronic immunodeficiency state that is the representative of uraemia.[7]

The leucocyte count is normal, but slight neutrophilic leucocytosis might be seen[41].

12). PLATELETS AND HEMOSTASIS

The relationship of bleeding tendency with uremia is known for long[40]. Today's dialysis techniques and the use of erythropoietin for the correction of anemia have decreased the occurrence of uremic bleeding, which, limits the surgery and various procedures which are invasive in these patients[41]. The association between the bleeding diseases and thrombosis is an important feature in the chronic kidney disease[8]

Clinical Presentations of Uremic Bleeding:

Epistaxis and Echymoses are the main bleeding presentations presently, with bleeding in the gastrointestinal tract , or subdural hematoma often[7].

The etiology of uremic bleeding is the major concern since many years. The pathophysiology is considered to be of many factors; though, platelet-platelet and platelet with vessel wall interactions seems to be of some importance[41].

Factors Involved in this Uremic Bleeding Tendency:

1. Factors which are related to the vessel wall

a. Decrease in the production of the von Willebrand's factor
b. Enhanced prostacyclin production
c. Then Enhanced nitric oxide production

2. Factors which are related to platelets

a. Abnormal motility of calcium ions in platelets

b. Defective COX (cyclooxygenase) activity (reduced ability to generate thromboxane A_2)

c. Defect in the activation of glycoprotein IIb-IIIa receptors

d. High levels of the cyclic adenosine monophosphate

e. Low levels of the serotonin and adenosine diphosphate

3. Factors which are related to the blood

a. Firstly its Anemia

b. Deranged radial transport of the platelets

c. Then there is Altered transfer of adenosine diphosphate from RBCs to the platelets

d. Uremic toxins which involves guanidinosuccinic acid, phenol, phenolic acid, urea.

Non functioning of the platelets in the renal failure is related to the high levels of minute , partly dialyzable molecules known as uremic toxins which involves urea, creatinine, phenolic acid ,guanidinosuccinic acid, , and parathyroid hormone[42.] So the term "*Uremic thrombocytopathy*".[43]

The non functioning of the platelets are characteristic of uremia and is multifactorial. Platelet count is normally within the range or low in patients with uremia. Decreased platelet count is seen in few cases which develops as a part of a bone marrow hypoplasia[44]. Platelet volume and the circulating platelet mass are decreased in chronic renal failure, due to a reduction in thrombopoietin concentrations or its activity. The

mean platelet life is decreased in uraemic patients.[7] High levels of platelets occurs in CKD with iron deficiency and which follows the administration of erythropoietin[45].

Defective Plasma coagulation are not so common in chronic renal failure. Not normal prothrombin time is seen in minor cases is due to abberant platelet procoagulant function and increased activated partial thromboplastin time which may be attributed.

Diagnosis of uremic bleeding: few tests have been used to detect the bleeding tendency in patients with uremia, but only identification of the bleeding time is helpful in differentiating bleeders from the non bleeders[42].

Drugs- NSAIDs abnormal complex of coagulation of the factor VIII and vWF[46] Antibiotics, and no correlation between the quantity and function of few aspects of factor VIII complex[7]

Prothrombotic state

The prothrombotic state in uraemia caused from the endothelial damage, high levels of the factor VIII complex and increased fibrinogen concentrations.[47] Reduction in the levels of antithrombin III, is seen with the decrease in protein C anticoagulant activity with normal protein C amidolytic activity and antigen and decreased protein S, may further contribute to the thrombotic ability.[7]

METHODOLOGY

Source of data:

Patients with chronic renal disease referred to Dhiraj hospital , Sumandeep vidyapeeth University , Waghodia, Vadodara.

Method of collection of data:

The clinical diagnosis of the patients with chronic renal disease was done based on elevation of Serum Creatinine consistently for more than 2-3 months. Estimated Glomerular Filtration Rate (eGFR) was calculated by the use of the formula **Cockcroft-Gault equation** i.e., **140 – age x body wt(kg) 72 x S.Creatinine(mg/dl)**

Based on estimated GFR,CKD patients were categorized in clinical stages of CKD as follows;

STAGE _____eGFR, ml/min per 1.73m^2

0 >90

1 ≥90

2 60-89

3 30-59

4 15-29

5 <15.

Patients in the stages of the chronic kidney disease were studied for the changes in clinical manifestations and hematological findings. Clinical history in detail was gathered from the CKD patients. Details were collected from hospital records too.

After the informed written consent was obtained, blood was collected (before the start

of dialysis procedure in case of stage V CKD) under hygenic precautions for,

I. Investigations done for the assessment of renal failure which is Serum Creatinine

II. Investigations done for assessment of hematological changes in the findings which includes Complete hemogram, blood peripheral smear study, reticulocyte count, blood grouping.

Complete blood count was done using using SYSMEX and BECKMAN COULTER AUTOMATED 7-PART HEMATOLOGY ANALYZER. 21 parameters were obtained which were HB, HCT, MCV, MCH, MCHC,RBC, RDW-SD, RDW-CV, WBC, NEUT%, LYMPH%, MONO%, EOSINO%, BASO%, NEUT#, LYMPH#, MONO#, EOSINO#, BASO#, PLT and MPV. Also RBC, WBC and PLT histograms with scatter plot for WBC differential and WBC BASO were obtained.

Table 6: Investigations done and their procedures:

INVESTIGATION	METHOD
Complete blood count	Labomed vision 2000 microscope BECKMAN COULTER 7 PART ANALYSER SYXMEX kx 21
Blood grouping	Forward grouping and Reverse grouping
Rh typing	Tube method and gel card method
Peripheral smear examination	Using H & E stain
Reticulocyte count	Supravital stain- methylene blue
Absolute reticulocyte count	Reticulocyte count % × RBC count
Biochemical investigations	Biochemical auto analyzer-EM 200

STATISTICAL TEST

Results are expressed as mean ±SD, range values, number and percentages. The Unpaired T-test was used for comparing between two groups One way ANOVA was used for multiple group comparisions. Categorical data was analysed by chi-square test.

INCLUSION CRITERIA:

1. Case of CKD referred to the Dhiraj hospital.
2. Either sex, giving history of hematuria with fever and vomiting and deranged RFT All patients giving history of reduced urine output with high pus cells in their 24 hr urine study.

EXCLUSION CRITERIA:

1. All patients on dialysis and on high dose haematinics or erythropoietin therapy.
2. Acute or chronic inflammatory disease.
3. Malignancy or known hematological disorder
4. Recent severe hemorrhagic episode

RESULTS

Forty patients with chronic renal disease or chronic kidney disease were included in this study.

The study includes 27 males (67.5%) with 13 females (32.5%). Sex distribution is depicted in the figure below.

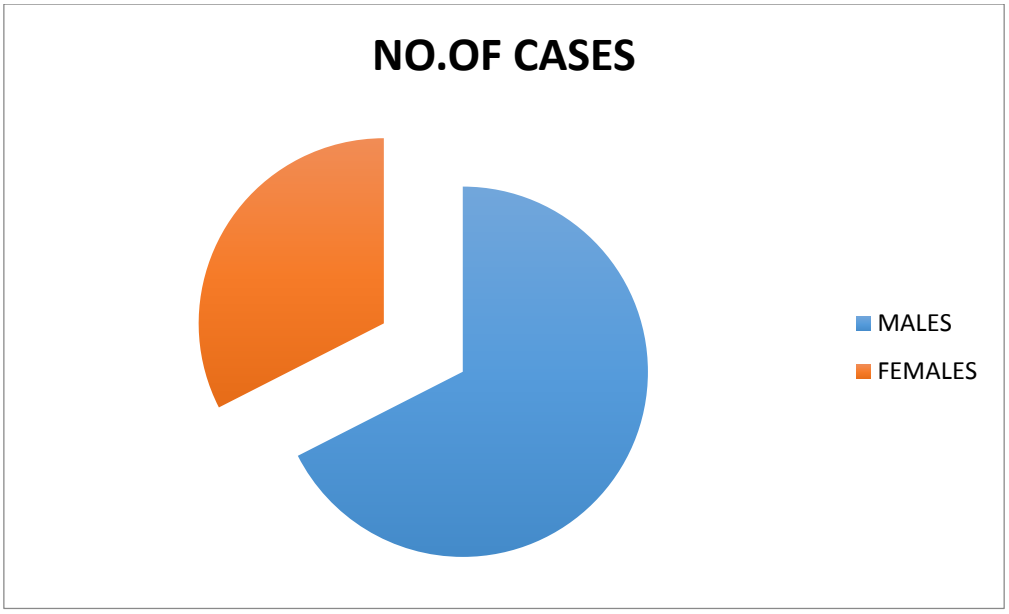


Figure 4: Sex distribution

Age distribution:

The age of the study population was between 6 months to 81 years, with the mean age being 50.3 ±17.0 years. Figure 5 depicts the age distribution across age groups. Majority of the patients (47.5%) belonged to the age group of 51-60 years.

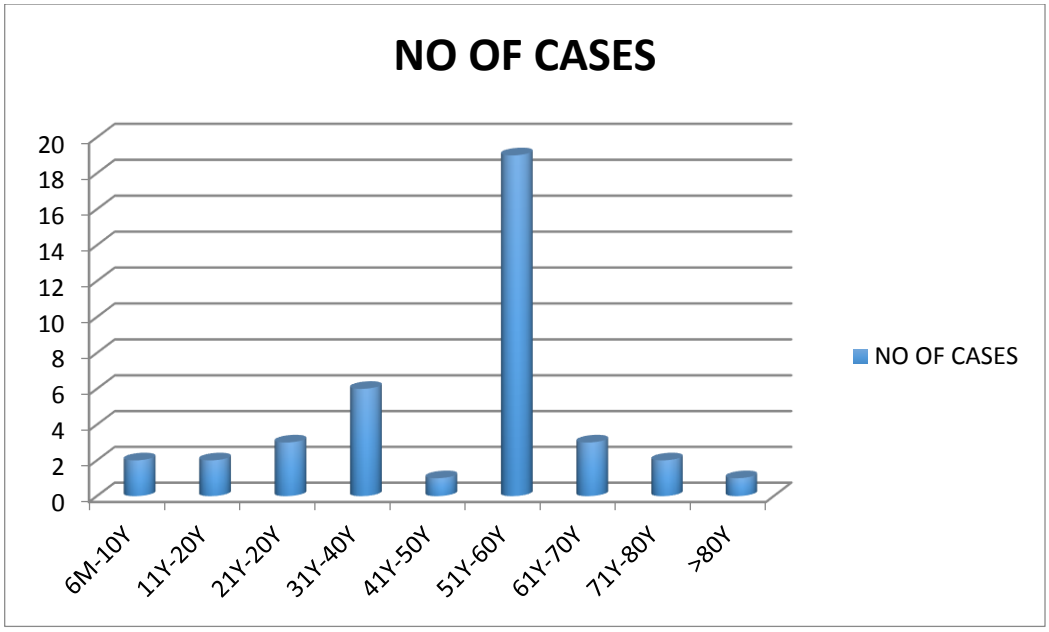


Figure 5: Age distribution

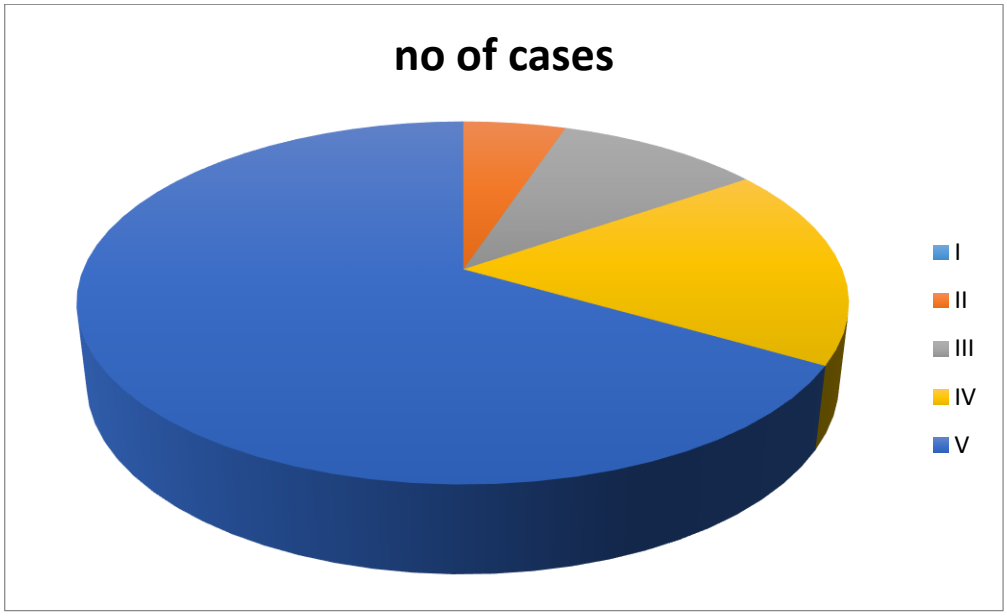
CKD in children: 12.5% of the study population was from pediatric age group (<20 years) with a male preponderance (60%). Congenital kidney diseases being the common cause.

