"A STUDY OF CORRELATION BETWEEN NEUTROPHIL TO LYMPHOCYTE RATIO AND PLATELET TO LYMPHOCYTE RATIO IN PATIENTS OF CHRONIC KIDNEY DISEASE AT KLE'S Dr. PRABHAKAR KORE HOSPITAL AND MRC, BELAGAVI."

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Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"A STUDY OF CORRELATION BETWEEN NEUTROPHIL TO LYMPHOCYTE RATION AND PLATELET TO LYMPHOCYTE RATION IN PATIENTS OF CHRONIC KIDNEY DISEASE AT KLE'S DR. PRABHAKAR KORE HOSPITAL AND MRC,BELAGAVI",** is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

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LIST OF ABBREVIATIONS USED

AGE	:	ADVANCED GLYCATION END-PRODUCTS
ATP	:	ADENOSINE TRIPHOSPHATE
BPH	:	BENIGN PROTATE HYPERTROPHY
CGN	:	CHRONIC GLOMERULONEPHRITIS
CKD	:	CHRONIC KIDNEY DISEASE
COPD	:	CHRONIC OBSTRUCTIVE PULMONARY DISEASE
CTID	:	CHRONIC TUBULOINTERSTITIAL DISEASE
CVD	:	CARDIOVASCULAR DISEASE
DCM	:	DILATED CARDIOMYOPATHY
DM	:	DIABETES MELLITUS
eGFR	:	ESTIMATED GLOMERULAR FILTRATION RATE
EPO	:	ERYTHROPOIETIN
ESR	:	ERYTHROCYTE SEDIMENTATION RATE
ESRD	:	END STAGE RENAL DISEASE
FF	:	FILTRATION FRACTION
Hb	:	HEMOGLOBIN
HS-CRP	:	HIGH SENSITIVE C REACTIVE PROTEIN
HTN	:	HYPERTENSION
IFTA	:	INTERSTITIAL FIBROSIS/TUBULAR ATROPHY
IHD	:	ISCHEMIC HEART DISEASE
KDIGO	:	KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES
MDRD	:	MODIFICATION OF DIET IN RENAL DISEASE
MHD	:	MAINTENANCE HEMODIALYSIS
NKF	:	NATIONAL KIDNEY FOUNDATION

NLR	:	NEUTROPHIL TO LYMPHOCYTE RATIO
PLR	:	PLATELET TO LYMPHOCYTE RATIO
RAAS	:	RENIN ANGIOTENSIN ALDOSTERONE SYSTEM
RAGE	:	RECEPTOR FOR AGE
RPF	:	RENAL PLASMA FLOW
SD	:	STANDARD DEVIATION
SGLT	:	SODIUM-GLUCOSE COTRANSPORTERS
SNGFR	:	SINGLE NEPHRON GFR
Tc	:	TOTAL COUNT
WBC	:	WHOLE BLOOD COUNT

ABSTRACT

BACKGROUND AND OBJECTIVES:

Inflammation is recognized as one of the central pathophysiological factors in chronic kidney disease. Nowadays we have widely recognized monitoring and diagnostic markers such as high sensitive C reactive Protein (hs-CRP), serum albumin, erythrocytes sedimentation rate (ESR), ferritin and many others. However, in the present social economic status and in developing countries like India, it is important that we search for cost-effective biological markers after extrapolating their utility from other areas. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have begun to be used in kidney patients particularly as a marker of end-organ damage and inflammation.NLR and PLR have demonstrated to be a simple and affordable laboratory parameter that give important information on inflammation in CKD patients. Objective of our study was to know correlation between NLR and PLR in patients of chronic kidney disease.

METHODOLOGY:

The present one-year cross-sectional study was done in the General Medicine Department and Department of Nephrology, Dr. Prabhakar Kore Hospital and Medical Research Centre, KLE University, Belagavi. A total of 100 patients with CKD were included in the study. Patients were subjected to relevant clinical examination, laboratory workup like Sr. Creatinine, Neutrophils, Lymphocytes, Platelets and Hemoglobin, GFR, NLR and PLR was calculated for all patients.

RESULTS:

100 cases included in our study were either in stage four or stage five of chronic kidney disease and all were on maintenance haemodialysis. Males predominated with male: female ratio - 4:1. Most of our patients presented with

generalized weakness and easy fatiguability and most observed clinical finding was pallor and oedema. Diabetes was commonest etiological factor followed by hypertension and chronic tubulointerstitial nephritis. NLR alone though reflected an altered ratio but did not have positive correlation in our patients. Similarly, PLR was also altered and again did not show positive correlation. However, when NLR and PLR were compared reflected a positive correlation in this patient. The serum creatinine levels were raised in patients of older age group. Also, we observed low hemoglobin percentage (slightly more hemoglobin percentage in males compared to females) in most of our patients.

INTERPRETATION AND CONCLUSION

In our present study 100 patients with chronic kidney disease who were on maintenance hemodialysis (clinical staging 4 and 5), the commonest etiological factor for chronic kidney disease was diabetes followed by hypertension and CTIN. There is no correlation with NLR alone similarly PLR alone but there is a positive correlation between NLR and PLR in CKD. Comparison of lab parameters did not have significant correlation. Gender did not influence in these patients of CKD. These simple, cost effective, non-invasive parameters which can be done in all the lab including periphery can be used as a marker of inflammation in these patients. In future these ratios with large sample size can be made used in these patients to stage them, to see whether they require haemodialysis as maintenance therapy.

KEY WORDS:

Chronic kidney disease, Neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR).

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INTRODUCTION

A range of pathophysiologic processes referred to as chronic kidney disease (CKD) encompass impaired kidney function and a progressive decline in glomerular filtration rate (G.F.R). If amassed toxins are not purged by renal replacement therapies, people with End stage renal disease (ESRD) will die.[1] Incidence and prevalence of CKD have increased causing social and economic burden to health care system.

Chronic kidney disease is defined as kidney damage or glomerular filtration rate (G.F.R) <60ml/min/1.73 m^2 for 3 months or more, irrespective of cause.[2] Main causes of CKD are diabetes mellitus and hypertensive nephrosclerosis.[3] Inflammation is recognized as one of the central pathophysiological factors in kidney diseases. Nowadays, we have widely recognized monitoring and diagnostic markers such as high sensitive C reactive Protein (hs-CRP), serum albumin, erythrocytes sedimentation rate (ESR), ferritin and many others. However, in the present social economic status and in developing countries like India, it is important that we search for cost-effective biological markers after extrapolating their utility from other areas.

Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have been used in cardiovascular diseases, various malignancies and even in Covid 19 as a marker of prognostication and mortality indicator.[4] Now NLR and PLR have begun to be used in kidney patients, particularly as a marker of end-organ damage and inflammation and more recently, as a predictor of death.[5] NLR and PLR have demonstrated to be a simple and affordable laboratory parameter that give important information on inflammation in CKD patients.[6] Inflammatory indicators like

neutrophilia and relative lymphocytopenia have been shown in several studies to be independent markers of many illnesses, including complications of Diabetes mellitus like Diabetic nephropathy [7,8]. However, making a diagnosis only on the basis of WBC, neutrophil, or lymphocyte counts has biases of its own, in contrast to NLR, a dynamic indicator with a stronger predictive value.[8,9] Platelets play a key role in atherosclerosis, atherothrombosis, and the pathogenesis of inflammation.[10,11] However, in systemic inflammatory disorders including malignancies and atherosclerotic heart disease, platelet distribution, platelet count, and PLR are signs of a bad prognosis.[10,11] PLR is a strong marker of inflammation in patients with ESRD.[12]

We aim to determine the NLR and PLR in Chronic kidney disease patients and see if there is any correlation. Neutrophils, platelets and lymphocytes counts are routinely done cost effective and easily available and can be used as simple tool in chronic kidney disease to benefit lot of people in a developing country like India. Review of literature shows that NLR ratio and PLR ratio is altered in chronic kidney disease so the study done to find correlation between NLR, PLR and chronic kidney disease patient.

AIM AND OBJECTIVE

To study correlation between neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) in patients of chronic kidney disease.

To measure and study the correlation of NLR and PLR with other renal parameters in chronic kidney disease.

REVIEW OF LITERATURE

Chronic kidney disease (CKD) is now in the center of a worldwide epidemic. Chronic degenerative illnesses are becoming increasingly common as a result of greater life expectancy and a drop in morbidity and mortality from infectious diseases throughout time. In contrast to other chronic non-infectious diseases, chronic kidney disease offers a very genuine window of opportunity to maintain a comfortable standard of living even after the disease has reached its fatal stage. The length of artificial life extension is mainly correlated with the patient's and/or his provider's financial means. In lesser developed nations like India, the family is typically the one to bear the most financial burden. Therefore, it is imperative that we address this issue from its "preventable" beginning rather than only at the therapeutic conclusion of the disease.

The European Renal Association (ERA) and the National Kidney Foundation (NKF) of the United States have issued guidelines for effective therapies for avoiding CKD and its development at each stage as well as identified the phases of CKD. As opposed to the name "kidney," which is readily recognized by the general public, "renal" is not a word that is easily comprehended by laypersons. The idea of "failure" is no longer appropriate for a disease since medical intervention has been very successful in delaying the illness's course from the first stage to the last "end stage."[(13)]

DEFINITION.

CKD is described by the National Kidney Foundation as,

CRITERIA:

1. "Kidney damage for > 3 months, either structural or functional abnormality with or without decreased GFR, manifested by either pathologic abnormalities or markers of kidney damage in blood, urine or in imaging studies".[14]

2. "GFR <60 ml/min/1.73 sq m for > 3 months with or without kidney damage".

In order to improve management and prognostication, the revised classification system (2012) now includes a three-dimensional operational definition for CKD that encompasses cause, GFR category, and albuminuria. The risk of CKD progression is closely linked to both the GFR and the amount of albuminuria. Figure no.1 shows staging of CKD, classified by measurement of both of these parameters.[1][15]

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (ml/min/1.73 m²) description and range				Persistent albuminuria categories description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Figure 1: Kidney disease improving global outcome (KDIGO) classification of chronic kidney disease. Gradation of color from green to red corresponds to increasing risk and progression of CKD (green: low risk; Yellow: moderately increased risk; Orange: high risk; Red: very high risk)

Stage 3 CKD has been further subdivided into stage 3A (GFR 45 to 59 ml/min) and stage 3B (GFR 30 mL/min to 44 mL/min), since people in stage 3B are far more likely to go to stage 5 than those in stage 3A. eGFR 15 ml/min/1.73 sqm with or without RRT is the threshold for CKD Stage 5, whereas ESRD refers to renal failure in which dialysis or a kidney transplant are necessary to maintain life. Due to the fact that not all patients with CKD stage 5 get RRT, the terms "CKD stage 5" and "ESRD" are not interchangeable. Stage 5 of CKD has been further divided into stages 5D and 5T depending on whether the patient is receiving dialysis or a kidney

transplant. After a kidney transplant, according to the GFR criteria above, the patient might be classified as stage 5T-1 to stage 5T-4 if kidney function declines.[13]

GFR ESTIMATION:

GFR, a measurement of renal function, is the rate at which fluid enters nephrons following filtration. Instead of only using the serum creatinine concentration to stage CKD, one must estimate the GFR.

The estimation of kidney function from serum creatinine is frequently done using two formulae.[1][16]

1. Cockcroft-Gault formula:

$$\text{CrCl (mL/min)} = \frac{(140\text{-age}) \times \text{Lean Body Weight (kg)}}{\text{Serum Creatinine (mg/dL)} \times 72} \quad (\times 0.85 \text{ if female})$$

2. MDRD study Equation:

   "eGFR (ml/min/1.73m^2) = 186.3 x (Serum Creatinine)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.21 if African American)".

