# A STUDY ON HEMATOLOGICAL PROFILE IN PATIENTS OF CHRONIC RENAL FAILURE WITH SPECIAL REFERENCE TO SERUM IRON PROFILE

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**ABSTRACT: INTRODUCTION:** Chronic kidney disease is a worldwide public health problem. Chronic renal failure is defined by the National Kidney Foundation as either damage or a glomerular filtration rate less than 60ml/minute/1.73m$^2$ of body surface area for more than 3 months. The primary cause of anemia in patients with chronic renal failure is insufficient production of erythropoietin by the diseased kidneys. As there is paucity of data regarding the haematological changes in chronic renal failure in this region, the present study was aimed to achieve the following objectives.

**AIMS AND OBJECTIVES**: 1. To assess the various hematological changes in chronic renal failure. 2. To assess the correlation between hematological and biochemical parameters.

**MATERIALS AND METHODS**: The present study was conducted in the department of Medicine, in a tertiary care hospital, Assam for one year.

**STUDY DESIGN:** Hospital based, single centred observational study. All patients with features of chronic renal failure, who were admitted in medicine wards, were taken randomly for the study.

**RESULTS:** The series included 100 cases of which the highest number 37% were in the age group of 51-60 years. Male preponderance was observed with males being 65% and females 35%. Generalized weakness and swelling were the commonest symptoms observed in 76% and 74% cases and pallor, hypertension, pedal edema, ascites and acidotic breathing on examination were found in 85%, 70%, 57%, 17% and 17% cases respectively. 72% patients had serum creatinine between 5.1 to 10 mg/dl. A negative co-relationship was observed between serum creatinine and hemoglogin.

All cases had anemia of which 52% had hemoglobin between 7 to 10 gm/dl, 61% had normocytic normochronic anemia and 20% had absolute iron deficiency. Diabetes was the commonest etiology in 42%, followed by hypertension 35%, undiagnosed 12%, chronic glomerulonephritis 7%, polycystic kidney and obstructive nephropathy in 2% each respectively.

**CONCLUSION:** Anemia is the commonest haematological manifestation with normocytic normochromic anemia being the commonest morphological type. Absolute iron deficiency was significantly associated with chronic renal failure. Diabetes and hypertension were the commonest etiological factors. The concentration of haemoglobin showed negative correlationship with serum creatinine which was statistically significant.

KEYWORDS: Anemia, Ascites, Creatinine, Diabetes Mellitus, Edema, Erythropoietin, Glomerular Filtration Rate, Hemoglobin, Hypertension, Iron.

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**INTRODUCTION:** Chronic kidney disease (CKD) is a worldwide public health problem.[1] The hallmark of CKD is structural and /or functional damage of the glomeruli of the kidney, resulting in progressive decrease in glomerular filtration rate (GFR).

There have been discrepancies worldwide regarding the definition, classification and laboratory testing of CKD resulting in lack of uniformity. In 2000, the National Kidney Foundation (NKF) and the Dialysis Outcome Quality Initiative (DOQI) advisory board approved the development of clinical practice guidelines to define the chronic kidney disease and to classify stages in the progression of kidney disease. Chronic kidney disease is defined by the National Kidney Foundation as either damage or a GFR less than 60 ml/minute/1.73 m$^2$ of body surface area (BSA) for more than 3 months.

**DEFINITION CRITERIA:**

1. Kidney damage more than 3 months as defined by structural or functional abnormalities of kidneys with or without decreased GFR, manifest by either.

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a) Pathological abnormalities.
b) Markers of kidney damage including abnormal components of blood and urine or abnormality in imaging tests.

2. eGFR <60ml/min/1.73 $m^2$ of BSA for >3 months with or without kidney damage.[2]

CKD encompasses a spectrum of disorders associated with abnormal kidney function and progressive decline in GFR. The stages of CKD are defined by guidelines of the National Kidney Foundation [Kidney Dialysis Outcomes Quality Initiative (KDOQI)] and are divided into 5 stages.[2]

The term chronic renal failure (CRF) applies to the process of continuing significant irreversible reduction in nephron number and typically corresponds to CKD stage 3-5. The stage 5 is also called as end stage renal disease (ESRD), where they become dependent on dialysis, renal replacement /transplant to avoid life threatening uremia.