Table 7: CKD in children

Number of cases	
5 (12.5%)	Male: 3 (60%)
	Female: 2 (30%)

Stage distribution

Figure 6 depicts the stage distribution in the study population.



Majority of the patients (65%) in the study were in stage V CKD, followed by stage IV (17.5%), stage III (10%) and stage II (5%). No cases of stage I were seen.

Etiological distribution: The following table depicts the etiological distribution of CKD in this study.

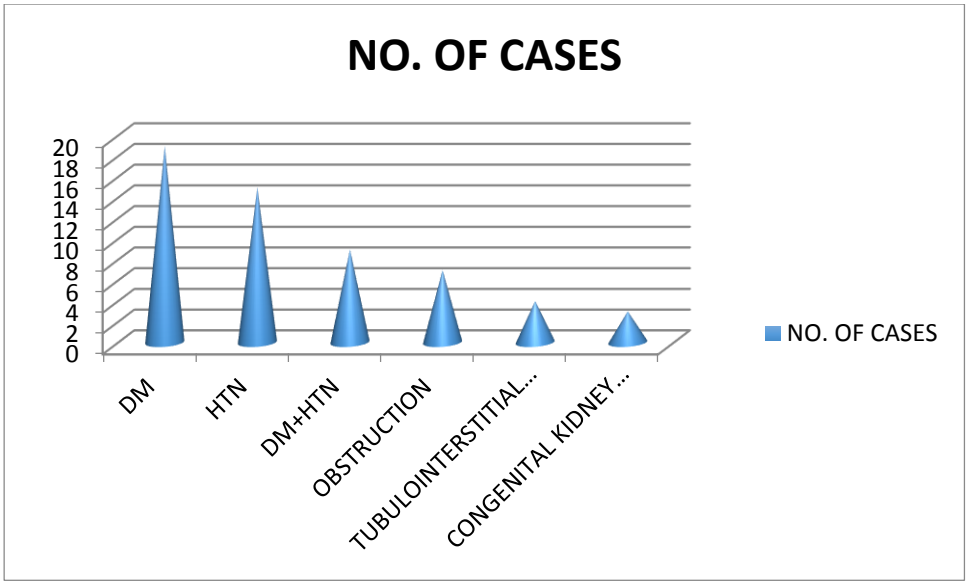


Figure 7**: Etiological distribution of CKD**

Diabetes was the leading cause of CKD (47.5%) followed by hypertension (37.5).

Presenting symptoms:

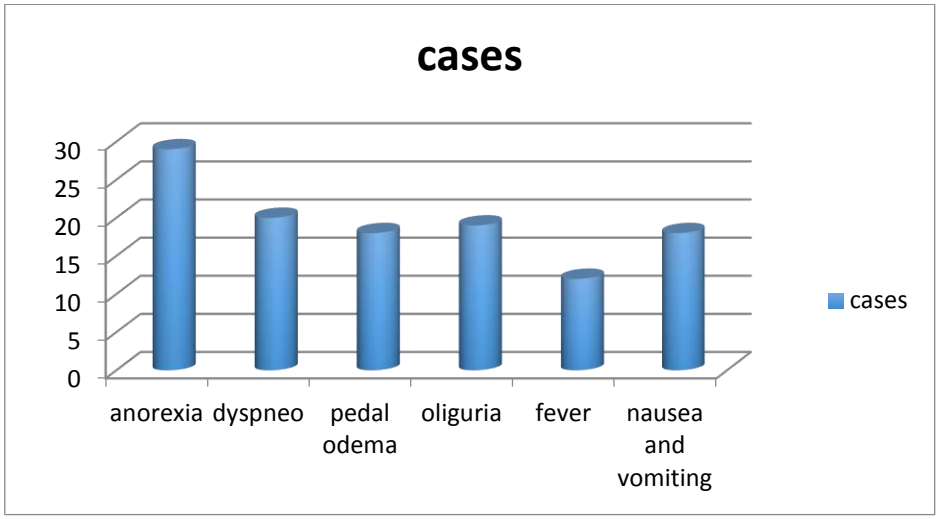


Figure 8 shows the presenting symptoms in the study group.

Signs:

Pallor and signs of volume overload (Pedal edema, pulmonary edema and ascites) were frequently seen in CKD. Table 8 shows the distribution of pallor.

Table 8: Distribution of Pallor in various stages of CKD

Pallor	Stage II	Stage III	Stage IV	Stage V
Absent	1	0	0	0
Mild	1	1	2	4
Moderate	0	2	3	17
Severe	0	0	3	5

The association between the degree of pallor and the stage of CKD is significant.

Hemoglobin:

Table 9 depicts the distribution of Hemoglobin in the study group. Hemoglobin ranged from 4.5 g/dl to 15.4 g/dl, with a mean hemoglobin of 9.03 ±2.4 g/dl.

Table 9: Hemoglobin distribution in CKD

Hemoglobin (g/dl)	Number of cases	Percentage
<4	0	0.0%
4.1-6	3	8%
6.1-8	17	42%
8.1-10	12	30%
10.1-12	6	14.0%
12.1-14	2	5%
>14.1	0	0.0%

Correlation of Hemoglobin with the stage of CKD:Table 10 depicts the distribution of hemoglobin among the stages of CKD. There is fall in hemoglobin level as there is progression of CKD.

Table 10: Distribution of Hemoglobin in various stages of CKD ANOVA, F=36.4, P<0.001, SIGNIFICANT

Hemoglobin (g/dl)	Stage II	Stage III	Stage IV	Stage V
4.1-6	1	0	0	0
6.1-8	0	2	5	11
8.1-10	0	1	2	8
10.1-12	1	0	1	7
12.1-14	0	0	0	0
>14.1	0	0	0	0

There is significant inverse correlation between the hemoglobin levels with the stage of CKD.

RBC Count:

The distribution of RBC count in the study group is shown in figure 9. The RBC count ranged from 1.51 – 55 x10^{12}/l with a mean of 3.4 ±0.73 x10^{12}/l. Table 11 depicts the distribution of RBC count in various stages of CKD. There is fall in the RBC count as the stage progresses.

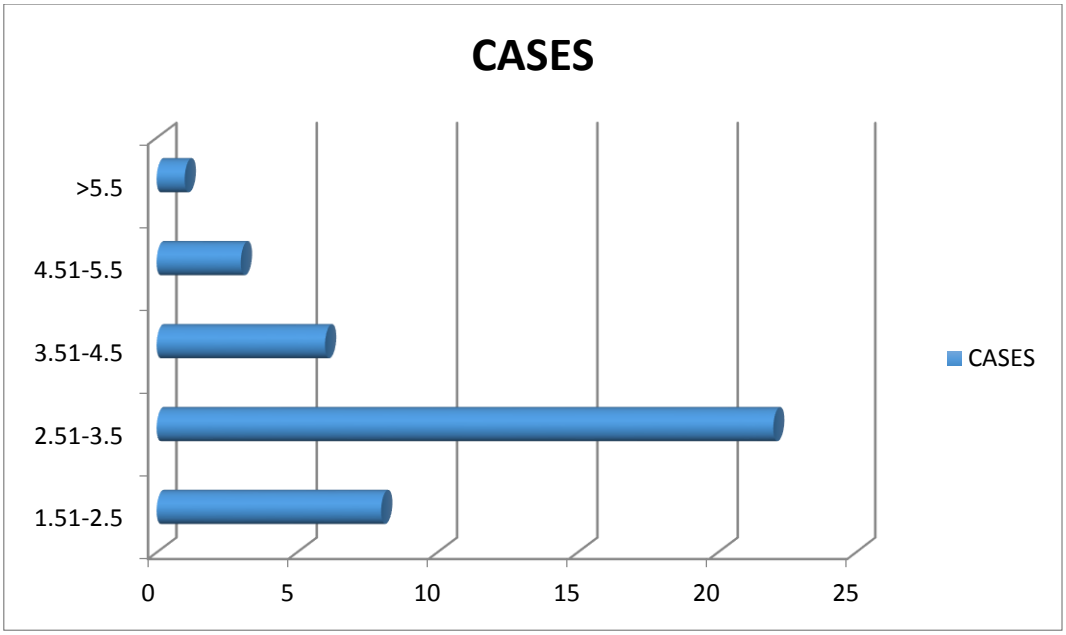


Figure 9: Distribution of RBC count

Table 11: Distribution of RBC count in various stages of CKD ANOVA, F=30.6, P<0.001, SIGNIFICANT

RBC count (x10^{12}/l)	Stage II	Stage III	Stage IV	Stage V
1.51-2.5	0	0	0	8
2.51-3.5	2	1	5	14
3.51-4.5	1	0	1	4
4.51-5.5	1	1	0	1
>5.51	0	1	0	0
Mean ±SD	4.39 ±0.0	4.65 ±0.57	2.88 ±0.67	1.94 ±0.71

The fall in RBC count with the progression of the stage of CKD is statistically significant.

Figure 10 depicts the distribution of Absolute reticulocyte count in the study population. The absolute count ranged from 18.8 – 100.4 x10^{9}/l, with a mean ARC of 18.8 ±19.8x10^{9}/l.

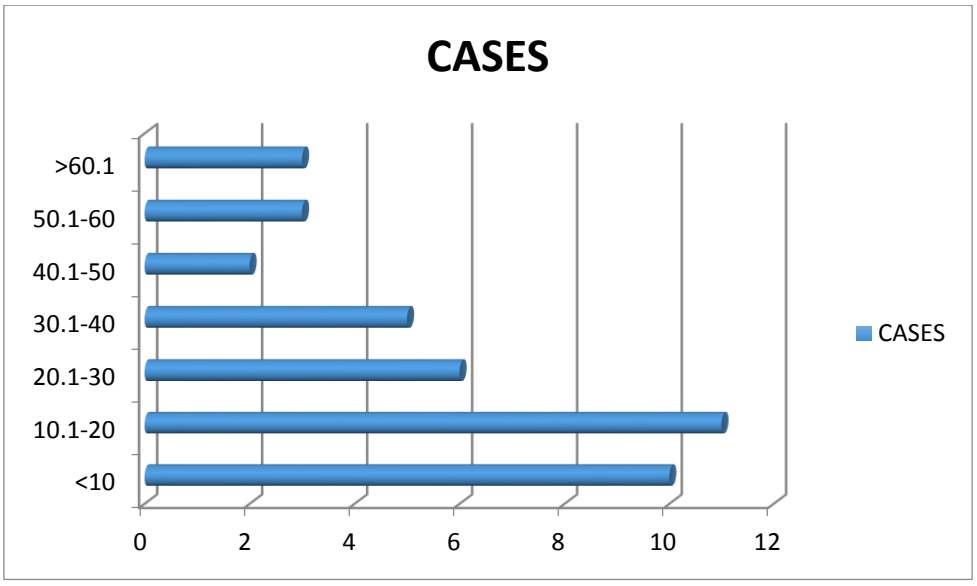


Figure 10: Distribution of Absolute reticulocyte count

Table 12 shows the distribution on absolute reticulocyte count among various stages of CKD. There is fall in ARC with progression of the stage of CKD.

Table 12: Distribution of ARC in various stages of CKD ANOVA, F=27.1, P<0.001, SIGNIFICANT

ARC ($x10^9$/l)	Stage II	Stage III	Stage IV	Stage V
<10	0	0	0	8
10.1-20	0	0	0	10
20.1-30	0	0	3	4
30.1-40	0	1	2	2
40.1-50	0	0	1	0
50.1-60	1	2	0	0
>60.1	1	1	1	0
Mean ±SD	57.8 ±0.0	52.0 ±16.5	34.5 ±17.4	14.0 ±12.1

The inverse correlation between absolute reticulocyte count and CKD stage is significant.