GFR with age: From the peak GFR (~120 mL/min per 1.73 m2) reached during the third decade of life, the typical yearly mean drop in GFR with age is 1 mL/min per 1.73 m2, reaching a mean value of 70 mL/min per 1.73 m2 at age 70. Reduced GFR is expected with aging, the mean GFR is lower in women than in men.[17]

AETIOLOGY OF CKD AND EPIDEMIOLOGY

CKD affects more than 10% of the world's population and the prevalence has risen in recent years. A more recent study performed a comprehensive systematic review and meta-analysis of 100 studies comprising 6,908,440 patients, and reported a global prevalence of 13.4% for CKD stages 1–5 and 10.6% for CKD stages 3–5[18]. The US Centers for Disease Control and Prevention (CDC) estimate that 15% of adults in the US (about 37 million individuals) have CKD. Noteworthy statistics include the fact that 90% of individuals with CKD are unaware of their condition and that 1 in 2 patients with very low kidney function who are not on dialysis are unaware they have CKD. One in three persons with diabetes and one in five adults with hypertension may have CKD, according to the CDC.[19] Diabetic glomerulosclerosis appears to be the most prevalent cause of CKD in people of all races [13]. The most frequent causes of CKD in India according to Indian CKD registry are illustrated below in Table 1[20].

Table 1 – Etiology of CKD in India [20]

No.	DISEASE	PERCENTAGE
1	Diabetic nephropathy	31.3
2	Undetermined	16
3	Chronic glomerulonephritis	13.8
4	Hypertensive nephrosclerosis	12.9
5	Chronic interstitial nephritis	7
6	Obstructive uropathy	3.4
7	ADPKD	2.6
8	Miscellaneous	11.7
9	Renovascular disease	0.8
10	Graft failure	0.3

PATHOPHYSIOLOGY OF CHRONIC KIDNEY DISEASE

Although the usefulness of the term "chronic kidney disease" has been questioned, the concept of CKD is strongly supported by evidence that in response to nephron loss, a common pathway of mechanisms provokes a vicious cycle of progressive kidney damage that eventuates in further nephron loss and explains the progressive nature of diverse causes. The advancement of CKD is primarily fueled by glomerular hemodynamic adaptations to nephron loss that result in glomerular capillary hypertension and glomerular hyperfiltration. Trials demonstrating that RAAS inhibitors and SGLT2 inhibitors, medications that work by separate mechanisms to lower glomerular capillary hydraulic pressure, provide renoprotection, provide substantial support for this concept. Together with hemodynamic variables, nonhemodynamic factors such as proteinuria, oxidative stress, tubulointerstitial fibrosis, acidosis, and renal hypertrophy cause progressive kidney injury.

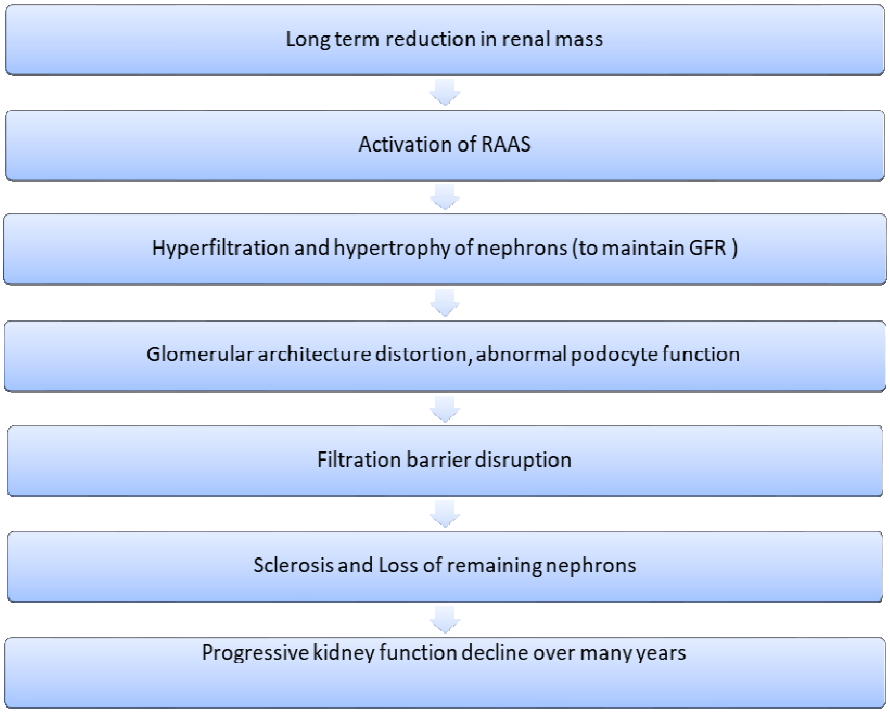


Figure no.2 Pathophysiology of CKD [(17)]

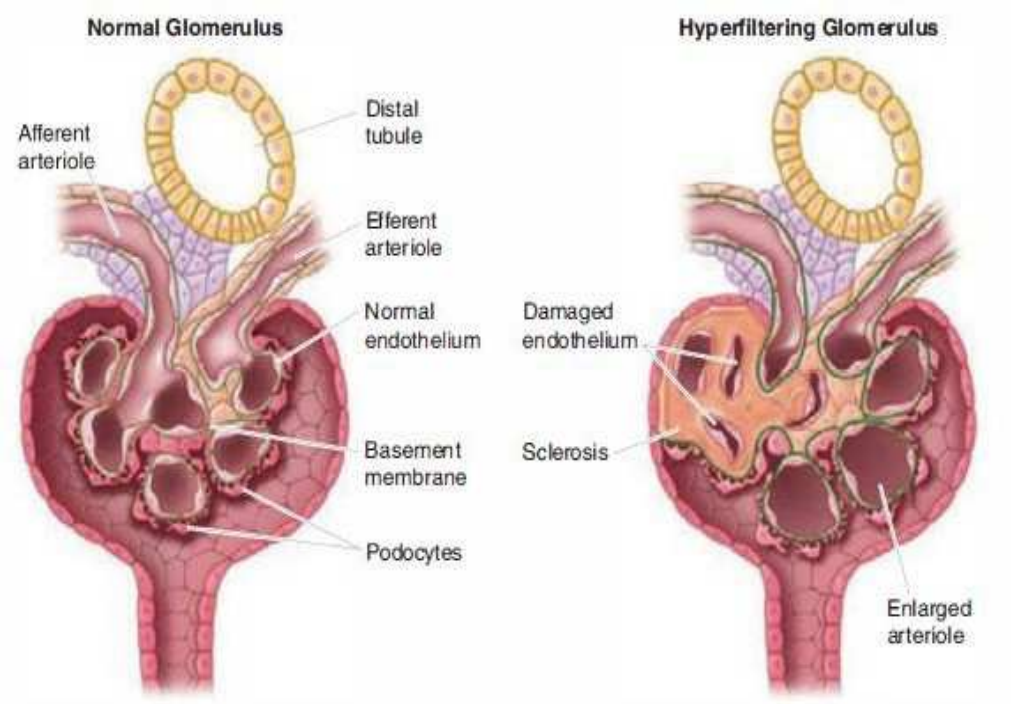


Figure 3 Left: Schema of the normal glomerular architecture. Right: Secondary glomerular changes associated with reduction in nephron number, including enlargement of capillary lumens and focal adhesions, which are thought to occur consequent to compensatory hyperfiltration and hypertrophy in remaining nephrons.[17]

The responses to reduction in nephron number are mediated by vasoactive hormones, growth factors and cytokines[17]. In the early stages, basal GFR can be normal or high, but the expected increase in response to the protein challenge is reduced and this early stage is commonly seen in diabetic nephropathy. It is detected by estimating the GFR by means of the creatinine concentration. When these parameters are mildly elevated, a significant chronic nephron injury has occurred. When the GFR is 30% of normal, the patient may remain asymptomatic with higher serum concentrations of urea and creatinine. A detailed examination shows nocturia, mild anemia, malnutrition and abnormal serum levels of calcium and phosphorus.

When the GFR is below 30% of normal, there will be uremic events with severe biochemical abnormalities. In mild to moderate renal impairment, clinical conditions such as infection, hypovolemia, uncontrolled hypertension, drug or radiocontrast nephrotoxicity, compromise kidney function and cause overt uremia. As GFR falls below 5-10% of normal, patient needs renal replacement therapy to survive.

CLINICAL PRESENTATION OF CKD

The symptoms, signs and metabolic abnormalities related to CKD may be brought on by changes in the kidney's normal homoeostasis processes or by a buildup of uremic toxins, which cause the clinical syndrome of "uremia."[(21)]

UREMIA

Azotemia is a term used for retention of nitrogenous waste products. Uremia is a clinical condition due to multiorgan system derangement in advanced stages of renal insufficiency and is caused by nitrogen containing nonvolatile products of metabolism normally excreted by kidney.

Manifestations of uremia:

a. **Nervous system:**

- Headache, malaise, insomnia, fatigue and cramps.
- Restless legs, motor weakness, polyneuritis, irritability.
- Dementia, drowsiness, flapping tremors, convulsion, stupor.

b. **Gastrointestinal system**:

- Nausea and anorexia, vomiting, diminution in taste and smell.
- Gastritis, gastrointestinal ulcer with bleeding, pancreatitis.

c. **Cardiovascular system**:

- Pericarditis, hypertension, hypotension, cardiomyopathy, decreased diastolic compliance, edema, atheromatosis, cardiomyopathy.

d. **Hematological system**:

- Anemia, thrombocytopenia, bleeding manifestations.

e. **Pulmonary system**:

- Pleuritis, uremic lung, pulmonary edema.

f. **Skin**:

- Pruritus, retarded wound healing, melanosis and nail atrophy.

g. **Bone disease**:

- Osteodystrophy, hyperparathyroidism, osteomalacia, adynamic bone disease.

h. **Others**:

- Thirst, weight loss, impotence, uremic fetor, hypothermia,

Table no 2 Common clinical presentations in CKD [(21)]

• Asymptomatic in most cases (even till stage 5)
• Pedal edema, puffiness of face
• Dyspnea, orthopnea
• Nausea, vomiting, abdominal discomfort
• Itching, dryness of skin
• Decreased appetite, malaise, weakness
• Polyuria (in early stages), nocturia, oliguria
• Unexplained anemia (pallor)

Increased systemic inflammation is linked to CKD. In conjunction with other acute-phase reactants, elevated amounts of C-reactive protein are seen, whereas declining levels of so-called negative acute-phase reactants including albumin and fetuin are seen. Thus, the malnutrition-inflammation-atherosclerosis/calcification triad, which in turn leads to the acceleration of vascular disease and comorbidities associated with advanced renal disease, is crucial in the inflammation associated with CKD. Cardiovascular disease is the primary cause of death in these patients[17].Diabetic nephropathy is a common cause of CKD in India.[1] Newly diagnosed CKD patients often have hypertension. CKD is attributed to hypertension, when no evidence for the primary disease process is present.

METABOLIC EFFECTS OF UREMIA

Loss of kidney function has numerous metabolic effects. Some of the most prominent are listed in Table no. 3 below. A few can be related to the loss of specific renal processes, such as the hydroxylation of vitamin D. However, most have no clear cause, and can at present only be attributed to the retention of uremic solutes.[22]

Table no. 3 Metabolic effects of uremia

Sr.no	
1.	Increased oxidant levels
2.	Reduced resting energy expenditure
3.	Reduced body temperature
4.	Insulin resistance
5.	Muscle wasting
6.	Amenorrhea and sexual dysfunction
7.	Platelet dysfunction
8.	Shortened erythrocyte life span
9.	Albumin oxidation
10.	Reduced muscle membrane potential
11.	Granulocyte and lymphocyte dysfunction

LABORATORY

URINE ANALYSIS-

Dipstick testing can be used to screen for the presence of blood, protein, ketones, glucose, nitrates, and leucocytes as well as to determine the pH and osmolality of urine. Erythrocytes, which can indicate bleeding from the urogenital tract (from the kidney to the tip of the penis), dysmorphic erythrocytes; which point to the presence of nephritis, red cell casts; which point to glomerular disease, broad, waxy casts, which can be seen in CKD, and crystals, which may be seen in patients with renal stone disease, can all be found in urine using urine microscopy or flow cytometry.