The exact prevalence of CKD in India is not known due to lack of regular national registry data and is provided only by small observational studies or personnel experiences, and the quality of data is quite uneven.[3] There are few population based studies in India- Mani MK (2005)[4], Agarwal SK, Dash SC (2005) [5] and Modi GK, Jha V(2006).[6] The prevalence of CKD according to Mani MK and Agarwal SK were 0.86% and 0.79% respectively.

According to the study conducted by Agarwal, Dash et al[5] at Delhi in 2005, the causes of CKD were diabetes (41%), hypertension (22%), chronic glomerulonephritis (16%), chronic interstitial nephritis (5.4%), ischaemic nephropathy (5.4%), obstructive uropathy (2.75%), miscellaneous (2.7%) and unknown cause (5.4%).

Hematological abnormalities are usually evident/manifested in CKD stages 3-5 i.e. eGFR<60ml/min/1.73$m^2$BSA.[7,8]

Hematological abnormalities in CRF are:

1. Anemia.
2. Leukocytopenia.
3. Bleeding diathesis.
4. Hypocellular bone marrow.
5. Shortened RBC lifespan.
6. Splenomegaly/ hypersplenism.

The primary cause of anemia in patients with CKD is insufficient production of erythropoietin by the diseased kidneys. Other factors include iron, folate & B12 deficiency due to nutritional insufficiency or increased blood loss [9,10], acute and chronic inflammation with impaired iron utilization, severe hyperparathyroidism with consequent bone marrow fibrosis and shortened red cell survival in the uremic environment.[11,12]

Untreated prolonged anemia leads to a number of physiologic disorders, including: cardiovascular complications like decreased tissue oxygenation, increased cardiac output, ventricular dilatation and ventricular hypertrophy and increased mortality and morbidity.

Renal insufficiency is also associated with bleeding tendency attributed to platelet dysfunction due to abnormal platelet aggregation and adhesiveness, along with prolonged bleeding time, decreased activity of platelet factor III and impaired prothrombin consumption.[13]

CKD patients also have a greater susceptibility to thromboembolism, especially if there is nephrotic range proteinuria, the later results in hypoalbuminemia and loss of anticoagulant factors, which can lead to thrombophilic state.

White blood cells count may be decreased in uremic patients and anemia correction is followed with increase in natural killer cells and improvement of leukocyte phagocytic function.

CKD is also a common clinical scenario in this remote area of North Eastern region of India, which is faced by physicians almost daily and a lot of patients get admitted in the hospitals, with various signs and symptoms. Moreover, vital information regarding the investigations, diagnosis and treatment of the patients are still lacking in many aspects, namely renal biopsy. In India, especially in this North Eastern state of Assam and particularly in Barak Valley region where adequate studies are yet to be conducted to know about the hematological manifestations in chronic renal failure.

At the department of Medicine, Silchar Medical College & Hospital, which is located in the Cachar District of Barak Valley in Assam, we have been able to investigate, diagnose a few cases (cause of CKD) and manage those cases conservatively (renal replacement therapy by hemodialysis). Many patients who are candidates for renal transplantation are often referred to higher centres for further management, as such facilities are lacking in our institution.

So, the present study was undertaken with the following aims and objectives.

1. To assess the various hematological changes in CRF (CKD stage 3to5).
2. To assess the correlation between hematological parameters and biochemical parameters.

**MATERIALS AND METHODS:** The present study was conducted in the department of Medicine, Silchar Medical College & Hospital, Silchar, Assam for a period of one year from 1st June 2012 to 31st May 2013.

**STUDY DESIGN:** The present study was a hospital based single centred observational study.

**DATA COLLECTION METHODS:** All the patients with history and signs and symptoms of CRF, who are admitted in medicine wards, were taken randomly for this study. A detailed clinical history was taken and complete physical examination was done in each and every case. All data were recorded in predesigned proforma from the patients and /or attendants after fulfilment of inclusion criteria. Informed and written consent was obtained from all the cases and / or attendants.