Correlation between Hemoglobin, RBC count and ARC:

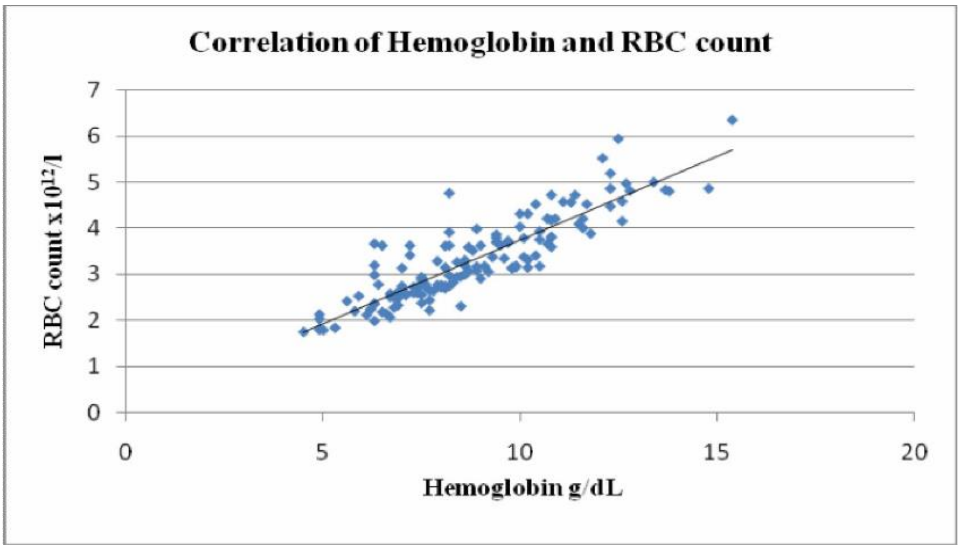


Figure 11: Correlation of Hemoglobin and RBC count

Linear correlation between hemoglobin level and RBC count is seen.

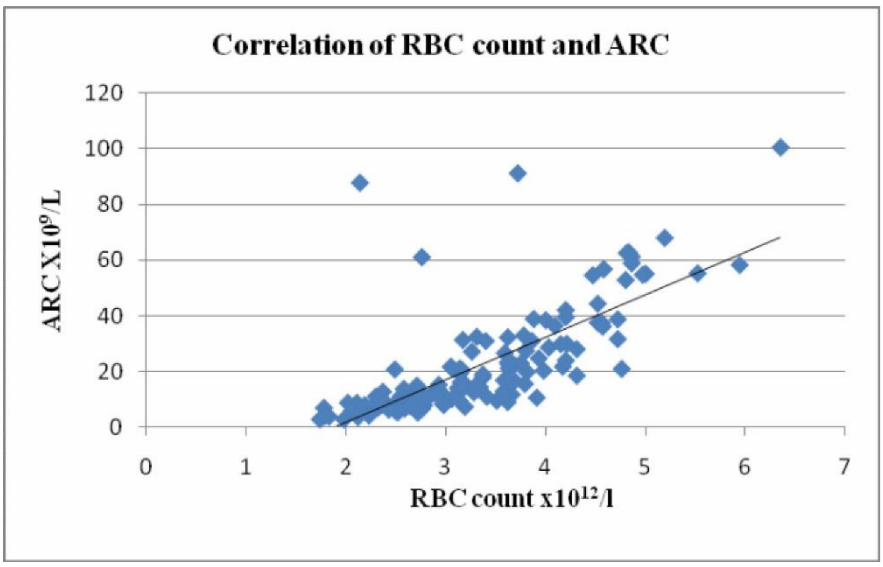


Figure 12: Correlation of RBC count and ARC

Linear correlation between RBC count and ARC in CKD is seen.

Red cell distribution width (RDW-CV):

RDW-CV was not significant in various stages of chronic renal disease as it was normal in almost all leaving 9 cases in which it was increased.

Peripheral Smear: Figure 13 shows the peripheral smear picture in the study group.

Most of the patients with chronic renal disease showed normocytic normochromic blood picture.

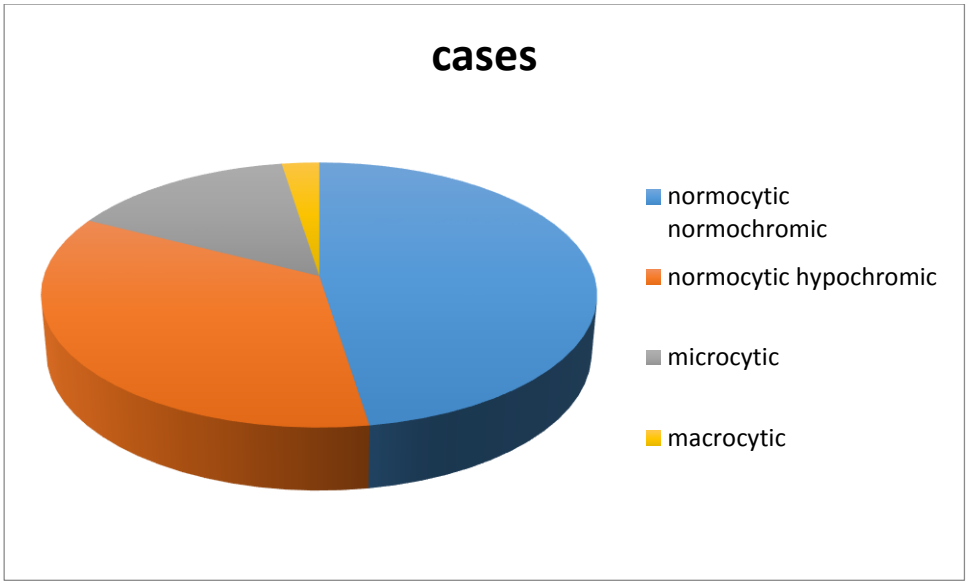


Figure 13: Peripheral smear in CKD

White Blood Cells: The distribution of WBC count in the study group is shown in figure 15. The WBCcount ranged from 4.1 – 22.4 x10^9/l, with a mean value of 11.06 ± 4.9 x10^9/l.

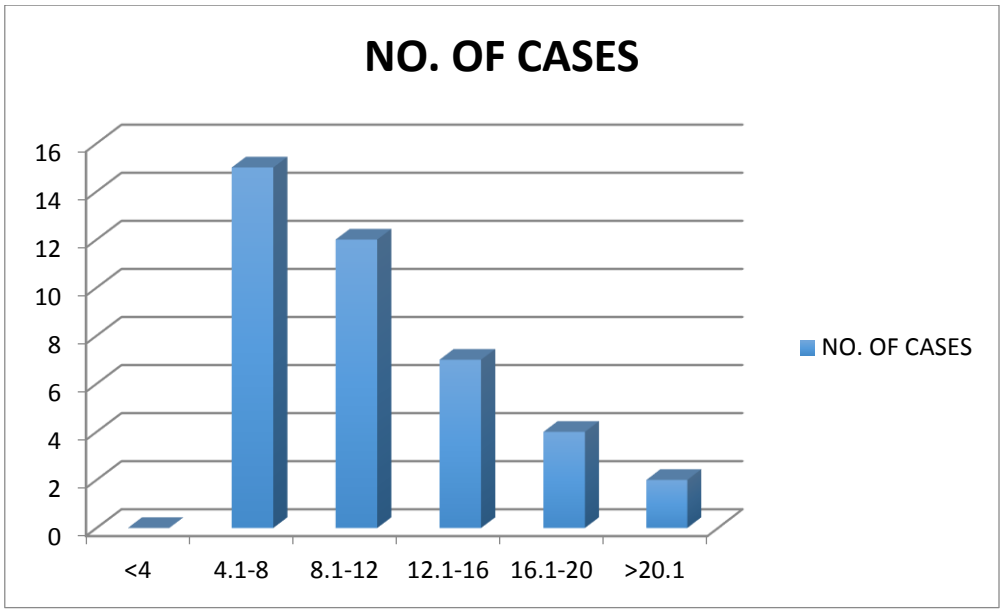


Figure 14: Distribution on WBC count in CKD

PLATLET COUNT

Figure 16 shows the distribution of platelet count in the study group. The Platelet count ranged from 151 - 534 x10^9/l, with a mean value of 300 ± 230.6 x10^9/l.

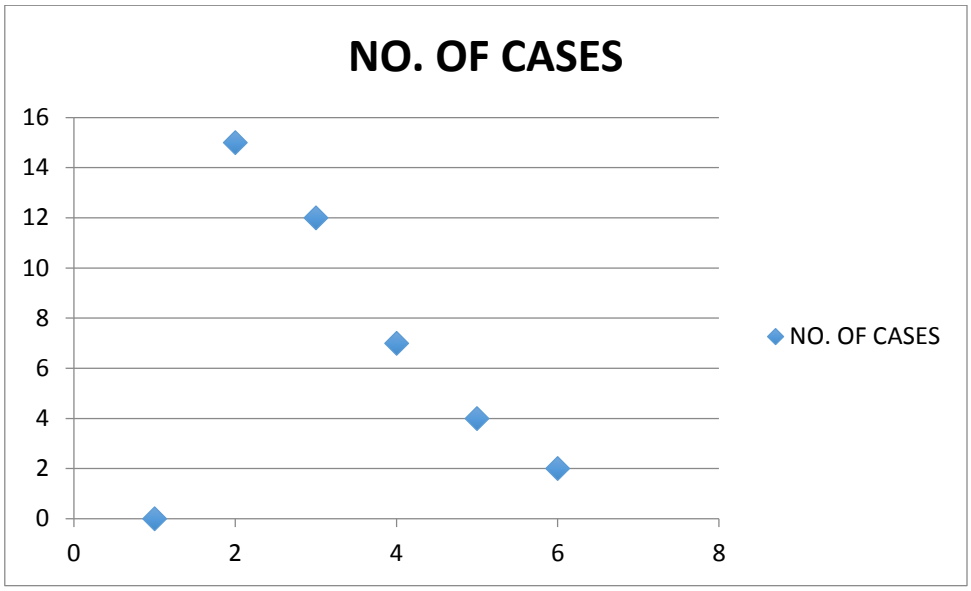


Figure 15: Distribution of Platelet count in CKD

Iron profile in CKD with microcytic anemia:

The iron profile of 6 cases of microcytic anemia shows normal with increased serum ferritim level iron status which is serum ferritin

Remaining all cases shows normal iron profile..

Blood Group:

Table 25 shows the Distribution of various blood groups in the study population.

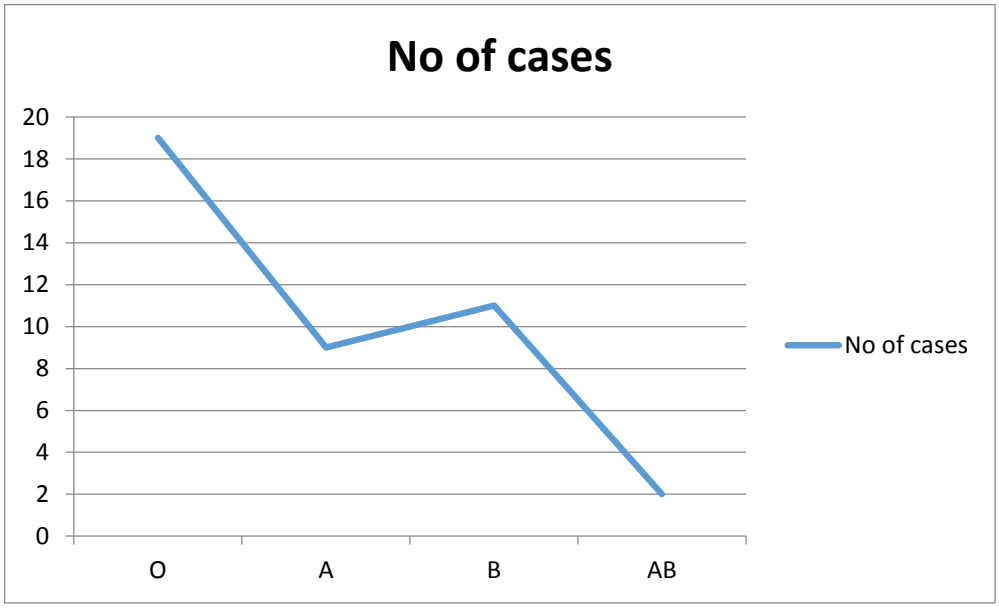


Fig 16: Distribution of blood groups in CKD

Biochemistry: Majority of patients of CKD had proteinuria (85.9%) with microalbuminuria seen in15.3% patients.