BLOOD TESTS-

Hematology:

In CKD, a normocytic normochromic anemia is typical. Other abnormalities that indicate underlying disease processes may be seen, such as neutrophilia and an elevated erythrocyte sedimentation rate (ESR) in sepsis or vasculitis, lymphopenia and an elevated ESR in systemic lupus erythematosus (SLE), and fragmented red blood cells in HUS and TTP.

Biochemistry:

Raised serum creatinine levels (normal range 0.5-1.2 mg/ml) may indicate a decreased GFR. Although serum urea levels are frequently elevated in renal illness, this analyte has little usefulness as a gauge of GFR since levels rise in response to protein consumption, after gastrointestinal bleeding, and during catabolic conditions.

In CKD, serum calcium levels tend to decrease and phosphate levels to rise, which is related to elevated parathyroid hormone (PTH) levels brought on by the kidney's decreased generation of 1,25(OH)2D (secondary hyperparathyroidism), may be followed in certain cases by elevated blood alkaline phosphatase levels, a sign of renal osteodystrophy.

Immunology:

Patients with renal illness due to SLE may test positive for antinuclear antibodies (ANA), antibodies to extractable nuclear antigens, and anti-double-stranded DNA antibodies. In addition to decreased complement levels in SLE, systemic vasculitis, and HUS, antineutrophil cytoplasmic antibodies (ANCA) and antibodies to GBM may also be seen in individuals with nephritis due to systemic vasculitis.

IMAGING -

Ultrasonography:

Kidney size can be determined; a kidney less than 9 cm in length indicates significant irreversible renal disease. A difference in size of more than 1.5 cm between the two kidneys is observed in unilateral renal disease.

Computed tomography:

Computed tomography urography (CTU) uses imaging and contrast material to evaluate or detect blood in urine, kidney or bladder stones, and cancer in the urinary tract. It is often performed using x-ray (IVP), or CT or MRI.

Intravenous Pyelogram (IVP):

Rapid sequence IVP is done for renal artery stenosis by injecting a contrast solution through vein into circulatory system.

Cystoscopy:

It is an endoscopy of the urinary bladder via the urethra carried out with a cystoscope. It can be flexible or rigid cystoscope.

Radionuclide Studies:

Radionuclide studies can measure renal function.

- Technetium diethylenetriamine pentaacetic acid (^{99m}Tc — DTPA) (dynamic renal scan) is freely filtered by the glomerulus and not reabsorbed and is used to estimate GFR.
- Technetium dimercaptosuccinate (^{99m}Tc — DMSA) is bound to the tubules and provides an assessment of functional renal mass.
- Radioiodinated (^{131}I) orthoiodohippurate is secreted into the renal tubules and assesses renal plasma flow (RPF).

RENAL BIOPSY-

To determine the kind and severity of renal disease, as well as the prognosis and treatment requirements, a renal biopsy is performed. To achieve precise needle insertion into a kidney pole, the treatment is carried out transcutaneously with ultrasonography or contrast radiography as the guiding technologies. Evaluation of the specimen using immunohistology, electron microscopy, and light microscopy may all be necessary.

ANEMIA IN CKD

Anemia is a condition marked by a decreased mass of red blood cells (RBCs) and hemoglobin (Hb) content in the blood, which has an impact on the body's ability to transfer oxygen to its tissues and organs. since direct measures of red cell mass are laborious and difficult to obtain. Anemia is described as a drop below the normal range for hemoglobin concentration and hematocrit (Hct); these levels depend on gender, race, and age; anemia is more common in elderly persons. Anemia is defined relatively arbitrarily. Anemia is characterized by a Hb value below 12.0 g/dL for adult women and 13.0 g/dL for adult males, according to the World Health Organization (WHO). This definition has been adopted in the clinical practice guideline for anemia in chronic kidney disease, which was created by Kidney Disease: Improving Global Outcomes (KDIGO).[(15)]

The most common form of anemia in CKD is a normochromic, normocytic, or slightly hypochromic anemia, with insufficient production of erythrocytes. The cause is multifactorial, with contributors such as relative EPO deficiency, blood loss, iron deficiency, chronic inflammation, hemolysis, drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), and other factors, which may include circulating inhibitors of erythropoiesis. The preponderance of evidence has demonstrated that EPO deficiency is the major cause of anemia in those with CKD. If the severity of the anemia is substantially worse than anticipated, if larger than typical doses of rhEPO are required, or if leukopenia or thrombocytopenia are present, it is important to rule out other contributory reasons.[(22)]

Anemia is relatively uncommon in earlier stages (stages G l-3) of CKD. Anemia is often not a frequent or severe consequence of CKD until the GFR is below

30 mL/min/1.73 m2, while the prevalence starts to considerably rise with an eGFR below 60 mL/min/173 m2. Patients with CKD and diabetes mellitus typically get anemia sooner in the course of the disease and with greater severity. In general, Hb measurement screening for anemia should start at CKD stage G3. The majority of the time, serum EPO concentrations are on par with or greater than those in individuals without CKD. In mild to severe CKD, mean serum EPO concentrations rise with increasing anemia, but not enough. When the GFR falls below around 40 mL/min/l.73 m2, mean serum EPO concentrations start to depend more on GFR than on Hb concentration. The ability to produce EPO is preserved even with advanced CKD, and some degree of responsiveness to lower Hb is retained.[(22)]

HYPERTENSION AND CKD

In between 80 and 85 percent of CKD patients, hypertension is prevalent[(23)]. Patients with renal disease with a normal glomerular filtration rate (GFR) have a higher incidence of hypertension, which rises further as the GFR declines. For instance, data from the Modification of Diet in Renal Disease Study revealed that when the GFR decreased from 85 to 15 mL/min per 1.73 m2, the incidence of hypertension increased steadily from 65 to 95 percent [(24)]. A variety of factors can contribute to the increased prevalence of hypertension in patients with CKD:

- Sodium retention is generally of primary importance, even though the degree of extracellular volume expansion may be insufficient to induce edema.
- A portion of the hypertension that remains after the return to normovolemia is frequently caused by increased RAAS activity, especially in patients with vascular illness since renal ischemia is a strong stimulant for renin production. Scarring-induced regional ischemia could potentially be at play.

- Kidney disease can occur as a result of hypertension or as a contributing factor (for example, hypertensive nephrosclerosis).
- Increased sympathetic nervous system activity may lead to hypertension [25]. The absence of the afferent signal in individuals who have had bilateral nephrectomy suggests that it may originate in part from the failing kidneys.
- The increase in intracellular calcium due to secondary hyperparathyroidism can cause vasoconstriction and hypertension [26]. The continuous injection of an active vitamin D analogue can lower intracellular calcium and systemic blood pressure by decreasing parathyroid hormone release.
- Blood pressure may rise as a result of erythropoietin therapy; the extent of this impact depends on how high the hematocrit was raised.
- Patients with uremia have been shown to have impaired nitric oxide production and endothelium-mediated vasodilatation [27]. Although the exact processes are unknown, several possible reasons include decreased nitric oxide availability brought on by an increase in oxidative stress or nitric oxide synthase uncoupling brought on by cofactor insufficiency.

Two more factors may be significant in addition to those that might increase mean arterial pressure:

- Patients with end-stage renal disease (ESRD) are more prone to develop isolated systolic hypertension and an increase in central pulse pressure [28]. Although the exact cause of this is unclear, increasing aortic stiffness most likely plays a significant part.
- Patients with CKD could not experience the typical nighttime drop in blood pressure (these people are referred to as "nondippers"), which could be a risk factor for hypertensive problems [29].

DIABETES AND CKD:

In the United States and around the world, diabetes is the main contributor to end-stage renal disease (ESRD) and chronic kidney disease (CKD). The etiology of diabetic kidney disease is diverse and complicated, with several overlapping causal routes. It is unknown if the natural course and pace of development of diabetic kidney damage vary depending on the type of diabetes. The great majority of persons with type 2 diabetes get the condition after the age of 40, and additional variables such as age-related renal senescence and hypertension can play a variable role in kidney function decrease. In addition, type 2 diabetes can be asymptomatic for years, resulting in a delay in diagnosis; therefore, the true time of onset of the hyperglycemic exposure is usually unknown.

Although previously rare, type 2 diabetes among youth is now common and is a well-recognized result of the obesity pandemic. Youth-onset type 2 diabetes appears to result in CKD complications earlier and with a more rapid rate of progression than with youth-onset type 1 diabetes. Among patients with diabetes, risk factors for diabetic kidney disease include older age, African American or American Indian ancestry, Hispanic ethnicity, low socioeconomic status, obesity, smoking, poor glycemic and blood pressure control and genetic factors.

PATHOGENESIS

The etiology of diabetic kidney disease is diverse and complicated, with several overlapping causal pathways.[30] Advanced glycation end products (AGE) and reactive oxygen species are produced as a result of hyperglycemia. A variety of mediators for cellular damage are produced as a result of these abnormal metabolic

products activating intercellular signaling for proinflammatory and profibrotic gene expression [31,32]. While hyperglycemia unquestionably plays a crucial role, pathogenic processes may also be triggered by hyperinsulinemia and insulin resistance. Ultimately, the main mediators of kidney tissue injury include changes in *glomerular hemodynamics, inflammation, and fibrosis.*

1. **Glomerular Hemodynamics** –

The diabetic milieu activates the renin-angiotensin-aldosterone system (RAAS) and numerous other downstream mediators, triggering kidney hypertrophy, increased renal plasma flow (RPF), and increased filtration fraction (FF), which together result in an abnormally elevated glomerular filtration rate (GFR) [33]. In the early stages of diabetes, "whole kidney GFR" and "single nephron GFR (SNGFR)" are increased. These states are often referred to as "glomerular hyperfiltration, [34,35] while increased RPF and FF are partly due to an increase in kidney size, they are predominantly the result of disproportionately reduced afferent versus efferent arteriolar resistance[36]. Increased circulating vasodilators, such as atrial natriuretic peptide, nitric oxide, and prostanoids, and a relative deficiency or resistance to insulin have a preferential impact on reducing afferent arteriole resistance. [34,35].By contrast, an increase in circulating vasoconstrictors, including angiotensin II, thromboxane and endothelin 1, have a greater effect on increasing efferent arteriole resistance. The imbalance in tone between afferent and efferent arterioles increases intraglomerular pressure, that over time, triggers a sclerotic response in diabetic kidney disease.[33]

Tubular function also has an impact on glomerular hemodynamics, via tubuloglomerular feedback [30]. Diabetes is associated with a decrease in sodium delivery to the macula densa. This occurs early in the course of diabetes as the proximal tubule hypertrophies and there is upregulation of the sodium-glucose

cotransporters (SGLT1 and SGLT2). Reabsorption of glucose and sodium is increased in relatively moderate hyperglycemia (>180 mg/dL), resulting in decreased sodium chloride delivery to the macula densa portion of the distal tubule.

Consequently, afferent arteriolar tone is further decreased, thereby producing increases in RPF, FF, and GFR. The impact of tubular function on progression of diabetic kidney disease is further underscored by findings that inhibition of SGLT2 results in an initial, short-term decline in estimated GFR (eGFR) but a long-term delay in kidney disease progression.[37–41] This effect is presumably due, sequentially, to decreased reabsorption of sodium and glucose in the proximal nephron, increasing distal delivery of sodium to the macula densa, restoration of tubuloglomerular feedback, and a reduction in glomerular hyperfiltration [41]. The initial decrease in eGFR after SGLT2 inhibition has been variably observed among those with an eGFR <45 mL/min/1.73 m2. Regardless of this initial eGFR decline, these drugs slow CKD progression in this population [42–44].