**INCLUSION CRITERIA:**

- All CKD patients who were admitted with stage 3 CKD (eGFR <60 ml/min/1.73$m^2$ BSA) and above whose criteria were met by definition.

**EXCLUSION CRITERIA:**

- CKD stage 1 and 2.
- Patients below 12 years of age.
- Patients with known haematological disorders or malignancy.
- Recent hemorrhagic episode.

Cleatinine clearance were calculated using Cockcroft- Gault formula:

$$\text{Creatinine clearance} = \frac{(140\text{-age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})}{72 \times (\text{S.creatinine in mg/dl})}$$

**STUDY VARIABLES:**

Different study variables those were evaluated:

1. Demographic & socioeconomic variables like age, sex, religion.
2. History of presenting symptoms, and history of similar illness in the past.
3. General survey and systemic examinations were done in details.
4. Investigations were done in 2 headings:-
   a) To establish the etiological factors of CKD, which included: Urine analysis, blood glucose levels including random, fasting, postprandial and HbA1C, S. creatinine, urea and serum electrolytes. USG of whole abdomen to see different findings of CKD like increased echogenicity, cortico-medullary differentiation, decreased renal size etc.
   b) Variable haematological parameters like complete blood count, peripheral smear, iron profile (s. Iron, TIBC, s. Transferrin, s. Ferritin) and bone marrow examination was done when indicated.

**STATISTICAL METHODS:** The data are divided into parametric and non-parametric variables for statistical analysis. The most important parametric variable in the present study were Hb and creatinine levels. Statistical methods were applied to assess whether there is any correlation between haemoglobin level and creatinine levels. For this purpose Pearson's product moment correlation test was employed.

The non parametric variables include the blood picture. The percentage of patients with various blood pictures are analysed and depicted in histogram and other graphical pictures.

P value < 0.05 was taken as level for statistical significance.

**RESULTS AND OBSERVATIONS:** The present study was carried out in a tertiary care hospital, in the department of Medicine. Total 100 cases were included in the study after fulfilment of inclusion and exclusion criteria. All cases were examined meticulously and laboratory tests and imaging were done.

Present study showed highest number cases in the age group of 51-60 year (37% of cases) and maximum number of the cases were between 4$^{th}$ and 5$^{th}$ decade (71% of cases) with mean age of 49.88 years (+ 10.47).

In the present study out of 100 cases 65% were males and 35% were females, showing male preponderance of CRF. This showed statistically significant male preponderance (p=0.013).

In the present study, 76% patients presented with generalized weakness, which was the most common symptom, followed by swelling (facial puffiness, pedal edema, abdominal distension) with 74% cases. Decreased urine output and GI symptoms (anorexia, nausea, vomiting, hiccups) were found in 68% and 67% cases respectively. Other symptoms were easy fatigability in 58%, breathlessness in 27%, seizure in 5%, easy bruising in 5% and hematuria in 2% of cases.

Among the clinical findings, pallor (85%) was the most common finding in the present study, followed by hypertension (70%), pedal edema in 57%, ascites and acidotic breathing in 17% each, chest crepitaion in 15% and cyanosis in 4% cases.

The serum creatinine in the present study varies from 4.1 to 16.6 mg/dl with mean of 8.85+ 2.20 mg/dl. Majority of the cases were having S. creatinine between 5.1-10 mg/dl (72%) followed by 24% in the range 10.1-15 mg/dl.

In the present series 58% cases were having random blood sugar <200mg/dl and 42% cases with blood sugar > 200mg/dl with mean value of 191.33+ 107.23 mg/dl.

In the present series, 35% cases had hyponatremia and 16% cases had hypernatremia which was statistically significant (p= 0.003).

In the present study, 16% cases had hypokalemia and 20% had hyperkalemia which were statistically significant (p<0.05).

In the present series all the cases showed some degree of USG abnormality involving the parenchyma. Increased renal echogenicity were seen in maximum number of cases (52%) followed by loss of CMD in 45% and decreased kidney size in 34% cases.