FIGURES

FIG 17: AUTOMATED HEMATOLOGY ANALYZER (SYSMEX KX-21)

Fig 18:Beckman coulter

FIG19 :EM 200

FIG 20: SERUM FERRITIN ANALYZER MISPA i2

PERIPHERAL SMEAR FINDINGS IN CKD

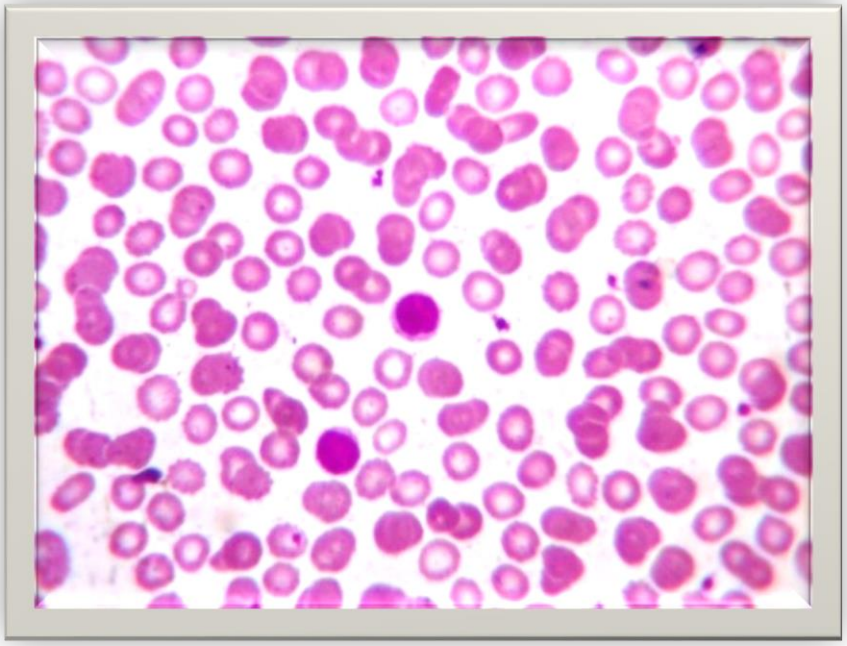


Figure 21: Normocytic normochromic RBCs

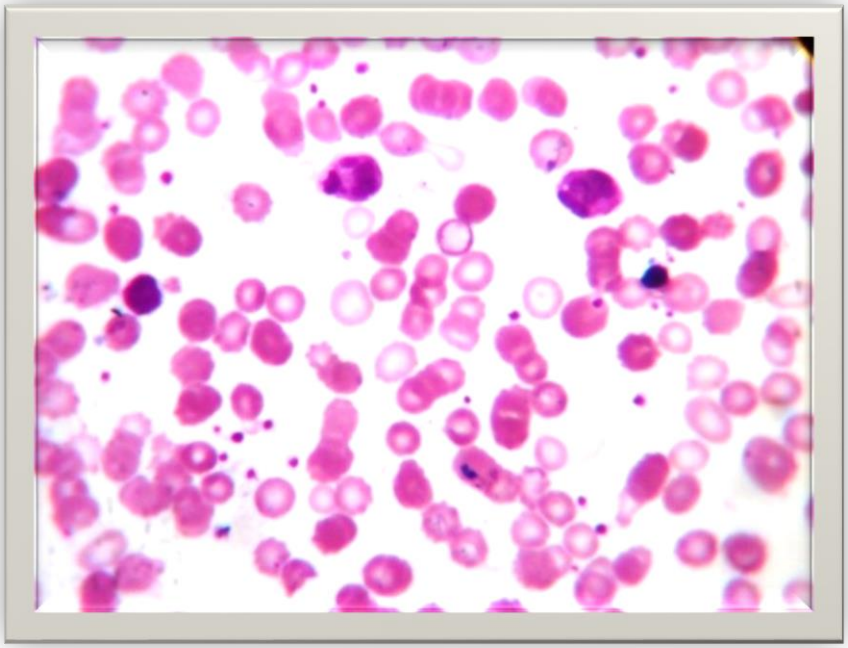


Figure 22: Anisocytosis

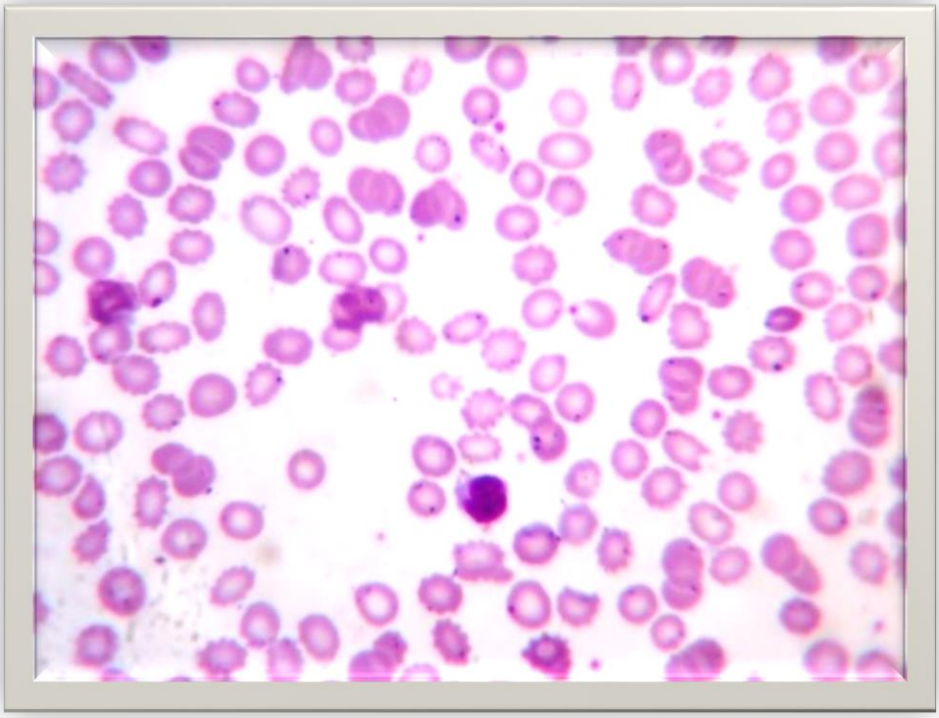


Figure 23: Burr cells, Elliptocytes, Schistocytes

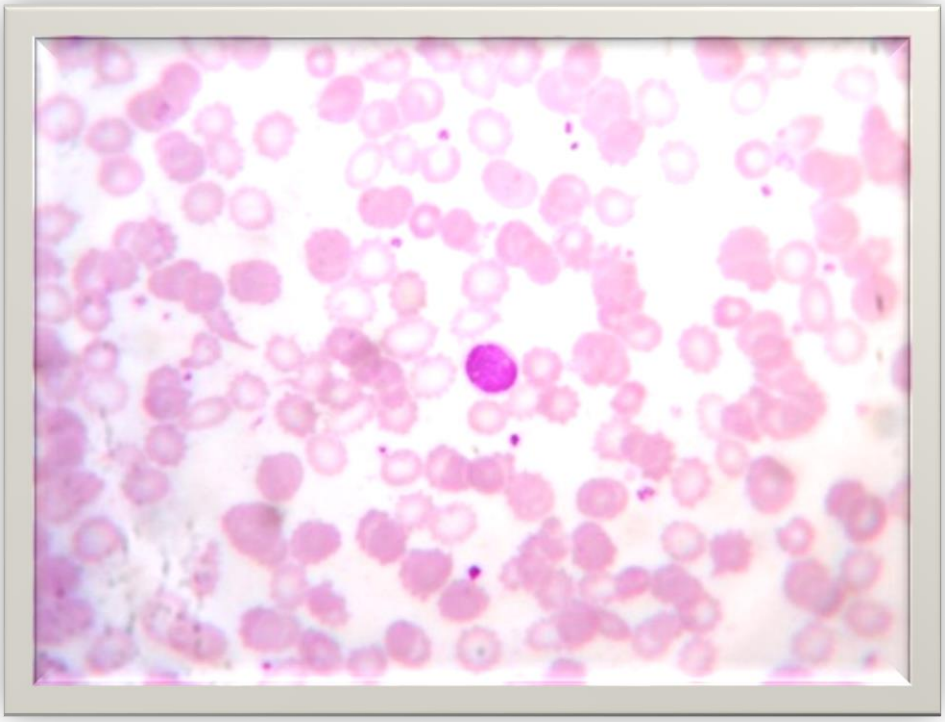


Figure 24: Normocytic Hypochromic RBCs

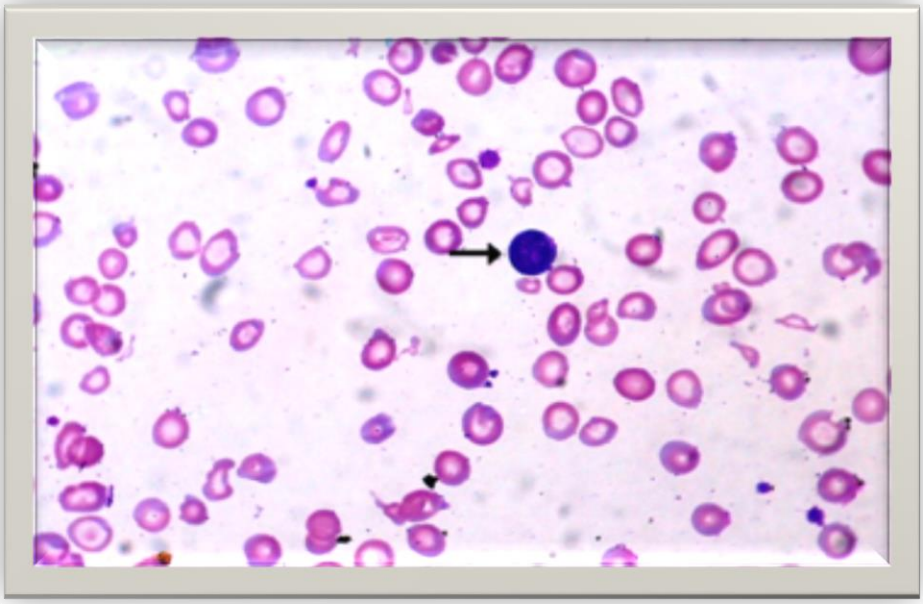


FIG 25: Microcytic Hypochromic Anemia showing microcytes and a small lymphocyte (Black arrow) [Field stain, (x100)oil immersion]

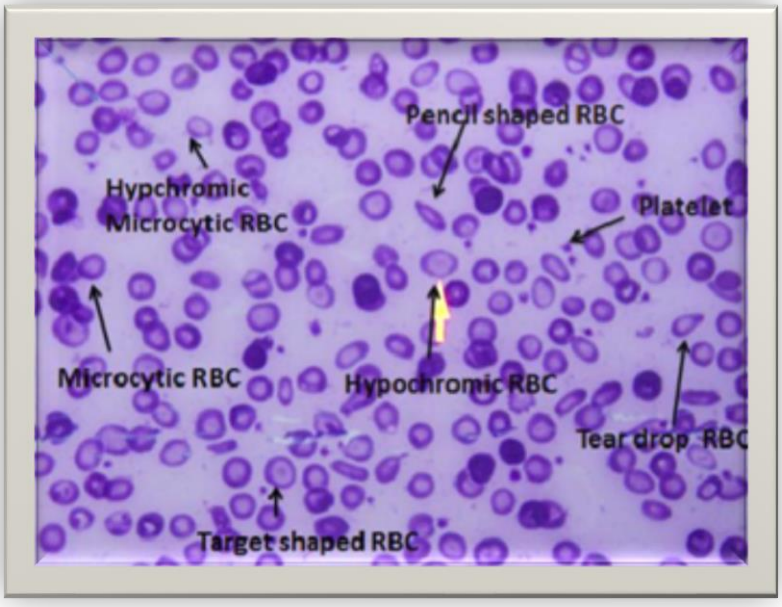


FIG 26: Microcytic Hypochromic Anemia showing marked anisopoikilocytosis with microcytes, pencil shaped cells, target cells and tear drop cells.[Field stain, (x100) oil immersion]

FIG 27: Microcytic Hypochromic Anemia exhibiting marked anisopoikilocytosis, seen are tear drop cells(Purple arrow) and target cells(Red arrow).[Field stain,(x100)oil immersion]

DISCUSSION

CKD is a progressive renal failure which is characterised by many presentations and haematological aberrations.