Further exacerbation of glomerular hyperfiltration also occurs in diabetes due to impaired autoregulatory responses of the afferent arterioles to fluctuations in blood pressure.[45] Thus, increases in blood pressure, which would normally result in protective increases in vascular tone, are transmitted along to the glomerular capillaries.

These anomalous vascular changes result in increased intraglomerular pressure and SNGFR, causing physical stress to capillary walls, podocytes, and mesangium, ultimately triggering a profibrotic response. As glomeruli become sclerosed and whole kidney GFR decreases, RPF is shunted to the remaining viable glomeruli, causing further increases in SNGFR of the less damaged glomeruli. Numerous studies in type 1 and type 2 diabetes have subsequently demonstrated an association between

elevated estimated GFR (eGFR) and worsening albuminuria[34], although a direct link between hyperfiltration and worsening eGFR has not yet been demonstrated.

Glomerular hyperfiltration — Hyperfiltration can be defined at the level of the single nephron, wherein the ratio between GFR and effective RPF (i.e., FF) is elevated due to either altered glomerular hemodynamics or glomerular damage with hypertrophy of remnant nephrons [34,45,46].

2. **Innate immunity, oxidative stress, and inflammation** –

Innate immunity is an increasingly recognized contributor to the pathogenesis of diabetic kidney disease. Integral to the innate immunity are oxidative stress and inflammation (figure no.4). Hyperglycemia as well as insulin resistance and dyslipidemia cause increased formation of AGE, which, upon binding to AGE receptors (RAGE) located on multiple cell types in the kidney, induces production of numerous cytokines (tumor necrosis factor [TNF], interleukin 6 (IL-6), IL-1beta) via activation of nuclear transcription factors, such as NF-kappa B.[47,48] A similar signaling pathway occurs via stimulation of toll-like receptors by exposure to hyperglycemia and damaged cellular components (as occurs with oxidative stress). Oxidative stress and inflammation are tightly intertwined, creating a vicious cycle wherein one process begets the other [32,49].

Macrophage infiltration is a hallmark of diabetic kidney disease, the magnitude of which correlates with worsening disease [50,51]. Macrophages can be recruited and activated by hyperglycemic stress, angiotensin II, oxidized low-density lipoproteins, AGE, and kidney injury molecule 1.[52] The result is increased oxidative stress and production of injurious cytokines including transforming growth factor (TGF)-beta and platelet derived growth factor. Macrophages are also a rich source of TNF-alpha, a pleiotropic cytokine resulting in renal hypertrophy, podocyte and

tubular epithelial cell injury, and the triggering of a cascade of other cytokines [50,53]. Hyperglycemia also results in increased shunting of glucose through non-glycolytic pathways such as the polyol pathway, which increases oxidative stress. Protein kinase C (PKC) is also activated by a hyperglycemic environment, resulting in decreased production of endothelial nitric oxide synthase (eNOS) and increased levels of the endothelin 1 and vascular endothelial growth factor (VEGF), which promote endothelial instability and NF-kappaB stimulated cytokine production.

Mesangial cell hypertrophy and matrix accumulation, hallmarks of diabetic glomerulosclerosis, are mediated by the transforming growth factor-beta (TGF-beta) system [54,55]. TGF-beta production by the mesangial cell is activated by a hyperglycemic environment and angiotensin II and has been found to not only trigger glomerular extracellular mesangial matrix production but also to decrease the production of matrix metalloproteinases, which are responsible for keeping extracellular matrix in check through degradation [54]. A primary mediator of TGF-beta on mesangial expansion is connective tissue growth factor (CTGF); however, CTGF can also be directly stimulated by hyperglycemia, mechanical strain, and AGE.[56] Vascular proliferation and endothelial permeability are increased in diabetic kidney disease and are thought to be mediated by VEGF [57], particularly when accompanied by diabetes-induced downregulation of endothelial nitric oxide production [58].

3. **Interstitial fibrosis and tubular atrophy (IFTA)** –

As diabetic kidney disease progresses, there is a clear relationship between the degree of interstitial fibrosis/tubular atrophy (IFTA) and the decline in eGFR.[59] Hyperglycemia results in shunting of glucose through the hexosamine pathway and subsequently increased production of TGF-beta and plasminogen activator inhibitor 1

(PAI-1).[60] Damage to the proximal tubular cell from AGE, angiotensin II, and albuminuria also results in increased TGF-beta with the consequent conversion of pericytes into myofibroblasts (epithelial to mesenchymal transformation), infiltration of macrophages, and an excess of collagen and fibronectin deposition.[30,61]

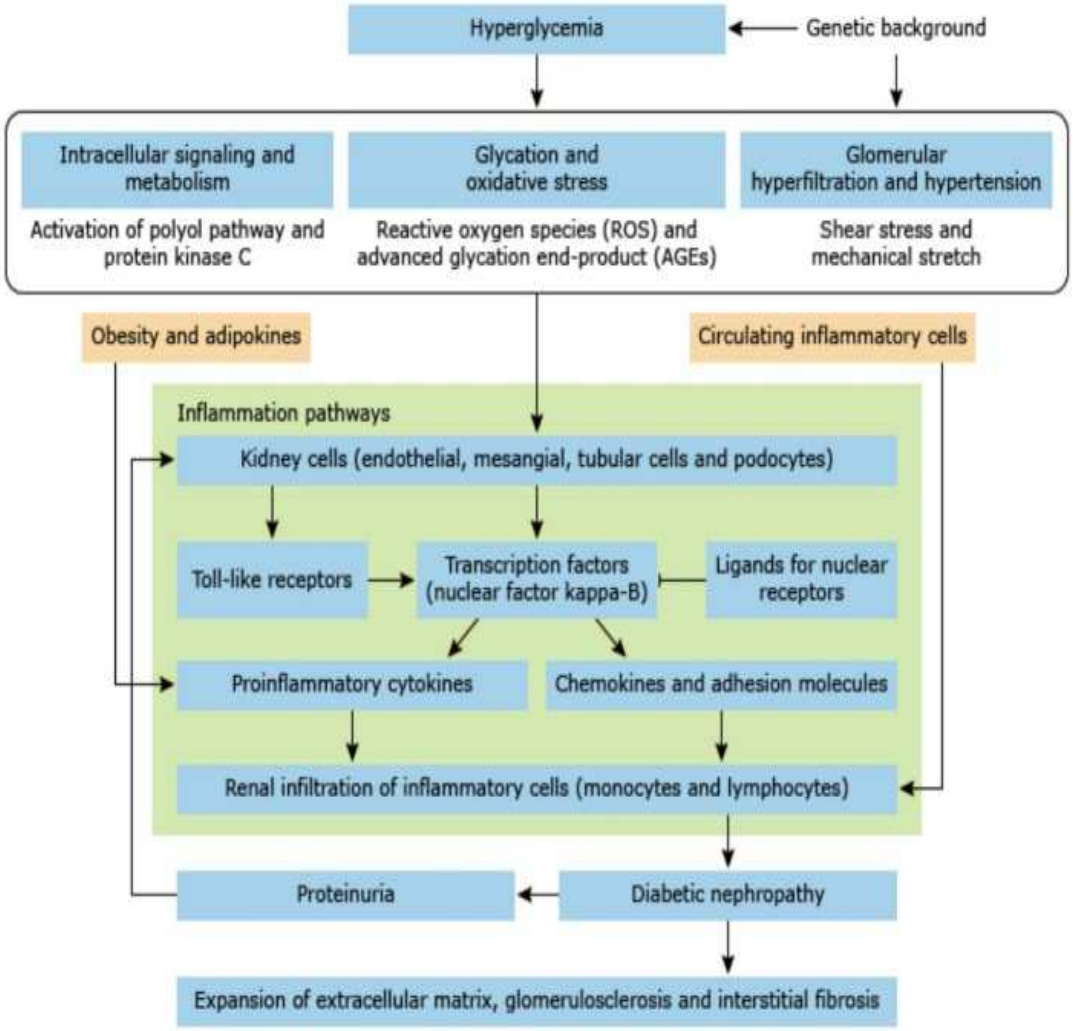


Figure no.4 Inflammation and the pathogenesis of diabetic nephropathy[47]

NEUTROPHIL TO LYMPHOCYTE RATIO (NLR)

Definition:

The NLR is simply the number of neutrophils (ANC) divided by the number of lymphocytes(ALC)

Calculation: $$NLR = \frac{\text{absolute neutrophil count}}{\text{absolute lymphocyte count}}$$

Normal range: 0.78 and 3.53[62]

In recent years, NLR used as a potential new marker of subclinical inflammation [63]. Neutrophils, the active nonspecific inflammatory mediator, serve as the body's first line of defense, while lymphocytes are the regulating or protective component of inflammation. Under physiological stress, the number of neutrophils tends to increase whilst the number of lymphocytes decreases. These changes can be measured by NLR an easy-to-compute ratio, and can be linked to how much physiological stress is present. NLR is a novel marker of chronic inflammation that shows a balance between these two interdependent immune system components[64].

NLR was first demonstrated as a useful parameter after a correlation of a relationship between the neutrophil lymphocyte ratio to reactions of the immune response was noted.[65] In a recent study, 95% of healthy adult subjects had a ratio between 0.78 and 3.53[62]. The first study to demonstrate that pretherapeutic NLR can be used as a predictor of chemotherapy sensitivity to thoracic esophageal cancer was demonstrated by Hiroshi Sato, Yasuhiro Tsubosa, and Tatsuyuki Kawano in a 2012 study published in the World Journal of Surgery journal.[66]

Zahorec R. et al in their study population of 90 ICU oncological patients, observed rapid serial changes in white blood cell populations, as a response of the immune system to surgical stress, sepsis or systemic inflammation and also observed a correlation between the severity of the clinical course and the grade of neutrophilia and lymphocytopenia. NLR reflects the amount of physiologic stress and therefore they also suggested the term: "neutrophil-lymphocyte stress factor", as a ratio of neutrophil to lymphocyte counts, which can routinely be used in clinical ICU practice in intervals of 6-12 and 24 hours. They also formed the NLR stress-o-meter to provide a general concept of NLR interpretation which may vary depending on specific patient population and disease state.[65]

Table no. 4: The correlation between NLR and physiological stress levels[65]

Neutrophil Lymphocyte Ratio	Physiological stress level
1 – 3	Normal
4 – 5	-
6 – 8	Mild
9 – 18	Moderate
>18	Severe

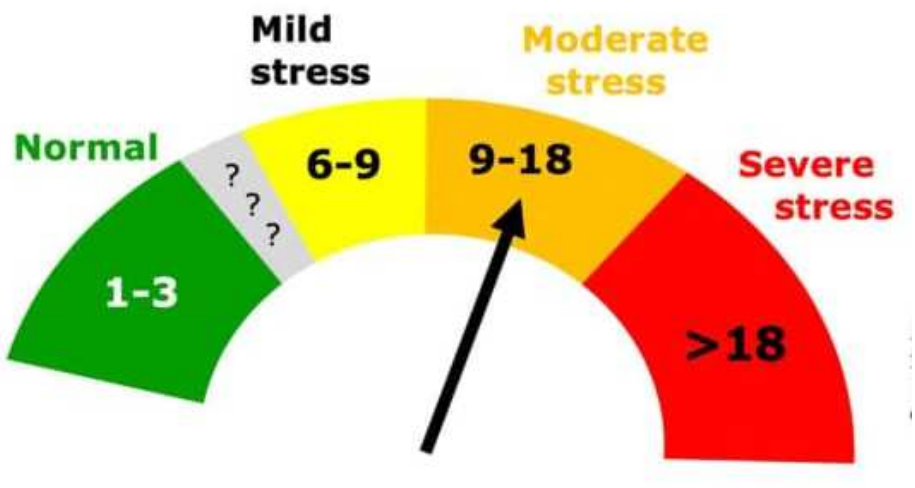


Figure no.5 NLR stress-O-meter [(65)]

NLR can act as a red flag alerting of a dysregulated immune system, whether from inflammation, malignancy or other causes. Critically ill patients will often have an NLR of 9 or higher. NLR tends to increase rapidly following acute physiologic stress (<6 hours). NLR performed better than standard white blood cell count in determining physiological stress, but it has not been proven to have any differentiating properties, for example differentiating hemorrhagic shock from septic shock. Limitations of the NLR include a direct increase if the patient is under exogenous steroid therapy, or if the patient suffers from an active hematological disorder that affects cell count.[(65)]

Tsai et al. had shown that NLR strongly correlated with the risk of ischemic CVDs.[(67)] An increased NLR is associated with a poor prognosis of various cancers, such as esophageal cancer or advanced pancreatic cancer.[(68)]NLR can be used as a prognostic marker for COVID-19 given the significant difference in NLR between those who died and those who recovered from COVID-19.[(69)] Interestingly, NLR has been found to have a positive relation with not only the presence but also the severity

of metabolic syndrome.[70] A study by Imtiaz et al. has suggested that chronic diseases such as hypertension and diabetes have a significant association with systemic inflammation, as reflected by NLR.[71] Now it has been proposed as marker of inflammation in patients with CKD.[12]

PLATELET TO LYMPHOCYTE RATIO (PLR)

Definition:

The PLR is simply the number of platelets divided by the number of lymphocytes.