Anemia was present in all the cases, Hb ranging from 3.8 to 10.8 gm/dl. Majority of cases were with Hb between 7 to 10 gm/dl.

Platelet count was <1 lac/mm$^3$ in 8%, 1-1.5 lac/mm$^3$ in 48%, >1.5-2 lac/mm$^3$ in 42% and >2 lac/mm$^3$ in only 2% cases. Thrombocytopenia in CKD in the present study is not statistically significant (p= 0.33).

In the present series leukopenia was seen in 7% cases and leukocytosis in 14% cases, rest were having normal count. Leukocytosis in CKD in the present study is statistically significant (p= 0.0001).

In the present study maximum no of cases were having normocytic normochromic anemia (61%), followed by dimorphic (18%) and microcytic anemia (12%). Normocytic mormochromic anemia was most common type of anemia in CKD in the present series though not significant statistically (p=0.071).

In the present study 33% cases had normal iron status and absolute iron deficiency, functional iron deficiency and iron overload were found in 20%, 43% and 4% cases respectively. Maximum number of cases had functional iron deficiency (43%).

Absolute iron deficiency in CKD was noted to have statistical significance (p<0.05).

Among the cases of CKD, diabetes was found to be the commonest etiology (42%), followed by hypertension (35%), undiagnosed (12%), chronic glomerulonephritis

(7%), polycystic kidney and obstructive nephropathy in 2% each respectively.

In the present study maximum cases of CKD were found in stage 5 disease (49%).

By using Pearson's product moment correlation formula, we got correlation R= - 0.3468. This shows that there was negative correlation between S. Creatinine and Hb levels. (p= 0.0004).

**DISCUSSION**: The present study was conducted in the department of Medicine of Silchar Medical College & Hospital, Silchar from 1st June to 31st May for a period of 1 year. Total 100 cases who met the inclusion criteria were taken up randomly for the study.

The age ranged from 18 to 80 years in the present series with mean of 49.88 + 10.47 years. Maximum cases were found in the age group of 51-60 years (37%) and lowest in 12-20 years (1%).

This finding is comparable to the studies of Talwar et al (2002) and Ajay K. Singh et al (2013) where they found mean age of 44.6 and 45.22 + 15.2 years respectively.[14,15]

Present study showed male preponderance, 65% males and 35% females which correlates with the study of Agarwal S K et al (2005) with 56.16% males.[16]

Most common symptom in the present series was generalized weakness (76%) followed by swelling (74%) and reduced urine output (68%). GI symptoms (anorexia, nausea, vomiting, hiccups) were found in 67%, easy fatigability in 58% and difficulty in breathing in 27%. The findings are comparable to the study of J. M. Malangone et al (1989).[17]

Creatinine level in the present series ranged from 4.1 - 16.6 mg/dl with mean of 8.85+ 2.2 mg/dl. Agarwal et al (2005), in a population based study found mean creatinine to be 2.89+ 2.2 mg/dl (range 1.9-10.7 mg/dl). The mean s. creatinine in the present study was higher because it was a hospital based study conducted in a tertiary care hospital.

In the present study majority of the patients were having random blood sugar(RBS) levels < 200mg/dl (58%) whereas 42% cases were having RBS >200 mg/dl with mean of 191.33+ 107.23 mg/dl which differs from study by Ajay K. Singh who found mean RBS 116.59+ 59.24 mg/dl.

In present study hyponatremia, hypernatremia and hyperkalemia were found in 35%, 16% and 20% cases respectively. Kovesdy et al found hyponatremia in 28% cases with CKD.[18]

In the present study anemia was present in all cases. The haemoglobin (Hb) level ranged from 3.8 to 10.8 gm/dl with mean of 7.59+ 1.42 gm/dl. Majority (90%) of the cases had Hb level between 5-10 gm/dl and 4% had Hb level less than 5 gm/dl. The present study is comparable to the study of Talwar et al (2002) where the mean Hb level was 7.1 gm/dl and prevalence of anemia in 94%.