The clinico-hematological study of CKD involving 40 patients was undertaken during period of Jan 2016 to June 2017 and diagnosis was made with the clinical and the laboratory data. Observations were gathered, results were analysed and discussed with earlier similar studies.

40 patients who were admitted in the Dhiraj hospital were the study population. The incidence was high in males (67.5%) than that in females (32.5%)

Table 13: Comparison of mean age and sex ratio in CKD

	Talwar et al 2002[78]	**Sardenberg et al 2006[69]**	**Anees et al 2009[79]**	**Morranne et al 2009[80]**	**Agarwal et al 2011[81]**	**Present study**
Mean age	44.6 yrs	66 yrs	51 yrs	59 yrs	67 yrs	50.3±17 years
Male: Female ratio	1.17:1	4.6:1	1.15:1	2.22:1	28.6:1	1.80:1

The present study shows that the mean age is in the 5^{th} decade which is relevant to the study by the Anees et al done in India. Studies by Agarwal et al, Moranne et al and Sardenberg et al reports higher mean age. This could be due to location differences in the studies as a result of higher life expectancy in the world.

The present study merges with all the other related studies in terms of increased in males, which is co-related to the high prevalence of risk factors for Chronic kidney disease in males.

The study shows that CKD affects all the age groups with higher occurrence in the elderly. This increasing occurence of CKD in the elderly shows the presence of different risk factors for renal failures such as diabetes and high blood pressure in the elderly. Though, high rates of CKD in the old age may occur because of an age-related decrease in the renal function

Table 14: Comparison of the stage prevalence in CKD

	Morranne et al 2009[80]	**Agarwal et al 2011[81]**	**Present study**
Stage I	0%	1%	0%
Stage II	12%	3%	5%
Stage III	48%	51%	10%
Stage IV	31%	38%	17.5%
Stage V	9%	6%	65%

Majority of the cases belonged to stage V chronic kidney disease with 26 cases, followed by stage IV with 8 cases. 4 cases were in stage III, 2 case belonged to stage II, while none of the cases were in stage 1.

The study shows us an higher occurrence of CKD patients in stage V. Agarwal et al and Moranne et al shows an higher prevalence in stage III and IV.

This is because that the present study is a hospital based and hospitalisation occurs more in stage V which is a result of complications and co- morbidities.

Table 15: Comparison of the etiological distributions in CKD

Etiology	Singh et al 1999[82]	Drueke et al 2006[83]	Dash et al 2006[84]	Anees et al 2009[79]	Morranne et al 2009[80]	Present study
Diabetes	22.5%	20%	29.7%	67.6%	10%	47.5%
Hypertension	17.5%	23%	14%	9.7%	10%	37.5%
Obstruction	10%	7%	9.3%	3.8%	-	17.5%
Tubulointestitial lesions	15%	14%	9.3%	-	20%	10%

Diabetes was the main cause of chronic kidney disease among the study group . Out of which 22.5% had associated hypertension. Hypertension as a cause was seen in 15 cases.

The difference in the distribution of etiology is related to the racial, location wise and living standared distribution in the study groups.

Table 16: Comparison of the symptoms in CKD

Symptoms	Singh et al 1999[82]	Talwar et al 2002[79]	Present study
Anorexia	85%	63%	72.5%
Dyspnea	50%	70%	50%
Pedal edema	80%	96%	45%
Oliguria	80%	55%	47%
Fever	-	18%	30%
Nausea and vomiting	60%	60%	45%

Anorexia, dyspnea, generalized weakness, pedal edema and oliguria were the most common symptoms commonly in stage V of the CKD.

Table 17: Comparison of the signs in CKD

	Talwar et al 2002[78]	Present study
Pallor	96%	98%

Pallor is quite commonly noted in CKD due to the fall in hemoglobin.

In the present study, the degree of pallor had a important correlation with the stage of CKD.

Study done by Agarwal et al observed a higher hemoglobin value in the CKD population in the western world.

Table 18: Comparison of hemoglobin in CKD

	Singh et al 1999[82]	Talwar et al 2002[78]	Agarwal et al 2011[81]	Present study
Mean Hemoglobin g/dl	6.93	7.1	13.1	8.5+_

CKD is associated with anemia in almost all the patients. The mean hemoglobin in the study in g/dl/. Talwar et al and Singh et al shown lower hemoglobin.

Hemoglobin levels reduces with the development of the stages in CKD. The present study shows a notable reduction in hemoglobin as the stage develops.

Table 19: Comparison of mean hemoglobin in different stages of CKD

	Khanam et al 2007[85]	Present study
Stage III	10.8	12.6
Stage IV	9.135	10
Stage V	7.39	7.5

Study by Khanam et al demonstrated a constant fall in the hemoglobin levels in CKD as the stage developes. But the mean hemoglobin was less in each stage when compared to this study.

	Singh et al 1999[82]	Talwar et al 2002[78]	Present study
Mean RBC count ($x10^{12}$/l)	2.31	2.54	3.4
Mean MCV (fL)	83.3	83.0	87
Mean MCH (pg)	27.2	27.14	25
Mean MCHC (g/dl)	33.0	32.2	31
Mean RDW (%)	-	15.35	14.3

Table 20: Comparison of the mean RBC count and RBC indices in CKD

The study shows that the mean RBC count is less in CKD. The RBC indices are within the normal limits. The present study shows similar results with studies of Singh et al and Talwar et al which also showed less RBC count but shows normal RBC indices..

The absolute reticulocyte count in the study is lesser than the normal. The fall in ARC raises as the stage developes.

From the above , it could be easily observed that the increase in anemia noted correlating with the stages of CKD is due to the fall in the RBC count as a result of reduced production, demonstrated by less absolute reticulocyte counts which reduces as the stage progresses.

The correlation between the RBC count and hemoglobin and between RBC count and absolute reticulocyte count suggests that the anemia in CKD is due to low RBC count, which is further due to low reticulocyte count which is a result of reduced erythropoiesis.

Mild difference is seen in RDW in different stages with high RDW as the stage progresses.

Table 21: Comparison of the peripheral smears in CKD

Type of anemia	Singh et al 1999[82]	Talwar et al 2002[78]	Present study
Normocytic	80%	32%	75%
Microcytic	25%	67%	16%
Macrocytic	5%	1%	1%

In the present study, normocytic normochromic blood smear was the main finding and the anemia also being of the normocytic normochromic type in many cases. Macrocytic anemia is seen in only 1 cases in the present study. Which is because of the less frequency of occurrence of Vitamin B12 deficiency in CKD as its levels are increased in kidney failure as a result of reduced clearance by the non functioning kidneys.

There were 6 cases of microcytic anemia in the study, iron studies in these cases demonstrated that microcytic anemia occurs in CKD even with satisfactory iron stores

which as a result of decreased iron utilization due to an inflammatory block which is caused by circulating inflammatory mediators in CKD.

The results of the present study are co-related with the study by Singh et al. Similarities are not there in the smear findings between different studies due to the variation in the sample size and in the study population.

The pattern of total WBCs and differential leukocyte count has been not well studied, this evaluation may not be of much importance to diagnose inflammatory illnesses.

Table 22: Comparison of mean WBC count

	Singh et al 1999[82]	**Sardenberg et al 2006[69]**	**Agarwal et al 2011[81]**	**Present study**
Mean WBC count x10^9/l	8.7	7.6	7.1	11.06

The mean platelet count in CKD in the present study is normal. The difference in the platelet count in various types of studies is attributed to the differences in the sample size and the study groups.

Table 23: Comparison of mean platelet count

	Singh et al 1999[82]	Talwar et al 2002[78]	Agarwal et al 2011[81]	Present study
Mean Platelet count x10^9/l	171	176	230.9	312

From the iron profile of CKD patients with microcytic anemia in the present study, it is noted that serum iron levels are normal in all the cases and hence functional iron deficiency is not present. Rather it could be due an inflammatory block in iron utilization as indicated by raised serum ferritin which is also an acute phase reactant in majority of patients.

The assessment of iron status is easy if the TSAT and serum ferritin are both high and low in the evaluated patients. Hence, it is recommended to repeat the iron studies following erythropoietin administration, where in, patients with functional deficiency will show a decrease in serum ferritin levels. This is not seen in inflammatory block.

Hamed et al in 1979 reported differences among the blood groups of patients with renal failure with that of normal subjects mainly in the B and O Groups with renal patients showing a 7 percent increase in Group B and a 10 percent decrease in Group O[47]. This is in accordance with the present study results showing an increase in Group O in CKD patients.

Limitations of the present study:

This is a hospital based study and the observations cannot be equated to the general population.

Urine protein-to-creatinine ratio could not be estimated.

Measurement of serum erythropoietin would have given much clear understanding of the anemia in CKD.

Role of hepcidin could not be evaluated.

Platelet aggregometry studies would have highlighted the qualitative platelet defects seen in CKD

CONCLUSION

The following were the conclusions of the study.

1. Chronic renal disease is seen in almost all the age groups with mostly in 50- 61 years.
2. Seen in males mostly.
3. Diabetes is the most common causes of chronic renal disease whereas in youngs congenital causes predominates.
4. Anemia with pallor is the most common complication of CKD, seen increasing as the stage progresses.
5. The reduction in the haemoglobin is seen due to the fall in the RBC count as a result of the decreased erythropoiesis.
6. The blood picture of anemia is mostly of normocytic normochromic type.
7. Microcytic anemia is also seen in few cases but its not that common with normal serum iron and increased serum ferritin level.
8. Bleeding is also seen in few patients. Platelet count is normal inmost of the cases.
9. As the stage progresses there is a fall in the absolute reticulocyte count.
10. Most common blood group seen was O blood group.

SUMMARY

1. 40 cases of chronic renal disease patients were studied for the aberrations and correlations in the hematological status.

2. CKD was seen in almost all the age groups. The age ranged from 6 months to 81 years with a mean age of 50.3 years.

3. Majority of patients were in stage V CKD.

4. Diabetes (47.5%) was the leading cause of CKD, followed by hypertension (37.5%).

5. Congenital causes (62.5%) were the most common cause of CKD in children.

6. Anorexia (72.5%), dyspnea (50%), pedal edema (45%) and oliguria (47%) were the most common symptoms in CKD.

7. Pallor was present in all cases of CKD stage V and stage IV

8. The mean hemoglobin in the present study was 9.03g/dl. The fall in mean hemoglobin had an inverse correlation with the stage of CKD.

9. Diabetics (10.0g/dl) had slightly lower mean hemoglobin than non-diabetics (10.9g/dl) in stage IV, but the difference was not statistically significant.

10. The mean RBC count was 3.4×10^{12}/l, with significant fall in the RBC count as the stage of CKD progressed.

11. The mean absolute reticulocyte count also showed significant decline as the stage progressed.

12. The anemia of CKD in majority cases was of normocytic normochromic type (47.5%), followed by normocytic hypochromic type (35.%).

13. The mean platelet count observed in the present study was 300 $x10^9$/l.

14. Blood group O was the most frequently blood group seen in CKD patients.

15. Out of 6 cases of microcytic anemia observed in the present study serum iron was normal with increased serum ferritin level in all.

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ANNEXURES

ANNEXURE 1- PROFORMA

ANNEXURE 2- ABBREVIATION

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ANNEXURE - 1

PROFORMA

"CLINICOHEMATOLOGICAL CORRELATION IN PATIENTS WITH CRONIC RENAL DISEASE"

Thesis of: Dr.BHAVYA SAXENA Guide: Dr.R.K.TANDON

Name of the patient:

Age:

Sex:

Address:

Occupation:

Education:

Marital status:

Income:

Date of admission:

Date of examination:

IPD/OPD number

PRESENTING COMPLAINTS

Breathlessness: + / -.Class I / II / III / IV. Orthopnea / PND

Generalized weakness: + / -. Resting / Exertional

Anorexia: + / -. To solid food / Liquid food

Oliguria / Anuria / Hematuria: + / -. Quantity-

Fever: + / -. Mild / Moderate / Severe. Remittent / Intermittent / Continuous

Headache / Giddiness: + / -. Continuous / Intermittent. Sitting / Standing

Nausea: + / -.With the sight of food / continuous Vomiting: + / -.Frequency- ; Projectile /Non-projectile; Vomitus- Hemetemesis: + / -.