Calculation: $PLR = \frac{\text{absolute platelet count}}{\text{absolute lymphocyte count}}$

Normal range: 61 to 239[72].

Platelets play a key role in atherosclerosis, atherothrombosis, and the pathogenesis of inflammation.[73,74] However, platelet count, platelet distribution, and platelet/lymphocyte (P/L) ratio are indicators of poor prognosis in systemic inflammatory diseases, including atherosclerotic cardiac disease and malignancies [73,74]. Physiological ageing does not cause significant changes in platelet count. However, the functions of platelets change and a procoagulant state may develop[75]. Additionally, significant changes in platelet function could occur and activation of platelets plays a major role in the cardiovascular damage observed during the progressive course of CKD.[76] Similar to the N/L ratio, the P/L ratio is used as an inflammation marker. However, there are limited data regarding its use in patients with CKD. Binnetoglu et al. demonstrated a significant correlation between P/L ratio and proteinuria in patients with stage 3–4 CKD [77]. Furthermore, Turkmen et al.

reported the P/L ratio being a strong indicator of inflammation in patients with ESRD.[12]

In a study by Peiyuan li et al. on 611 patients they found PLR or NLR was positively correlated with hs-CRP in non-dialysis patients with ESRD. The NLR might be better for identifying inflammation than PLR in this population.[78]

Orcun altunoren et al, in their study of 740 patients with CKD observed that NLR is an indicator of inflammation in CKD but it may not be an independent predictor of CKD progression except that the CKD is in a more advanced stage and reflects the associated inflammation.[79]

Erhan Tatar and et al. Conducted a study on 165 patients with stage 3-5 CKD observed that NLR was inversely correlated to the renal function parameters. eGFR and serum albumin concentration were negatively linked with the basal N/L ratio. They also noticed a large elevation in P/L ratio in the dead patients, but no connection between P/L ratio and either mortality or the need for renal replacement treatment could be found. Finally, they came to the conclusion that, due to its ease of use, low cost, and widespread usage in the fields of nephrology and gerontology, the N/L ratio is an essential measure in predicting death in senior patients with stage 3-5 CKD.[80]

Wadgaonkar Udit Rajendra with his co-authors in their case control study on 64 cases found the correlation value between blood urea, serum creatinine and NLR among cases showed a very weak positive correlation and suggested NLR to be a simple and reliable indicator of worsening renal function in CKD.[81]

The results of study by Khandare et al. on CKD patients have shown that there was a significant correlation between NLR and DN, implying that inflammation and endothelial dysfunction could be an integral part of DN. NLR was significantly and independently raised in patients with type 2 DM having increased albuminuria. NLR served as a predictor of worsening renal function.[8]

METHODOLOGY

STUDY SITE: This study was conducted in the General Medicine Department and Department of Nephrology, Dr. Prabhakar Kore Hospital and Medical Research Centre, KLE University, Belagavi.

STUDY DESIGN: A cross sectional study.

STUDY DURATION: The data for the present study was collected between January 2021 TO December 2021, for a period of one year.

SAMPLE SIZE: 100

Sample size - calculated by formula

$$\text{Sample size} = \frac{z^2 pq}{d^2}$$

Where, z2- standard normal variant at a 95% degree of confidence = 1.96

p - Expected proportion from population prevalence of CKD. Prevalence of CKD in this population is 46%.(82)

q = 100-p

d - margin of error = 10%

With a confidence level 95%, P = 46% and d = 10% the sample size is 96

To get confirmative results the sample size was increased to 100.

SAMPLE METHOD: Cross sectional study, all consecutive patients fulfilling the inclusion criteria were included in the study.

STATISTICAL METHODS: The information collected from the patients was noted in master chart. Multiple logistic regression was carried out. Analysis of the data was done using statistical software version SPSS 20.00, Descriptive statistics including frequency, percentage, mean and SD, Chi-square for independence, Mann-Whitney U test and Spearman's rank method for relationship were used and statistical significance was set at 5% level with $p<0.05$ considered significant.

INCLUSION CRITERIA

- All patients diagnosed with chronic kidney disease.
- Age of the patient more than 18

EXCLUSION CRITERIA

- Acute kidney injury
- Bacterial infection
- Blood or platelet transfusion in past 1 month.
- Chronic liver disease.
- History of diseases causing thrombocytopenia

ETHICAL CONSIDERATIONS: The present study was approved by the Institutional Committee of Human Ethics. Informed written consent was obtained from all the subjects included in the study. All the subjects participating in the study

were informed about the risks and benefits of the study. We maintained the study participant's confidentiality.

DATA COLLECTION TOOLS: All the data that was collected was documented in a study proforma.

METHODOLOGY:

- Diagnosis and Staging of Chronic kidney disease was defined according to KDIGO criteria. eGFR was calculated by using the Cockcroft-Gault formula. After taking informed consent, patient's details and a detailed clinical history were obtained.
- All patients were clinically examined including general physical examination, examination of cardiovascular system, respiratory system, per abdomen and nervous system for the signs and symptoms of CKD.
- After obtaining informed consent, about 6ml of blood was drawn to perform investigations.

Investigations performed on the patient are

- Sr. Creatinine.
- Neutrophils
- Lymphocytes
- Platelets
- Hemoglobin

FOLLOW UP: No follow-up was done as the present study was a cross sectional study.

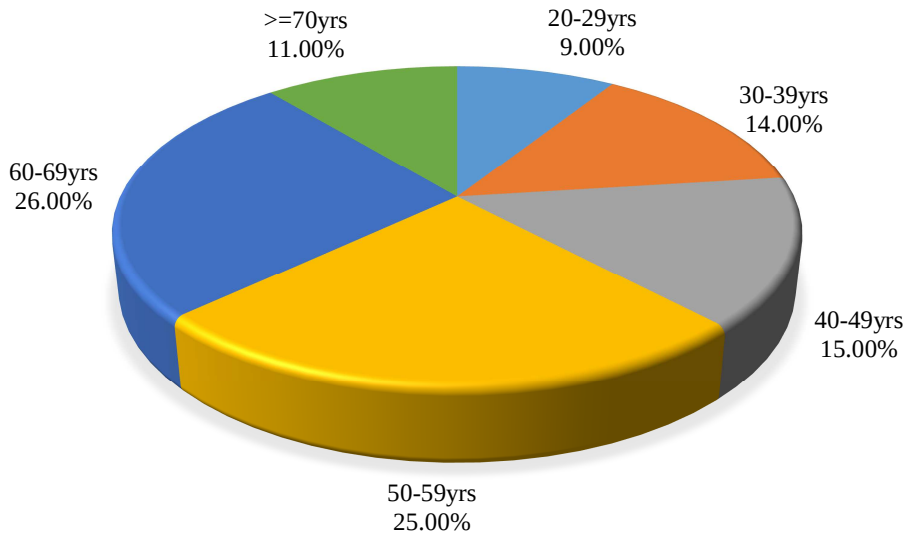
RESULTS

The present study was conducted in the department of General Medicine KLE's Dr. Prabhakar Kore hospital and MRC Belagavi from January 2021 to December 2021. A total of 100 cases were studied and the findings observed are tabulated as below

Table 5: Distribution of patients Age wise:

Age groups	No of patients	% Of patients
20-29yrs	9	9.00
30-39yrs	14	14.00
40-49yrs	15	15.00
50-59yrs	25	25.00
60-69yrs	26	26.00
>=70yrs	11	11.00
Total	100	100.00
Mean age	52.43	
SD age	15.05	

GRAPH NO. 1: DISTRIBUTION OF PATIENTS AGE WISE

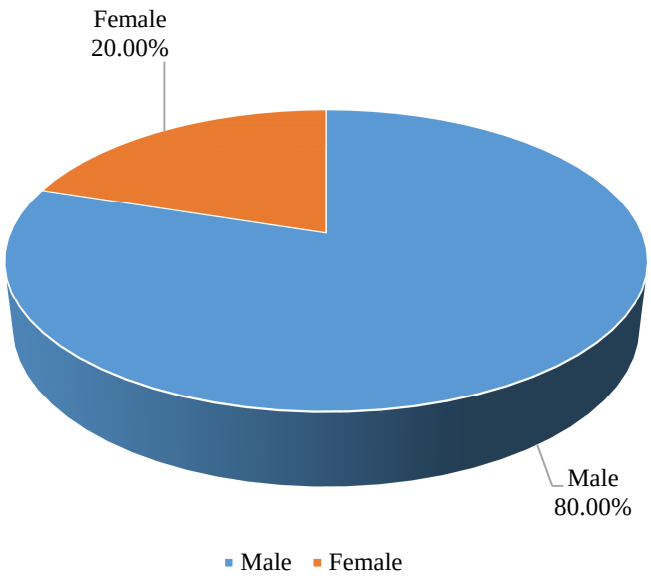


In our present study of 100 patients the age ranged from 20 years to 81 years. Youngest patient was 20 years old and the oldest was 81 years. We observed a greater number of patients in age group of 60-69 years i.e., 26 patients (26%),50-59 years 25 patients (25 %) and there were total 38 patients (38%) between the age of 20 to 49 years. Only 11(11%) patients were there in age group of more than 70 years. The mean age of patients present with CKD was 52.43years ± 15.05 years.

Table no. 6: Sex wise distribution:

Gender	No of patients	% Of patients
Male	80	80.00
Female	20	20.00
Total	100	100.00

GRAPH NO. 2 : SEX WISE DISTRIBUTION



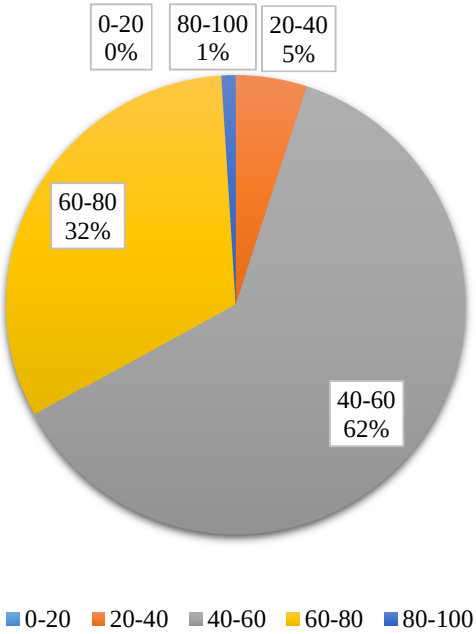
In our study of 100 patients 80 patients were male (80%) and females were only 20 (20%) accounting for male to female ratio of 4:1.