In the present series majority of cases had normocytic normochromic anemia (61%) followed by dimorphic anemia (18%) and microcytic anemia (12%). Arun S et al (2012), observed normocytic normochromic anemia in 60.22% cases.[19]

The present study showed thrombocytopenia in 56% cases which correlates with the study of Talwar et al. (2002) where thrombocytopenia was observed in 52% cases.

In the present series leukopenia was found in 7% cases which is similar to the study by Talwar et all with 6% leukopenia.[14]

In this study, 20% of cases had absolute iron deficiency and 43% had functional iron deficiency which correlates with the study by James et al. who found 28.4% and 41% of iron deficiency and functional iron deficiency respectively.[20]

The present study revealed diabetes mellitus (42%) being the commonest etiology of CKD followed by hypertension (35%), chronic glomerulonephritis (7%) and undiagnosed (12%). These findings almost correlate with the study of Agarwal et al. who found diabetes, hypertension, chronic glomerulonephritis and unknown causes in 41%, 22%, 16% and 5.4% cases respectively.[16]

**CONCLUSION:** The conclusions derived from the present study are documented as follows. Chronic renal failure manifests with various haematological abnormalities of which anemia being the commonest. Normochromic normocytic anemia though the commonest morphological type was however not statistically significant. Functional iron deficiency was predominant and absolute iron deficiency was statistically significant.

Diabetes mellitus and hypertension were the commonest etiological factors. The concentration of haemoglobin showed negative correlation ship with serum creatinine which was statistically significant (p=0.0004) indicating a proportional renal impairment with the degree of anemia.

Therefore, it is recommended that patients presenting with hypertension or diabetes mellitus or both, should be screened thoroughly for any evidence of CKD, and to evaluate accordingly so as to delay the progression of the disease. During evaluation of a case of anemia active search for any occult/underlying renal pathology should be done, to detect early CKD and to retard its progression by appropriate measures.

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| Sl. No. | Age in years | No. of cases | % |
|---|---|---|---|
| 1. | 11-20 | 1 | 1 |
| 2. | 21-30 | 3 | 3 |
| 3. | 31-40 | 10 | 10 |
| 4. | 41-50 | 34 | 34 |
| 5. | 51-60 | 37 | 37 |
| 6. | 61-70 | 11 | 11 |
| 7. | >70 | 4 | 4 |

***Table 1: Showing Age Distribution***

| Sex | No. of patients | % |
|---|---|---|
| Males | 65 | 65 |
| Females | 35 | 35 |

***Table 2: Showing sex distribution***

| Presenting complaints | No. of case | % |
|---|---|---|
| Generalized weakness | 76 | 76 |
| Swelling( Facial puffiness, pedal edema, abdominal distension) | 74 | 74 |
| Decreased urine output | 68 | 68 |
| GI symptoms( Anorexia, Nausea, vomiting, hiccups) | 67 | 67 |
| Easy fatigability | 58 | 58 |
| Breathlessness | 27 | 27 |
| Seizure | 5 | 5 |
| Easy bruising | 5 | 5 |
| Altered sensorium | 4 | 4 |
| Hematuria | 2 | 2 |

***Table 3: Showing Presenting Symptoms***

| Clinical findings | No. of cases | % |
|---|---|---|
| Pallor | 85 | 85 |
| Hypertension | 70 | 70 |
| Pedal edema | 57 | 57 |
| Ascites | 17 | 17 |
| Acidotic breathing | 17 | 17 |
| Chest crepitations | 15 | 15 |
| Pleural rub | 7 | 7 |
| Pericardial rub | 5 | 5 |
| Cyanosis | 4 | 4 |

***Table 4: Showing Clinical findings***

| Serum Creatinine (mg/dl) | No. of Cases | % |
|---|---|---|
| 1.5-5 | 1 | 1 |
| 5.1-10 | 72 | 72 |
| 10.1-15 | 24 | 24 |
| >15.1 | 3 | 3 |

***Table 5: Serum Creatinine Distribution***

| Random Blood sugar(mg/dl) | No. of cases | % |
|---|---|---|
| <200 | 58 | 58 |
| 200-300 | 22 | 22 |
| >300-400 | 12 | 12 |
| >400 | 8 | 8 |