FAMILY HISTORY

Hypertension / Diabetes Mellitus / Malignancy / IHD / Cystic kidneys / Renal failure / Autoimmune diseases / Congenital disorders

GENERAL PHYSICAL EXAMINATION

Built: Well / Normal / Poor Nourishment: Well / Normal / Poor Pallor: + / -.Mild / Moderate / Severe. Platynychia: +/- Koilonychia: +/- Icterus: + / -. Mild /Moderate / Severe Cyanosis: + / -. Central / Peripheral

Clubbing: + / -. Grade I / II / III / IV Lymphadenopathy: + / -. Generalised / Localised; Axillary / Cervical / Inguinal. Edema: + / -. Generalised / Localised / Pedal. Pitting / Non-pitting

SYSTEMIC EXAMINATION

PER ABDOMEN: Ascites: + / -. Mild / Moderate / Severe Hepatomegaly: + / -. Ms: cms. Tender / Non-tender Splenomegaly: +/ -. Ms: cms. Tender / Non-tender Kidneys: Palpable / Non-palpable. Rt / Lt. Renal angle tenderness : + / -. Mass abd / Abdominal Bruit / Operative scars: +/- Bowel sounds:_____ Genitalia: Normal / Abnormal

CARDIOVASCULAR SYSTEM: Heart sounds: S1 + / -; S2 + / -. S3 + / -. S4 + / -. Murmurs_____ / Pericardial rub: +/-

RESPIRATORY SYSTEM: Dullness: + / -. Stony / Woody. Region- Respiratory sounds: Vesicular / Bronchial. Additional sounds: + / -. Crepitations + / - fine / coarse; basal / extensive. Rhonchi + / -. Pleural rub: + / -.

CENTRAL NERVOUS SYSTEM:

CLINICAL DIAGNOSIS:

INVESTIGATIONS URINE ANALYSIS: **1. *Physical properties*:** a) Urine output –

b) Colour – c) pH – d) Specific gravity – e) Odour –

f) Turbidity – Present /Absent

2. Chemical properties:

a) Proteins – b) Microalbuminuria – c) Sugars – d) Blood – e) Ketone bodies – f) Urobilinogen – g) Bile salts – h) Bile pigments – i) Nitrites

3. Microscopy:

a) Cells – Epithelial cells RBCs /hpf) Present / Absent /hpf) Present / Absent /hpf) Present / Absent /hpf) Present / Absent /hpf) Present / Absent Pus cells Tubular cells Transitional cells (

b) Casts – Hyaline / Granular / Broad / Tubular / Epithelial / RBC / Fatty / Waxy: seen / not seen c) Crystals – + / - d) Micro-organisms – Present / Absent

COMPLETE HEMOGRAM

Hemoglobin :

RBC :

WBC :

DIFFERENTIAL COUNT: -

Lymphocytes : %

Monocytes : %

Neutrophils : %

Eosinophils : %

Basophils : %

Platelets :

HCT :

ESR :

MCV : μm^3

MCH : pg

MCHC : g/dl

RDW : %

MPV : μm^3

PDW : %

Reticulocyte count: %

Blood group:

PERIPHERAL SMEAR

RBCs: Are Normocytic Microcytes/Macrocytes/dimorphic. Mild/moderate/severe hypochromasia seen. Anisocytosis seen / not seen. Poikilicytosis (tear drop cells, pencil shaped cells, acanthocytes, fragmented cells, burr cells, elliptocytes, ovalocytes, crenated cells, annulocytes, sickle cells, spherocytes, target cells, schistocytes, stomatocytes) seen / not seen. Immature Erythroid series of cells (Normoblasts-early/intermediate/late_____/100 WBC) are seen / not seen. Inclusions (Basophilic stippling, Howell-jolly bodies, Pappenhiemer bodies, cabot rings) seen / not seen. Malarial parasites (PV/PF) seen / not seen.

WBCs: Are normal / increased / decreased in number. Predominant cells are Neutrophils / Lymphocytes. Hypersegmented neutrophils seen / not seen. Eosinophilia / Monocytosis seen / not seen. Shift to left (myeloblasts, promyelocytes, myelocytes, metamyelocytes, band forms) seen / not seen. Inclusions (toxic granules, cytoplasmic vacuolations, dohle bodies) seen / not seen. Atypical lymphocytes (plasmacytoid / monocytoid) seen / not seen.

PLATELETS: Are normal / increased / decreased in number and normal in morphology. Seen in good clumps and aggregates / seen discretely in singles. Giant platelets seen / not seen. Platelet sattelitesm seen / not seen.

IMPRESSION: NORMOCYTIC, NORMOCHROMIC / MICROCYTIC / MACROCYTIC / HYPOCHROMIC, DIMORPHIC BLOOD PICTURE / ANEMIA WITH NEUTROPHILIC / LYMPHOCYTIC LEUCOCYTOSIS / LEUCOPENIA, THROMBOCYTOSIS / THROMBOCYTOPENIA.

BIOCHEMICAL INVESTIGATIONS

Blood Urea :

Serum Creatinine :

ULTRASOUND ABDOMEN & PELVIS:

ANNEXURE II

LIST OF ABBREVIATIONS USED

(In alphabetical order)

ABBREVIATION EXPANSION

ACE	:	Angiotensin Converting Enzyme
ACR	:	Albumin-to-Creatinine Ratio
ADP	:	Adenosine Di-Phosphate
AER	:	Albumin Excretion Rate
AGEs	:	Advanced Glycosylated End-products
AGE	:	Acute Gastro-Enteritis
ARBs	:	Angiotensin Receptor Blockers
ARC	:	Absolute Reticulocyte Count
BFU-E	:	Burst Forming Unit-Erythroid
BT	:	Bleeding Time
CAKUT	:	Congenital Anomalies of Kidney and Urinary Tract
cAMP	:	Cyclic Adenosine Mono Phosphate
CBC	:	Complete Blood Count
CCr	:	Creatinine Clearance
CFU-E	:	Colony Forming Unit-Erythroid
CHr	:	Hemoglobin Content of Reticulocyte
CKD	:	Chronic Kidney Disease
CMD	:	Cortico-Medullary Junction
CRF	:	Chronic Renal Failure
CRI	:	Chronic Renal Insufficiency
CTGF	:	Connective Tissue Growth Factor

cGMP	:	Cyclic Guanosine Mono Phosphate
DKD	:	Diabetic Kidney Disease
DN	:	Diabetic Nephropathy
ECD	:	Endothelial Cell Dysfunction
EDTA	:	Ethylene Diamine Tetra Acetic acid
EPO	:	Erythropoietin
ESRD	:	End Stage Renal Disease
Fe	:	Iron
FSGS	:	Focal Segmental Glomerular Sclerosis
GFR	:	Glomerular Filtration Rate
GP IIb-IIIa	:	Glycoprotein IIb-IIIa
Hb	:	Hemoglobin
IL-6	:	Interleukin-6
IL-8	:	Interleukin8
IP-10	:	Interleukin-10
K/ DOQI	:	Kidney Disease Outcome Quality Initiative
LVH	:	Left Ventricular Hypertrophy
MCH	:	Mean Corpuscular Hemoglobin
MCHC	:	Mean Corpuscular Hemoglobin Concentration
MCV	:	Mean corpuscular Volume
NAG	:	N-acetyl-b-glucosaminidase
NKF	:	National Kidney Foundation
NON-DN	:	Non Diabetic Nephropathy
NSAIDs	:	Non-Steroidal Anti-Inflammatory Drugs
Pcr	:	Plasma Creatinine

PCR	:	Protein-Creatinine Ratio
PGI_2	:	Prostaglandin I_2
PMN	:	Polymorpho Nuclear cell
PTH	:	Parathyroid Hormone
RAAS RAS	:	Renin Angiorensin Aldosterone System Renin Angiotensin System
RBC	:	Red Blood Cell
RI	:	Reticulocyte Index
ROS	:	Reactive Oxygen Species
RPI	:	Reticulocyte Production Index
SCr	:	Serum Creatinine
SNS	:	Sympathetic Nervous System
Tc-DTPA	:	Technetium Diethylene Triamine Pentaacetic Acid
TGFβ	:	Transforming Growth Factor Beta
TNF-α	:	Tumor Necrosis Factor Alpha
TSAT	:	Transferrin Saturation
TXA_2	:	Thromboxane A_2
vWF	:	Von Willebrand Factor
WHO	:	World Health Organization

ANNEXURE-III

Sumandeep Vidyapeeth University

Pipariya, Ta. Waghodia, Dist. Vadodara Pin 391760

PARTICIPANT INFORMATION SHEET

Title of the study: "CLINICOHEMATOLOGICAL CORRELATION IN PATIENTS WITH CHRONIC RENAL DISEASE" at Dhiraj General Hospital, Pipariya.

Study No. Date

Invitation to participant

1 Purpose & nature of the study: This study is carried out to know the clinicohematological correlations in patients with chronic renal disease at Dhiraj general hospital.

2 Voluntary nature of the participation: It is an absolutely voluntary participation in the study program.

3 Study methods: It will be a prospective and observational (non interventional) type of study, which will include suspected patients of CKD till JUNE 2017.This work will be carried out in the *Department of Pathology, S.B.K.S.MI&RC, Pipariya.* The patients will be selected from indoor and outdoor at Dhiraj general hospital.

4 Participants responsibilities: After agreeing to participate in the study, the participant should extend full support. He/ She should provide real facts when inquired into and make her/his self available wherever required.

5 Expected adverse events, risks and solution: As such in this study no experiment will be done on patient so there is no issue of adverse effect or risk.

6 The benefits of participation: This study has both individual and community benefits. It will help to evaluate the role of anemia in CKD .All this will help a doctor to treat the patient better.

7 Confidentiality of the record: Information regarding patient's health and other personal facts if any will be kept confidential.

8 If any problem develops, you can contact:

NAME: Dr. Bhavya Saxena

ADDRESS: Department of Pathology, S.B.K.S. MI & RC, Pipariya. Tal: Waghodia. Dist: Vadodara.

MOBILE NO: 9638485163

9 Financial considerations: There is no worry about costs in this institute as this study is free of cost. Thus no additional financial burden will be caused to him. If in any case special investigation is needed the cost will be barred by the investigator.

10 Protection for patient and security: If any type of threat or untoward event, consequent to present study, is met with, the patient will be provided every type of protection. Nature of this protection can be decided when such an event actually is faced with.

11 Obtaining additional information: If need arises, the patient may be contacted to inquire about past, personal and family history. Also religious background, social customs, beliefs etc can be inquired into.

પરિશિષ્ટ – ૧
સુમનદિપ વિદ્યાપીઠ યુનિવર્સીટી, પીપરીયા,
તા.વાઘોડીયા, જિ. વડોદરા-૩૯૧૭૬૦

સહભાગીદારનું સહભાગી પત્રક

અભ્યાનું શીર્ષક **ધીરજ જનરલ હોસ્પિટલપ, પીપરીયા ખાતે ક્રોનિક રેનલ ડિસીઝ વાળા દર્દીઓનો ક્લિનીકોહેમોટોલોજીકલ કોરિલેશન વાા દર્દીઓનો અભ્યાસ.**

અભ્યાસનો ક્રમાંક : ..... તારીખઃ .....

દર્દીને આમંત્રણ :

(૧) અભ્યાસની પ્રકૃતિને હેતુ :- ધીરજ જનરલ હોસ્પિટલ, પીપરીયા ખાતે ક્રોનિક રેનલ ડિસીઝ વાળા દર્દીઓનો ક્લિનીકોહેમોટોલોજીકલ કોરિલેશન વાળા દર્દીઓનો આભ્યાસ.

(૨) સહભાગી સ્વૈચ્છીક રહેશે :- આ અભ્યાસમાં ભાગ લેવો કે ન લેવો તે સંપૂર્ણ સ્વૈચ્છીક બાબત છે.