Inference: We observed male preponderance in present study.

Table no.7: Weight wise distribution of patients:

Weight in kg	No. of patients	Percentage
0-20	0	0
20-40	5	5
40-60	62	62
60-80	32	32
80-100	1	1

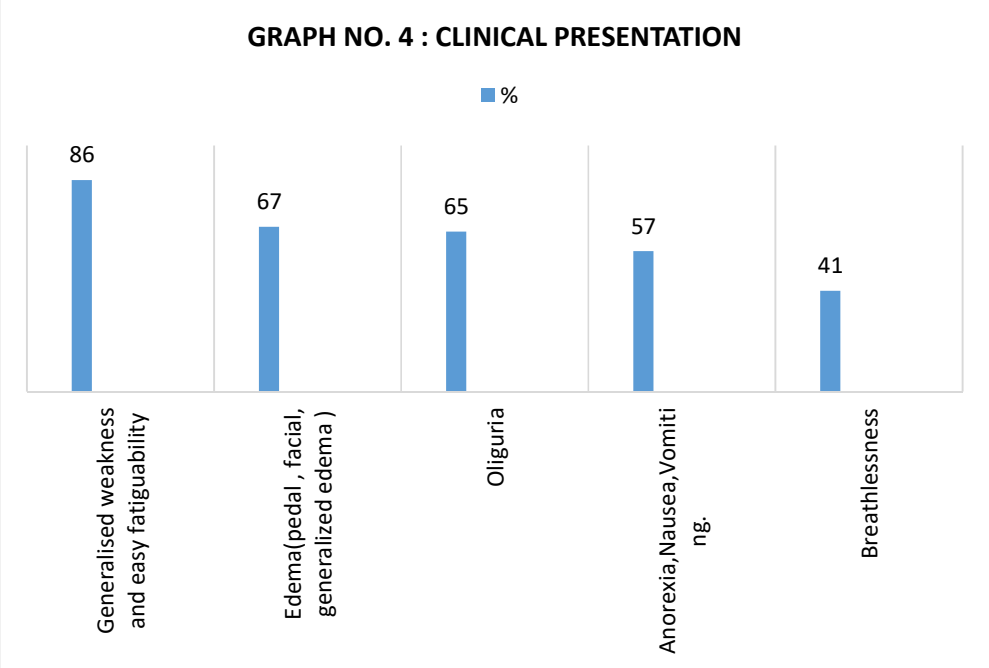
GRAPH NO. 3: WEIGHT WISE DISTRIBUTION



Majority of our patients were weighing between 40-60 kg. i.e., 62 (62 %), 32 (32%) were weighing between 60-80 kg, 5 (5%) patients were weighing between 20-40 kg. Only one patient weighing between 80-100 kg.

Table no. 8: Clinical presentation:

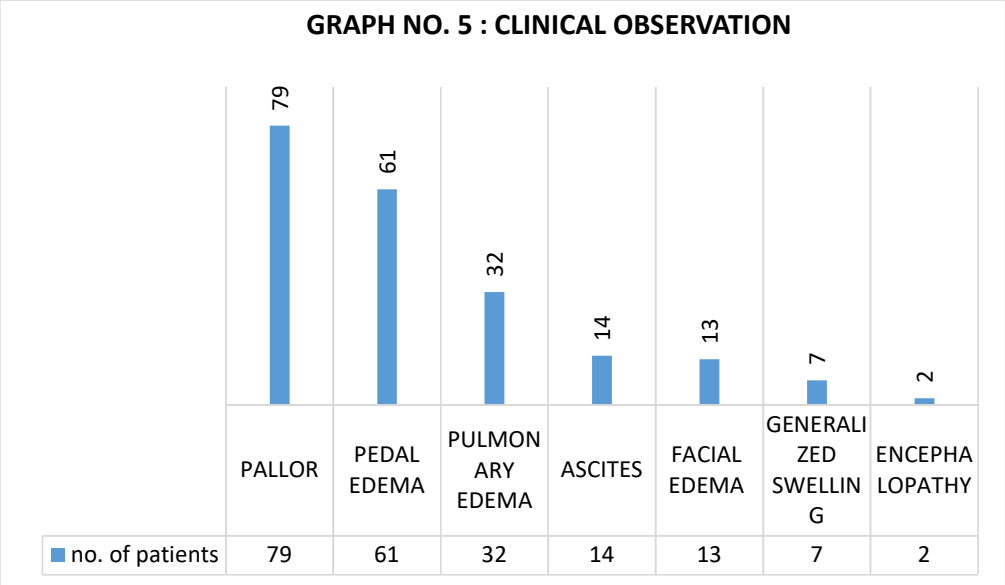
Symptoms	No of patients	% Of patients
Generalized weakness and easy fatiguability	86	86
Edema (pedal, facial or generalized edema)	67	67
Oliguria	65	65
Anorexia, Nausea, Vomiting,	57	57
Breathlessness	41	41



We observed in patients with CKD varied presentations. The most common presentation was generalized weakness and easy fatiguability 86 (86%) patients, 67 (67%) patients had edema [pedal edema, facial edema or generalized edema], oliguria 65(65%) patients, gastro intestinal complaints (anorexia, nausea, vomiting) 57(57%) patients, breathlessness 41(41%) patients. 2 patients presented with obtunded conscious level due to uremic encephalopathy.

Table no. 9: Clinical observation:

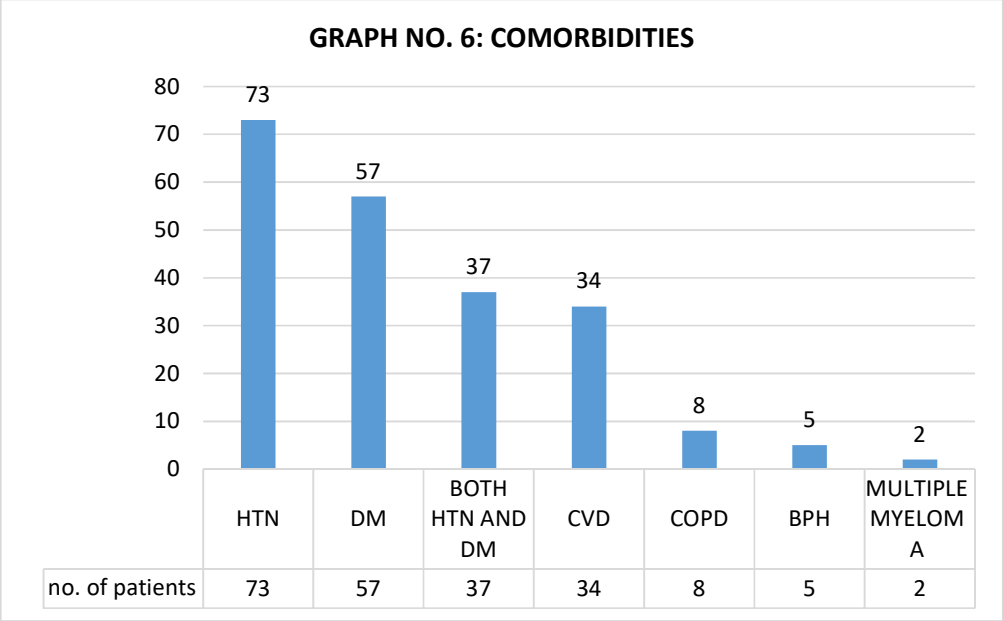
Clinical Observation	No. of Patients	Percentage %
Pallor	79	79
Pedal Edema	61	61
Pulmonary Edema	32	32
Ascites	14	14
Facial Edema	13	13
Generalized Swelling	7	7
Altered Sensorium (Encephalopathy)	2	2



In our present study of 100 patients, we found various clinical findings, the commonest was pallor 79(79%), pedal edema 61(61%), 32 patients presented with pulmonary edema picture, ascites 14 (14%), facial edema 13 (13%), generalized swelling 7 (7%) and 2 patients presented with altered sensorium due to uremic encephalopathy.

Table no. 10: Comorbidities:

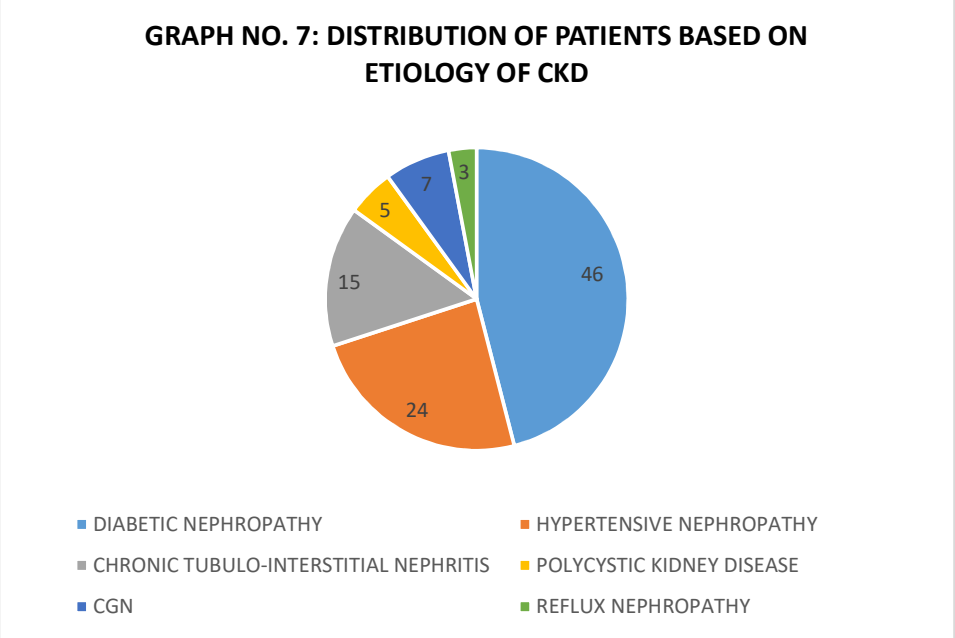
Comorbidities	Frequency
Hypertension	73
Diabetes	57
Both hypertension and diabetes	37
Cardiovascular disease (IHD -18, Left Ventricular Dysfunction- 11, DCM – 5)	34
Chronic Obstructive Pulmonary Disorder	8
BPH	5
Multiple myeloma	2



Most of our patients had hypertension 73(73%), 57(57%) had diabetes, 37 patients had both diabetes and hypertension. Cardiovascular disease present in 34 patients (34%) [IHD -18, left ventricular dysfunction- 11, DCM -5], 8 (8%) patients had COPD, 5 had BPH. 2 patients were found to have Multiple myeloma.