***Table 6: Showing Blood Sugar Levels***

| Serum Na (mEq/L) | No. of cases | % | p-value |
|---|---|---|---|
| <135 | 35 | 35 | 0.19 |
| 136-145 | 49 | 49 | 0.8703 |
| >145 | 16 | 16 | 0.0003 |

***Table 7: Serum Sodium Levels***

P= 0.19

| Serum K+(mEq/L) | No. of cases | % | p-value |
|---|---|---|---|
| <3.5 | 16 | 16 | 0 |
| 3.5-5.5 | 64 | 64 | 0.021 |
| >5.5 | 20 | 20 | 0 |

***Table 8: Potassium (K+) levels***

P <0.05

| USG findings | No. of cases | % |
|---|---|---|
| Decrease kidney size | 34 | 34 |
| Loss of CMD | 45 | 45 |
| Bright echogenicity | 52 | 52 |
| Hydronephrosis | 2 | 2 |

***Table 9: Distribution of ultra - sonography (USG) findings***

CMD = Corticomedullary differentiation

| Hb levels | No. of cases | % |
|---|---|---|
| <5 | 4 | 4 |
| 5-7 | 38 | 38 |
| >7-10 | 52 | 52 |
| >10 | 6 | 6 |

***Table 10: Hemoglobin (Hb) distribution in gm/dl***

P= 0.04

| Platelet count (lac/mm$^3$) | No. of cases | % |
|---|---|---|
| <1 | 8 | 8 |
| 1-1.5 | 48 | 48 |
| >1.5-2 | 42 | 42 |
| >2 | 2 | 2 |

***Table 11: Platelet count distribution***

| Leukocyte count (/mm$^3$) | No. of cases | % |
|---|---|---|
| <4000 | 7 | 7% |
| >4000-12000 | 79 | 79% |
| >12000 | 14 | 14% |

***Table 12: Leukocyte count distribution***

| Iron status | No. of cases | % |
|---|---|---|
| Normal | 33 | 33 |
| Absolute iron deficiency | 20 | 20 |
| Functional iron deficiency | 43 | 43 |
| Iron overload | 4 | 4 |

***Table 13: Distribution of Iron status***

| Etiological factor | No. of cases | % |
|---|---|---|
| Diabetes Mellitus | 42 | 42 |
| Hypertension | 35 | 35 |
| Chronic glomerulonephritis | 7 | 7 |
| Polycystic kidney disease | 2 | 2 |
| Obstructive nephropathy | 2 | 2 |
| Undiagnosed | 12 | 12 |

***Table 14: Distribution of cases with established etiology***

| Stage of CKD | eGFR (ml/min/1.73 $m^2$BSA | No. of cases | % |
|---|---|---|---|
| Stage 1 | >=90 | 0 | 0 |
| Stage 2 | 60-89 | 0 | 0 |
| Stage 3 | 30-59 | 20 | 20 |
| Stage 4 | 15-29 | 31 | 31 |
| Stage 5 | <15 | 49 | 49 |