(૩) અભ્યાસની પદ્ધતિ :- નિરીક્ષણાત્મક અને પ્રોસ્પેક્ટિવ પ્રકારનો આ અભ્યાસ છે. જેમાં જૂન ૨૦૧૭ સુધીના ક્રોનિક રેનલ ડીસીઝ ધરાવતાં દીર્દીઓનો સમાવેશ કરવામાં આવેલ છે. આ અભ્યાસ પોથોલોજી વિભાગ, SBKS, MI & RC, પીપરીયા ખાતે કરવામાં આવશે. આ દર્દીઓની પસંદગી ધીરજ જનરલ હોસ્પિટલ ખાતે આવેલ ઇનડોટ અને આઉડાંર પેશન્ટમાંથી થશે.

(૪) સહભાગીદારીની જવાબદારી :- અભ્યાસમાં સહભાગી થયા બાદ પૂર્ણ સહકાર આપે તેવી અપેક્ષા છે. જ્યારે પણ પૂછવામાં આવે ત્યારે સહભાગીએ પૂરેપૂરી વિગત અને સ્પષ્ટ સાચો જવાબ આપવાનો રહેશે.

(૫) અનપેક્ષિત આડઅસરો, જોખમો અને તેના નિવારણ :- આ અભ્યાસમાં કોઈ પ્રકારનો પ્રયોગ કે અખતરો કરવાનો નથી તેથી કોઈપણ પ્રકારની આડઅસર કે જોખમોની શક્યતા જ નથી.

(૬) સહભાગી થવાના ફાયદા :- આ અભ્યાસના વૈયક્તિક અને સામુહિક અને પ્રકારના ફાયદા છે. તેનાતી ક્રોનિક રેનલ ડિસીઝમાં એનીમિયાની ભૂમિકા શું છે તે ખબર પડશે. આમ થવાથી ડોક્ટરને દર્દીની સારવારમાં સરળતા રહેશે.

(૭) માહિતી ગોપનિયતા :- દર્દીની સ્વાસ્થ્ય વિષયક માહિતી તેમજ તેમની વ્યક્તિગત માહિતી ગોપનીય રખાશે.

(૮) જો કોઈ તકલીફ થાય તો કોનો સંપર્ક કરવો :

નામ : ડો. ભવ્યા સકસેના, સરનામું પોથોલોજી વિભાગ, SBKS, MI & RC, પીપરીયા, તા. વાઘોડીયા, જિ. વડોદરા, મો.નં. ૯૬૩૮૪૮૫૧૬૩

(૯) આર્થિક બાબતો :- સહભાગીદારે પૈસાની ચિંતા કરવાની જરૂર નથી કારણ કે, અભ્યાસ નિ:શુલ્ક થઈ રહ્યો છે. તેથી તમારે કોઈપણ પ્રકારનો ખર્ચ ઉપાડવાનો રહેતો નથી. જરૂર પડે કોઈ ખર્ચ થશે તો તે સંશોધક તે ઉપાડશે.

(૧૦) દર્દીની સલામતી અને સંરક્ષણ :- કોઈપણ પ્રકારની અનિચ્છનિય ઘટના કે પ્રસંગ બને તો દર્દીને દરેક પ્રકારનું સંરક્ષણ આપવામાં આવશે. સંરક્ષણ કયા પ્રકારનું રહેશે તે જે તે સમયે પરિસ્થિતિ ઉભી થયેથી નક્કી કરાશે.

(૧૧) વધારાની માહિતી માટે :- જો વધારાની માહિતી ની જરૂર પડશે , પરિસ્થિતિ ઉભી થશે તો દર્દીને બોલાને પૂછવામાં આવશે. જેમાં દર્દીની કે વ્યક્તિગત કે કૌટુંબિક બાબતો પૂછવામાં આવી શકે છે. ધાર્મિક, સામાજિક, માનતાઓ વિશે પણ પૂછપરછ થઈ શકે છે.

परिशिष्ट – ३

सुमनदिप विद्यापीठ, पीपरीया, तहसिल :वाघोडीया,

जिला : बडौदा. पीन नं : ३९१७६०

सहभागी का जानकारी पत्रक

अभ्यास का शीर्षक :- **धीरज अस्पताल पीपरीया में आनेवाले क्रोनिक रेनल डीसीझनवाले रोगीओं का क्लिनीकोहेमाटोलोजीकल कोरीलेशन के संदर्भमें अभ्यास**

अभ्यास क्रमांक : ..... दिनांक : .....

(१) अभ्यास की प्रकृति व उद्देश्य :- धीरज अस्पतालमें , पीपरीया में आनेवाले क्रोनिक रेनल डिसीझ वाले रोगीओं का क्लिनीकोहेमाटोलोजीकल किरीलेशन के संदर्भ में अभ्यास

(२) सहभागी स्वैच्छीक रुपसे : अभ्यास में हिस्सा लेना या ना लेना यह पूर्ण रुप से स्वैच्छीक होगा, मरीज की इच्छा पर निर्भर है की इस अभ्यास में हिस्सा ले या ना लें।

(३) अभ्यासकी रीति : यह एक निरीक्षणात्मक व प्रोस्पेक्टीव रीति का अभ्यास है, जून २०१७ तक आनेवाले मरीजों का समावेश कीया जाएगा। यह अभ्यास पेथोलो़जि विभाग, SBKS, MI&RC, पीपरीया में आयोजीत कीया जाएगा। मरीजों का वचन धीरज अस्पताल के इनडोर व आउटडोर मरीजों में से कीया जाएगा।

(४) सहभागीदारी की जीम्मेदारीयाँ : एकबार अभ्यास में सम्मिलित हो जाने के बाद मरीज सें संपूर्ण सहकार की अपेक्षा है। जो भी, जब भी पूछा जाए उसका जवाब विस्तार सें बिना कुछ छिपाए देना होगा।

(५) अनपेक्षित घटनाएम जोखिम व उसका निराकरण : यह कोई प्रयोगात्मक अभ्यास नहीं है इसिलीए कीसी भी प्रकार की दवाई या अन्य कीसी का परिक्षण नहीं कीया जाएगा। इसिलीए कोई भी अनपेक्षित घटना या जोखिम नहीं है।

(६) सहभागीता के फायदे : इस अभ्यास क वैयक्तिक व सामुदायिक दोनो फायदे हैं। इससे CKD में एनिमीया की भूमिका की जाँच भी कर सकते हैं औ डॉक्टर को मरीजों का इलाज करने में सहायता होगी।

(७) जानकारीयों की गोपनीयता : मरीज की सभी प्रकार की जानकारी गोपनीय रखी जाएगी।

(८) अगर कोई दिक्कत है तो कीसका संपर्क कीया जाए?

नाम : डॉ. भव्या सक्सेना

पता : पेथोलो़जी विभाग, SBKS, MI & RC, पीपरीया, तहसील : वाघोडीया, जिला बडौदा, दूरभाष क्रमांक : ९६३८४८५१६३

(६) आर्थिक पहलू : इस अभ्यास में मरीज क कीसी भी प्रकारका खर्च नहीं उठाना है। अगर कोई खर्च आता भी है तो वह खर्च संशोदक उठा लेंगे।

(१०)मरीज की सलामती व संरक्षण : अगर कोई भी दिक्कत या अनिच्छित घटना होती है तो मरीज की सलामती व संरक्षण दीया जाएगा, व उस संरक्षण का प्रकार कैसे व कितना दिया जाएगा वह परिस्थिति आने या खडी होने पर तय किया जाएगा।

(११)अतिरिक्त जानकारी की उपलब्धता : अगर जरुरत पडी तो, मरीज का संपर्क कर उनके भूत, वर्तमान के बारे में या फिर उनके धार्मिक, सामाजिक व मान्यताए इत्यादि के बारे में पृच्छा की जा सकती है और यह आशा रखी जाती है कि, सहभागी उसका विस्तार से जवाब दे।

ANNEXURE IV

Sumandeep Vidyapeeth University

Pipariya, Ta. Waghodia, Dist. Vadodara Pin 391760

Informed Consent Form (ICF) for Participants in Research Programmes involving studies on human beings Study title: **"CLINICOHEMATOLOGICAL CORRELATION IN PATIENTS WITH CHRONIC RENAL DISEASE"**

At Dhiraj General Hospital, Pipariya

Study Number: SVU/SBKS/ /2016-____

Participants Initials: _____

Participant's Name _____ Date of Birth / Age _____ (Years)

1 I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions.

2 I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

3 I understand that the investigator of this study, others working on the investigator's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records, both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I agree to this access. However, I understand that my identity will not be revealed in any information related to third party or published.

4 I agree not to restrict the use of any data or results that arise from his study provided such a use is only for scientific purpose(s).

5 I agree to take part in the above study.

Signature (or thumb impression) of the participant / legally acceptable representative_____ Signatory's Name _____

Study Investigator's Name_____ Signature of the investigator _____

Name of the witness _____

Signature of the impartial witness _____

Place: _____ Date _____

ANNEXURE II

હ્યુમન બેઇજિંગ પરના અભ્યાસક્રમોમાં સામેલ અભ્યાસક્રમો માટે સહભાગી સંમતિ

(આઈસીએફ)

અભ્યાનું શીર્ષક **ધીરજ જનરલ હોસ્પિટલપ, પીપરીયા ખાતે ક્રોનિક રેનલ ડિસીઝ વાળા દર્દીઓનો ક્લિનીકોહેમોટોલોજીકલ કોરિલેશન વાા દર્દીઓનો અભ્યાસ.**

અભ્યાસ નંબર: એસવીયુ / એસબીકેએસ / _____ / 2015-2018 _____

સહભાગીનું નામ: _____

જન્મ તારીખ: _____ ઉંમર: _____ વર્ષ

1. હું પુષ્ટિ કરું છું કે મેં ઉપરોક્ત અભ્યાસ માટે _____ ના માહિતી શીટ વાંચી અને સમજી લીધી છે અને પ્રશ્નો પૂછવાની તક મળી છે
2. હું સમજું છું કે અભ્યાસમાં મારી સહભાગિતા સ્વૈચ્છિક છે અને તે કોઈપણ કારણ વગર, કોઈપણ સમયે, મારી તબીબી સંભાળ અથવા કાયદેસરના અધિકારોને પ્રભાવિત કર્યા વગર કોઈપણ સમયે પાછી ખેંચી લેવા માટે મુક્ત છું
3. હું સમજી શકું છું કે આ અભ્યાસમાં તપાસ કરનાર, તપાસકર્તાની વતી કામ કરતા અન્ય લોકો, નૈતિક સમિતિ અને નિયમનકારી સત્તાવાળાઓને વર્તમાન અભ્યાસના સંદર્ભમાં અને આગળ કોઈ સંશોધન માટે, મારા સ્વાસ્થ્યના વિકમોને જોવાની મારી પરવાનગીની જરૂર નથી. તે સંબંધમાં હાથ ધરવામાં આવે છે, જો હું અભ્યાસમાંથી પાછો ખેંચી લો, તો હું આ ઍક્સેસથી સંમત છું જો કે હું સમજી શકું છું કે મારી ઓળખ તૃતીય પક્ષ સાથે સંબંધિત કોઈપણ માહિતીમાં અથવા પ્રકાશિત કરવામાં આવશે નહીં.
4. હું આ અભ્યાસમાંથી જન્મેલા કોઈપણ ડેટા અથવા પરિણામોના ઉપયોગને મર્યાદિત ન કરવા માટે સંમત છું, જો કે આવા ઉપયોગ વૈજ્ઞાનિક હેતુ (ઓ) માટે જ છે.
5. હું ઉપરના અભ્યાસમાં ભાગ લેવા માટે સંમત છું.