Table no.11: Distribution of patients based on etiology of CKD:

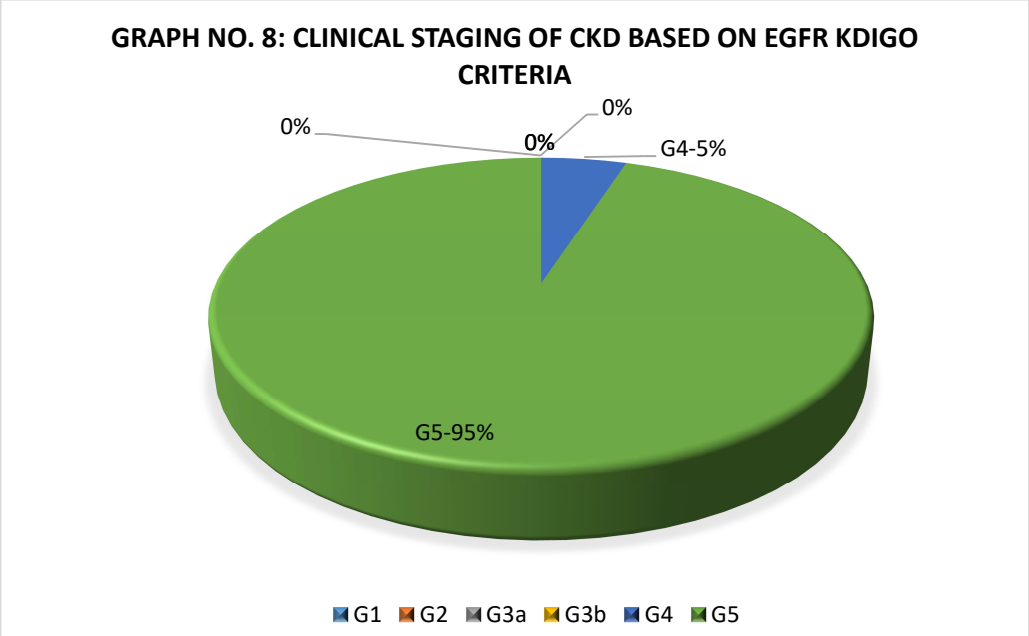
Etiology	
Diabetic nephropathy	46
Hypertensive nephropathy	24
Chronic tubulo-interstitial nephritis	15
Polycystic kidney disease	5
CGN	7
Reflux nephropathy	3



We observed the commonest cause of CKD in our patients is diabetic nephropathy 46 (46%) followed by hypertensive nephropathy 24 (24%), Chronic tubulo-interstitial nephritis 15 (15%), chronic glomerulonephritis 7 (7%), Polycystic kidney disease 5(5%) and 3 (3%) patients had reflux nephropathy.

Table no.12: Clinical staging of CKD based on eGFR KDIGO criteria:

Staging		eGFR	No of Patients	%
Stage 1	Normal or high	≥90	0	0
Stage 2	Mildly decreased	60-89	0	0
Stage 3a	Mildly to moderately decreased	45-59	0	0
Stage 3b	Moderately to severely decreased	30-44	0	0
Stage 4	Severely decreased	15-29	5	5
Stage 5	Kidney failure	<15	95	95
		Total	100	100



In our present study of 100 patients staging of CKD was based on eGFR (KDIGO criteria). Most of our patients enrolled were in stage 4 (5 patients (5%)) and stage 5 (95 patients (95%)) as depicted in above table no. 12.

Table no.13: Treatment of patients by Maintenance hemodialysis (MHD)

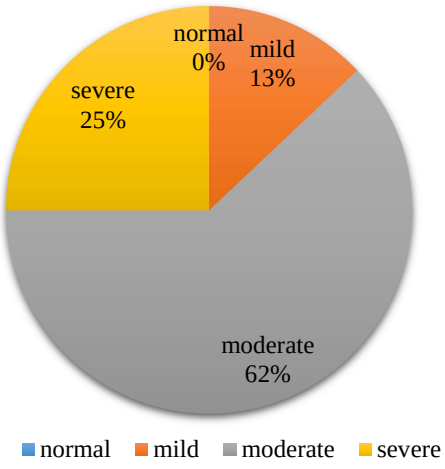
Duration (months)	No of patients	Percentage %
<12 months	16	16
13 months to 36 months	47	47
37 months to 60 months	23	23
>60 months	14	14

Table 13 shows number of patients on MHD. Most of our patients i.e., 47(47%) were on MHD from 13 to 36 months, 23 patients between 37 to 60 moths ,16 patient's less than 12 months and only 14 patients on MHD >60 months.

Table no 14: Distribution of patients based on hemoglobin percentage - WHO CRITERIA:

WHO grading	No. of patients (male, female)	Percentage
Normal (For males – 13g/dl or higher. For females 12 g/dl or higher)	0	0
Mild (For males 11-12.9g/dl For females 11- 11.9 g/dl)	13 (male 10, female 3)	13%
Moderate (8-10.9 g/dl)	62 (male 55, female 7)	62%
Severe (below 8 g/dl)	25 (male 15, female 10)	25%
Total	100	100.00

GRAPH NO. 9: DISTRIBUTION OF PATIENTS BASED ON HEMOGLOBIN PERCENTAGE

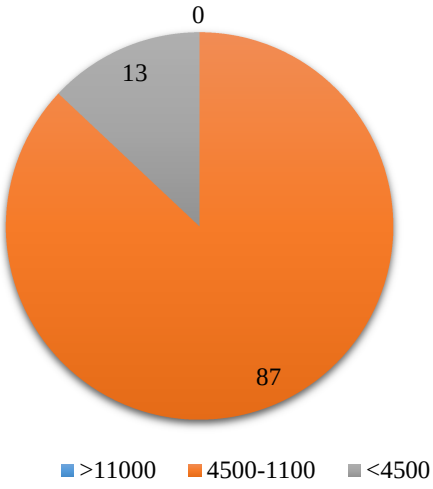


To our observation in patients of our study population majority of our patients had moderate to severe anemia (moderate 62, severe 25) and remaining 13 had mild anemia as depicted in above table.no 14.

Table no.15: Distribution of patients based on total WBC count:

WBC COUNT (cells/mm^3)	PATIENTS	PERCENTAGE
>11000	0	0 %
4500-11000	87	87%
<4500	13	13%
TOTAL	100	100%

GRAPH NO. 10: DISTRIBUTION OF PATIENTS BASED ON TOTAL WBC COUNT



Above table shows 87 patients (87%) total WBC count was between 4500 to 11000, remaining 13 had below 4500 cells/mm^3. None had above 11000 counts.

Table no. 16: Distribution of patients based on Absolute Neutrophil Count (ANC):

ANC (cells/mm^3)	No. of patients	Percentage
>7000	12	12
1500-7000	86	86
<1500	2	2

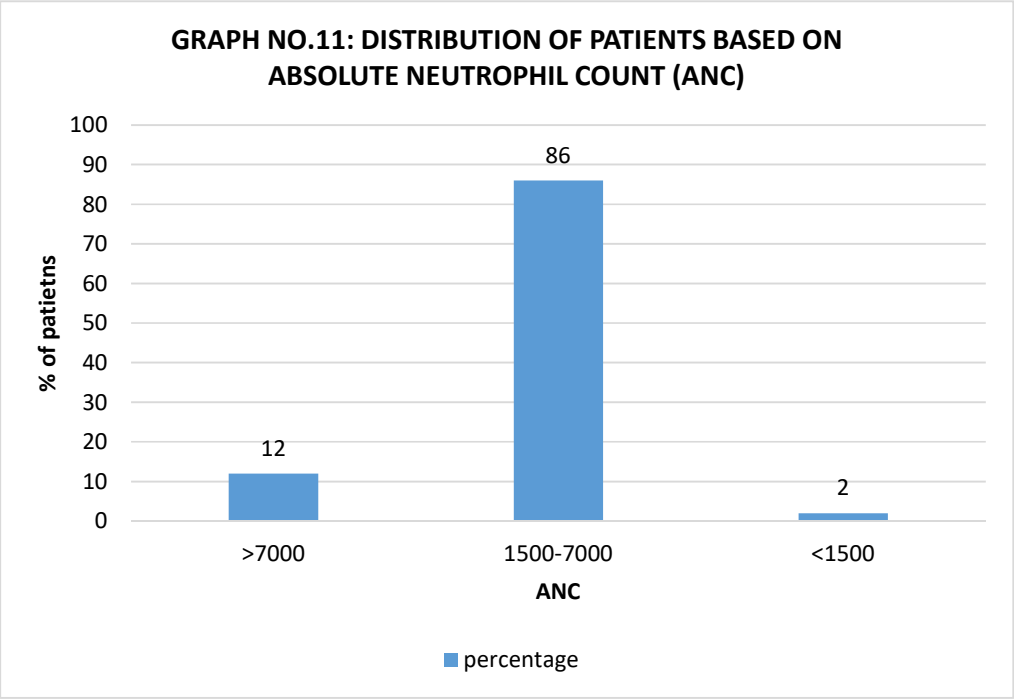
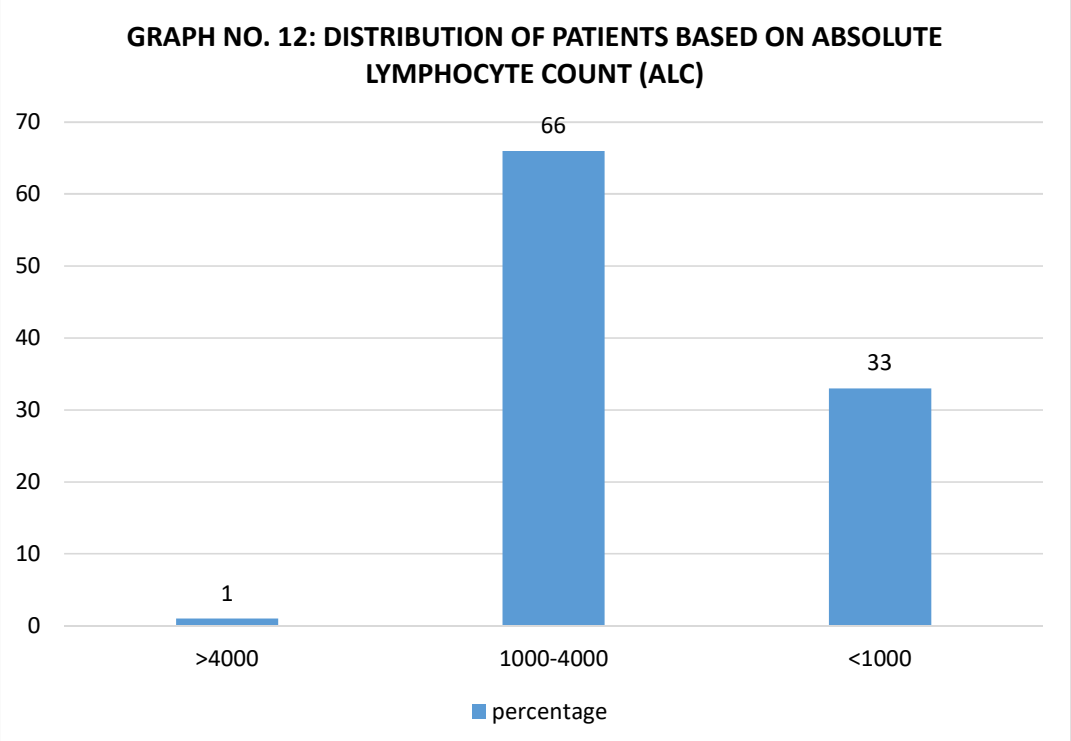


Table 16 shows most of our patients i.e., 86 (86%) had ANC ranging from 1500-7000, 12 patients had more than 7000 and only 2 patients had below 1500 cell/mm^3

Table no. 17: Distribution of patients based on Absolute Lymphocyte Count (ALC):

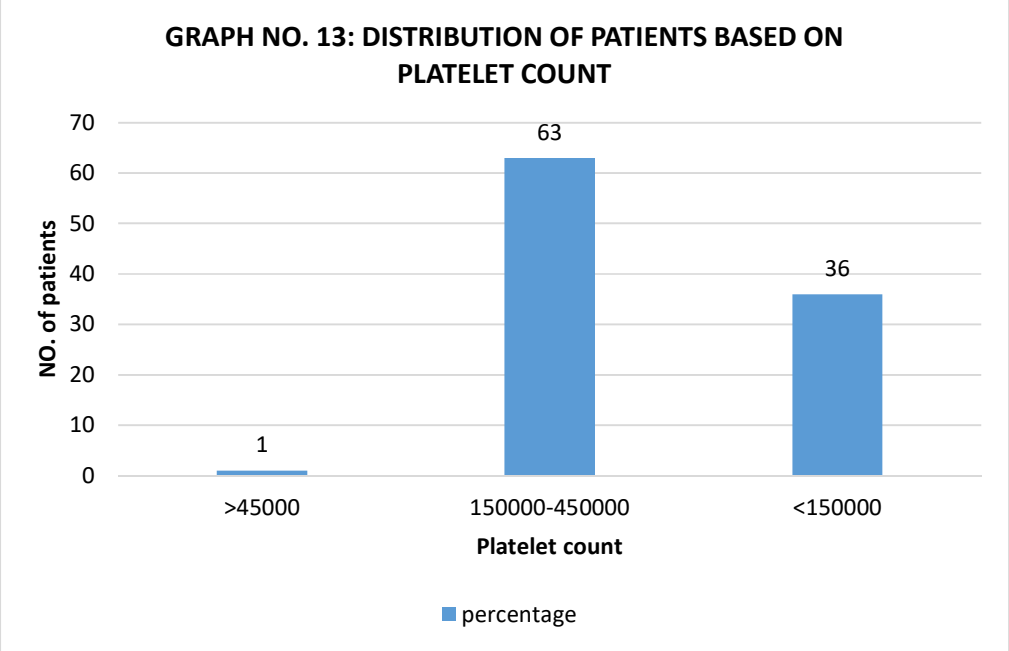
ALC (cells/mm^3)	No. of patients	percentage
>4000	1	1
1000-4000	66	66
<1000	33	33
Total	100	100%



In our 100 patients ALC ranged between 1000-4000 in 66 patients, less than 1000 in 33 patients and only 1 patient had more than 4000.