***Table 15: Distribution of stages of CKD***

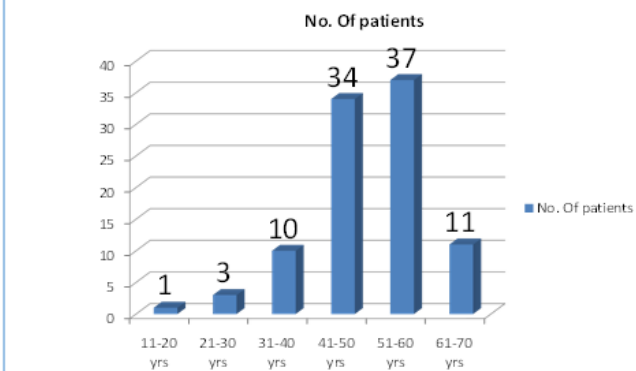


Fig 1: Bar diagram showing age distribution

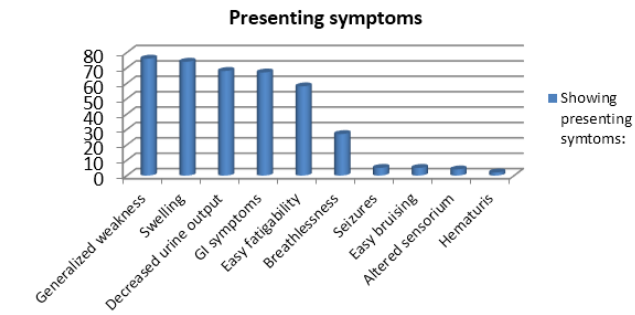


Fig 2: Showing presenting symptoms

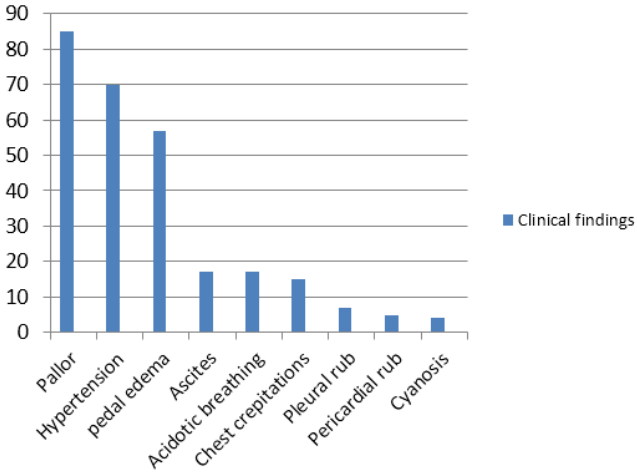


Fig3: Showing clinical findings

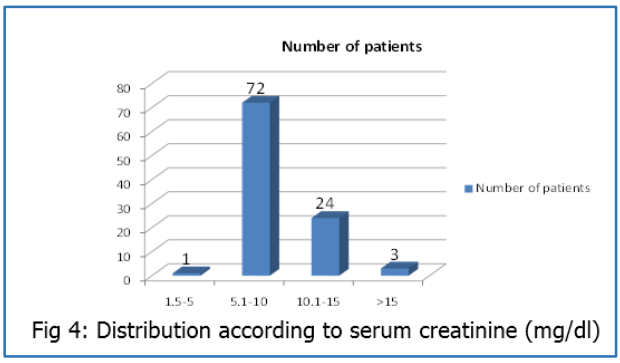


Fig 4: Distribution according to serum creatinine (mg/dl)

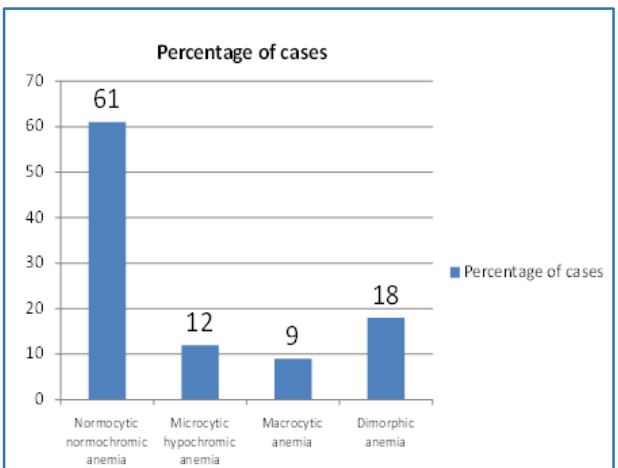


Fig 5: Ditribution of types of anemia

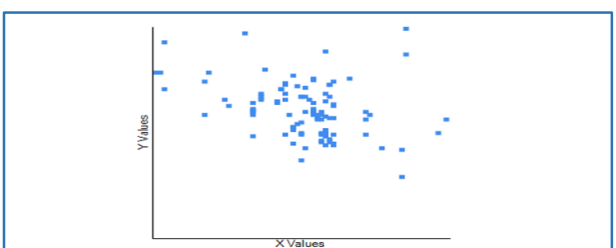


Fig 6: Pearson correlationship graph (X values= Hb in gm/dl and Y values= S. Creatinine in mg/dl)