સહભાગીની હસ્તાક્ષર / અંગૂઠાની છાપ

તારીખ: _____

કાયદેસરના સ્વીકૃત પ્રતિનિધિ સહી કરનારનું નામ _____

તપાસકર્તાની હસ્તાક્ષર _____ તારીખ: _____

અભ્યાસ તપાસનીસનું નામ _____ _____

નિષ્પક્ષ સાક્ષીના હસ્તાક્ષર _____તારીખ: _____

સાક્ષીનું નામ_____

ANNEXURE III

<u>मानव जाति पर अध्ययन कार्यक्रमों में भागीदारी के लिए भागीदारों के लिए सूचित सहमति पत्र (आईसीएफ)</u>

अभ्यास का शीर्षक :– **धीरज अस्पताल पीपरीया में आनेवाले क्रोनिक रेनल डीसीझनवाले रोगीओं का क्लिनीकोहेमाटोलोजीकल कोरीलेशन के संदर्भमें अभ्यास**

अध्ययन संख्या: एसवीयू / एसबीकेएस / _____ / 2015-2018 _____
प्रतिभागी का नाम: _____
जन्म तिथि: _____ आयु: _____ वर्ष

1. मैं पुष्टि करता हूं कि मैंने उपरोक्त अध्ययन के लिए _____ के सूचना पत्र को पढ़ और समझ लिया है और सवाल पूछने का अवसर मिला है
2. मैं समझता हूं कि अध्ययन में मेरी भागीदारी स्वैच्छिक है और मैं बिना किसी कारण के बिना किसी भी समय वापस लेने के लिए स्वतंत्र हूं, मेरी चिकित्सा देखभाल या कानूनी अधिकार प्रभावित हो सकता है
3. मैं समझता हूं कि इस अध्ययन के अन्वेषक, अन्वेषक की ओर से काम करने वाले अन्य, नैतिकता समिति और नियामक प्राधिकरणों को मेरे मौजूदा स्वास्थ्य अध्ययन के संबंध में मेरे स्वास्थ्य अभिलेखों की जांच करने की मेरी अनुमति की आवश्यकता नहीं होगी, दोनों इसके संबंध में आयोजित, यहां तक कि अगर मैं अध्ययन से वापस लेता हूं, तो मैं इस पहुंच से सहमत हूं। हालांकि मैं समझता हूं कि मेरी पहचान तीसरी पार्टी से संबंधित किसी भी जानकारी या प्रकाशित में प्रकाशित नहीं होगी।
4. मैं इस अध्ययन से उत्पन्न होने वाले किसी भी डेटा या परिणामों के उपयोग को प्रतिबंधित करने के लिए सहमत हूं, बशर्ते इस तरह का उपयोग केवल वैज्ञानिक उद्देश्य (ओं) के लिए है।
5. मैं उपरोक्त अध्ययन में भाग लेने के लिए सहमत हूं।

प्रतिभागी के हस्ताक्षर / अंगूठे का निशान
तारीख: _____

कानूनी रूप से स्वीकार्य प्रतिनिधि हस्ताक्षरकर्ता का नाम _____
जांचकर्ता के हस्ताक्षर _____ दिनांक: _____

अध्ययन अन्वेषक का नाम _____ _____

निष्पक्ष गवाह के हस्ताक्षर _____ दिनांक: _____

साक्षी का नाम_____

MASTER CHART

SR.NO	DATE	SEX	AGE	STAGE	DIABETES	HYPERTENSION	DIBETES WITH HYPERTENSION	OBSTRUCTION	TUBULO INTERSTIAL DISEASE	CONGENITAL KIDNEY DISEASE	ANOREXIA	DYSPNOEA	PEDAL ODEMA	OLIGURIA	FEVER
1	02/04/2016	M	52	IV	Y	Y	Y	N	N	N	Y	Y	Y	N	N
2	13/04/2016	F	10	II	N	N	N	N	N	Y	Y	Y	Y	Y	N
3	06/05/2016	M	81	V	Y	Y	Y	N	N	N	Y	N	Y	N	Y
4	21/06/2016	M	73	V	Y	Y	Y	N	N	N	Y	N	N	Y	Y
5	30/06/2016	M	62	V	Y	N	N	N	N	N	N	Y	Y	N	N
6	01/07/2016	M	53	V	Y	N	N	N	N	N	N	Y	N	Y	Y
7	10/07/2016	F	43	IV	Y	N	Y	N	N	N	Y	N	Y	N	Y
8	23/07/2016	M	27	IV	N	N	N	Y	N	N	N	Y	N	Y	N
9	11/08/2016	M	30	IV	N	N	N	N	Y	N	Y	N	Y	Y	N
10	25/08/2016	M	13	III	N	N	N	N	N	N	Y	N	Y	Y	N
11	27/08/2016	M	10	III	N	N	N	Y	N	Y	N	Y	N	N	N
12	30/08/2016	F	52	IV	Y	Y	Y	N	N	N	Y	N	Y	N	Y
13	01/09/2016	F	57	V	Y	N	Y	N	N	N	N	Y	N	Y	N
14	12/09/2026	F	68	V	Y	Y	Y	N	N	N	N	Y	N	Y	Y
15	15/09/2016	M	76	V	Y	N	Y	N	N	N	Y	N	Y	N	Y
16	20/09/2016	M	16	III	N	N	N	Y	N	N	Y	N	N	Y	N
17	22/09/2016	M	8	II	N	N	N	Y	N	N	Y	Y	Y	Y	N
18	25/09/2016	F	23	IV	N	N	N	Y	N	N	Y	N	Y	N	Y
19	03/10/2016	M	43	V	Y	N	N	N	N	N	Y	N	Y	Y	Y
20	05/10/2016	F	45	IV	Y	Y	Y	N	N	N	Y	Y	N	Y	N
21	07/10/2016	M	41	V	N	N	N	N	Y	N	Y	N	Y	N	N
22	10/10/2016	M	54	IV	Y	N	N	N	N	N	N	Y	N	Y	Y
23	20/10/2016	M	56	V	Y	Y	Y	N	N	N	N	Y	N	Y	N
24	22/10/2016	M	58	V	Y	N	N	N	N	N	Y	N	Y	Y	N
25	27/10/2016	F	67	V	Y	N	N	N	N	N	Y	Y	N	N	Y
26	29/10/2016	F	10	III	N	N	N	Y	N	Y	Y	N	N	N	N
27	13/11/2016	M	46	V	N	N	N	N	Y	N	Y	N	N	Y	N
28	15/11/2016	M	44	V	Y	N	N	N	N	N	N	Y	N	N	N
29	24/11/2016	F	53	V	N	N	N	N	Y	N	Y	N	Y	Y	N
30	01/12/2016	M	51	V	N	N	N	N	N	N	N	Y	N	N	N
31	22/12/2016	M	56	V	Y	N	N	N	N	N	Y	N	N	Y	N
32	17/01/2017	F	54	V	N	N	N	N	N	N	N	Y	N	N	N
33	22/02/2017	M	53	V	Y	Y	Y	N	N	N	Y	N	N	Y	Y
34	12/03/2017	F	59	V	Y	Y	Y	N	N	N	Y	N	Y	N	N
35	30/04/2017	M	51	V	N	Y	N	N	N	N	Y	N	Y	N	N
36	03/05/2017	M	50	V	N	Y	N	N	N	N	Y	Y	N	N	N
37	13/05/2017	M	48	V	N	N	N	Y	N	N	Y	Y	Y	N	N
38	01/06/2017	M	52	V	N	Y	N	N	N	N	Y	N	Y	N	N
39	05/06/2017	M	49	V	Y	N	N	N	N	N	Y	Y	Y	N	N
40	16/06/2017	F	54	V	N	Y	N	N	N	N	Y	Y	Y	N	N

MASTER CHART

SEX	NAUSEA AND VOMITING	PALLOR	HEMOGLOBIN	RBC COUNT	MCV	MCH	MCHC	RDW	WBC COUNT	PLATELET COUNT	PEREPHERAL SMEAR	BLOOD GROUP	ABSOLUTE RETICULOCYTE COUNT	IRON PROFILE
M	N	MILD	8	4.3	88	26	31	15	4.5	1.62	N/N	O	22	NORMAL
F	Y	ABSENT	5	3.8	88	27	34.8	16.7	11	2.4	N/N	O	61	NORMAL
M	N	MODERATE	7.6	2.8	90	17	30	13.6	12.7	2.3	N/H	A	11	NORMAL
M	Y	SEVERE	6.9	3.9	102	26	36.9	14.7	7.5	2.6	Macro/A	B	13	NORMAL
M	N	MODERATE	8	3.4	86	28	34	1.6	10.1	2.7	N/N	B	8	NORMAL
M	Y	MODERATE	7.4	4.2	89	29	37	14.2	17.6	3	N/N	B	6	NORMAL
F	N	SEVERE	7.6	2.6	93	18	36	14.7	22.4	4.3	N/H	O	27	NORMAL
M	N	MILD	7	2.8	65	35	31	15.2	7.6	3.8	MICRO/A	A	32	INCREASED
M	Y	MODERATE	6	3.2	87	34	29	15.2	5.6	5	N/N	AB	41	NORMAL
M	N	MILD	6.8	3.4	95	33	34	15	5.7	5.6	N/N	O	32	NORMAL
M	N	MODERATE	7.1	3.1	95	31	35.8	14.2	7.6	1.1	N/N	A	61	NORMAL
F	N	MODERATE	6.5	3.2	96	24	36.5	14.7	8	2.3	N/H	B	33	NORMAL
F	Y	MODERATE	6.4	3.1	88	23	34.2	14.3	10.3	2.1	N/H	B	3	NORMAL
F	Y	MODEARTE	9	3.52	57	22	31.5	13.9	12	2.3	MICRO/A	A	12	INCREASED
M	Y	SEVERE	8.9	1.6	98	34	32	14.9	11.9	1.7	N/N	A	14	NORMAL
M	Y	ABSENT	8.1	3.1	95	31	33	15.1	9.8	1.9	N/N	O	54	NORMAL
M	Y	MILD	10	4.4	89	29	33.8	15	8.9	2.3	N/N	O	55	NORMAL
F	Y	MODERATE	9.9	2.3	86	29	34.9	13	15.7	2.4	N/N	O	24	NORMAL
M	N	SEVERE	7.6	2.8	94	26	32.7	15.2	17.7	2.1	N/N	O	6	NORMAL
F	N	ABSENT	11	3.4	93	22	31.1	14.9	15.7	3.2	N/H	B	61	NORMAL
M	Y	MODERATE	12	2.4	99	27	32.6	17	14.6	2.7	N/N	B	8	NORMAL
M	Y	SEVERE	7.8	2.7	95	18	32.8	19	14.4	2.9	N/H	O	21	NORMAL
M	N	SEVERE	8	3.7	94	17	36.1	20	13.7	2.7	N/H	A	32	NORMAL
M	N	MODERATE	7.9	1.6	90	22	33	15	6.7	3.4	N/H	A	33	NORMAL
F	Y	MODERATE	10.4	1.8	88	25	34.9	20	5.7	3.2	N/H	A	22	NORMAL
F	Y	ABSENT	10.6	5.2	85	24	35.2	17.6	5.3	3.1	N/H	B	52	NORMAL
M	Y	SEVERE	9.1	2.8	68	19	34.2	16.9	6.8	1.8	MICRO/A	B	28	INCREASED
M	N	MODERATE	9.6	2.5	90	22	31	15.9	8.6	1.7	N/H	B	7	NORMAL
F	Y	MILD	9.4	3.1	93	18	32	15.6	7.8	1.6	N/H	O	17	NORMAL
M	N	MODERATE	10	2.5	68	30	32.1	14.9	6.3	3.2	MICRO/A	O	6	INCREASED
M	N	SEVERE	9.4	3.2	61	34	33	14.3	6.1	3.4	MICRO/A	O	8	INCREASED
F	Y	MODERATE	8.7	1.5	94	42	30.9	15	7.3	3.8	N/N	O	9	NORMAL
M	N	SEVERE	8.4	2	96	29	30	13.2	15.4	3.9	N/N	O	10	NORMAL
F	N	MODEARTE	9.9	3.2	86	33	34.1	13.3	18.9	4	N/N	O	15	NORMAL
M	N	MILD	9.3	2.8	90	34	37.4	13.9	19.8	3.8	N/N	B	17	NORMAL
M	Y	MODERATE	10.7	1.7	93	30	34.1	14.2	20.7	3.2	N/N	O	19	NORMAL
M	N	MODERATE	11	4.7	85	23	35.5	14.3	9.6	5.1	N/H	O	13	NORMAL
M	N	SEVERE	7.9	2.4	90	33	35.9	15	10.8	5.2	N/N	O	28	NORMAL
M	N	SEVERE	7	3.5	71	32	36.4	13.6	11	4.3	N/N	O	23	NORMAL
F	N	MILD	6.6	2.9	92	21	35	14.9	10.7	2.4	N/H	O	22	NORMAL