Table no. 18: Distribution of patients based on Platelet Count:

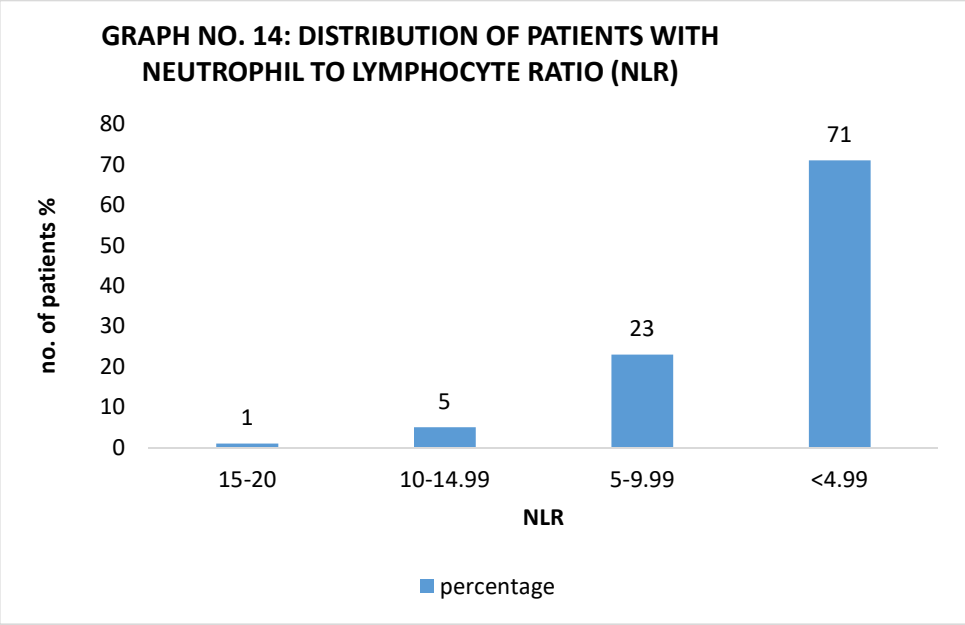
Absolute platelet count (per mm^3)	No of patients	Percentage
>4,50,000	1	1
1,50,000-4,50,000	63	63
<1,50,000	36	36
Total	100	100%



We observed 63 (63%) patients in our study had platelet count ranging between 1,50,000 to 4,50,000, 36 (36%) patients had below 1,50,000 and only one patient had count more than 4,50,000.

Table no. 19: Distribution of patients with Neutrophil to Lymphocyte ratio (NLR):

NLR	No of patients	Percentage
15-20	1	1
10-14.99	5	5
5-9.99	23	23
<4.99	71	71



Above table depicts the range of NLR and the observation made are as follows-71 patients had ratio less than 4.99, 23 patients had range of ratio from 5 to 9.99, 5 patients had 10 to 14.99. Only one patient had range between 15-20. The usual range of NLR is 0.7 to 3.2 observed by most of the workers. p value is 0.0001 which is statistically significant.

Table no. 20: Distribution of patients with Platelet to Lymphocyte ratio (PLR):

PLR	No of patients	Percentage
1500-2000	1	1
1000-1499	1	1
500-999	2	2
<499	96	96

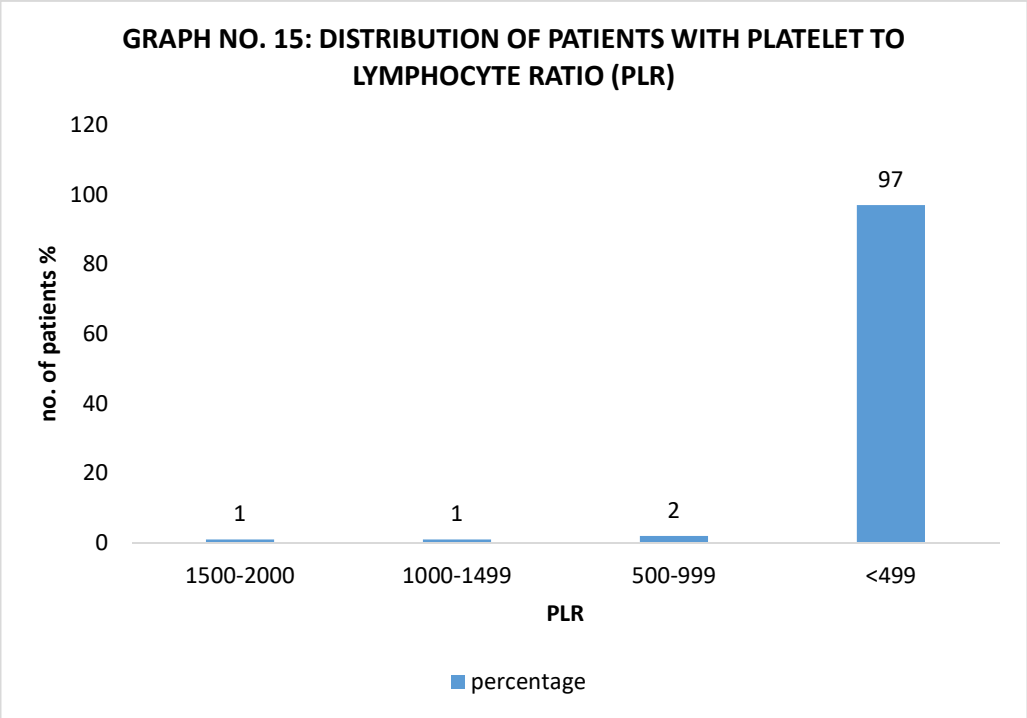


Table 20 shows PLR. Most of the patients had a ratio of <499, remaining 4 patients had a ratio as shown above. The usual range is 61 to 239. P value 0.0001 is statistically significant.

Table no. 21: Comparison of patients with etiology and NLR by Mann-Whitney U test:

Etiology	Status	Mean	Median	SD	Z-value	P-value
Diabetic nephropathy	Absent	4.27	3.34	2.90	-1.0097	0.3126
	Present	4.69	3.82	3.19		
Hypertensive nephropathy	Absent	4.58	3.68	3.21	0.2663	0.7900
	Present	4.10	3.40	2.38		
CTIN	Absent	4.59	3.72	3.09	1.0522	0.2927
	Present	3.75	3.19	2.65		
Polycystic kidney disease	Absent	4.42	3.50	3.04	-0.8382	0.4019
	Present	5.37	5.27	2.91		
CGN	Absent	4.36	3.68	2.85	0.0203	0.9838
	Present	5.85	3.00	4.96		
Reflux nephropathy	Absent	4.52	3.68	3.06	1.1012	0.2708
	Present	2.82	2.50	0.95		

Table 21 shows various etiologies and compared with NLR by Mann-Whitney U test are tabulated in the above table.

Table no 22: Comparison of patients with etiology and PLR by Mann-Whitney U test:

Etiology	Status	Mean	Median	SD	Z-value	P-value
Diabetic nephropathy	Absent	157.92	132.35	101.81	-0.9717	0.3312
	Present	218.31	149.39	298.11		
Hypertensive nephropathy	Absent	195.89	143.45	244.71	0.0646	0.9485
	Present	153.43	130.03	70.66		
CTIN	Absent	188.19	138.35	228.42	0.0048	0.9961
	Present	171.56	150.15	134.35		
Polycystic kidney disease	Absent	187.78	138.35	221.27	0.5219	0.6017
	Present	146.21	146.18	84.19		
CGN	Absent	186.15	140.72	221.36	0.2432	0.8079
	Present	179.68	110.43	147.53		
Reflux nephropathy	Absent	188.52	146.18	219.13	1.5963	0.1104
	Present	94.35	89.01	41.59		

Table 22 depicts various etiologies when compared with PLR by Mann-Whitney U test. Results obtained are shown in above table.

Table no. 23: Comparison of hemoglobin percentage with eGFR by Spearman's rank method:

Correlation between	N	Spearman R	t-value	p-value
Hb & GFR	100	-0.0028	-0.0281	0.9776

Graph no. 16: Scatter diagram showing correlation between Hb and GFR scores

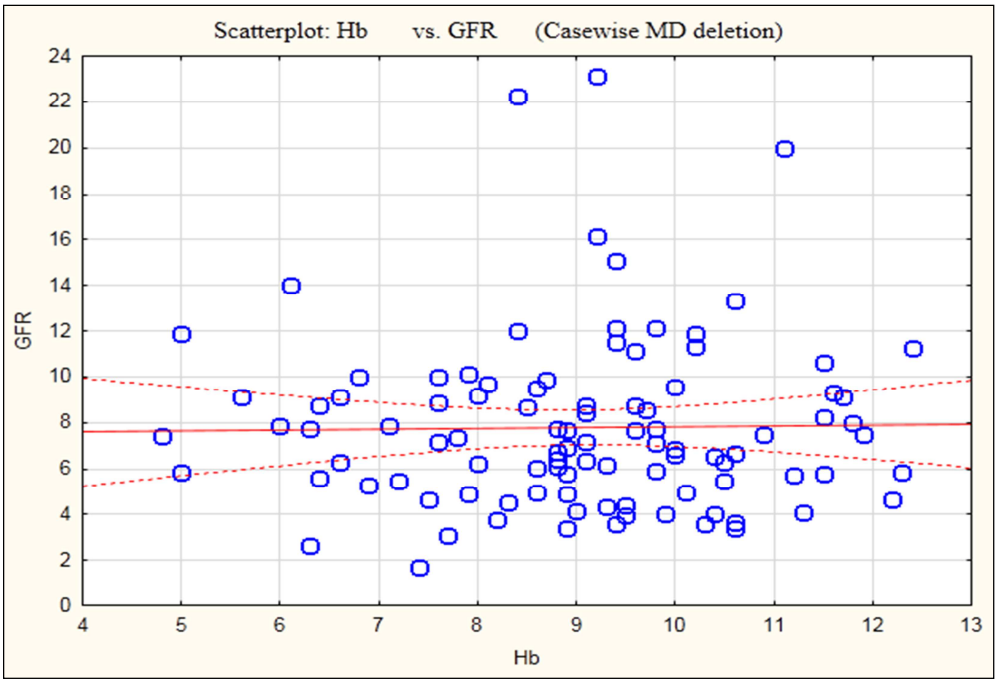


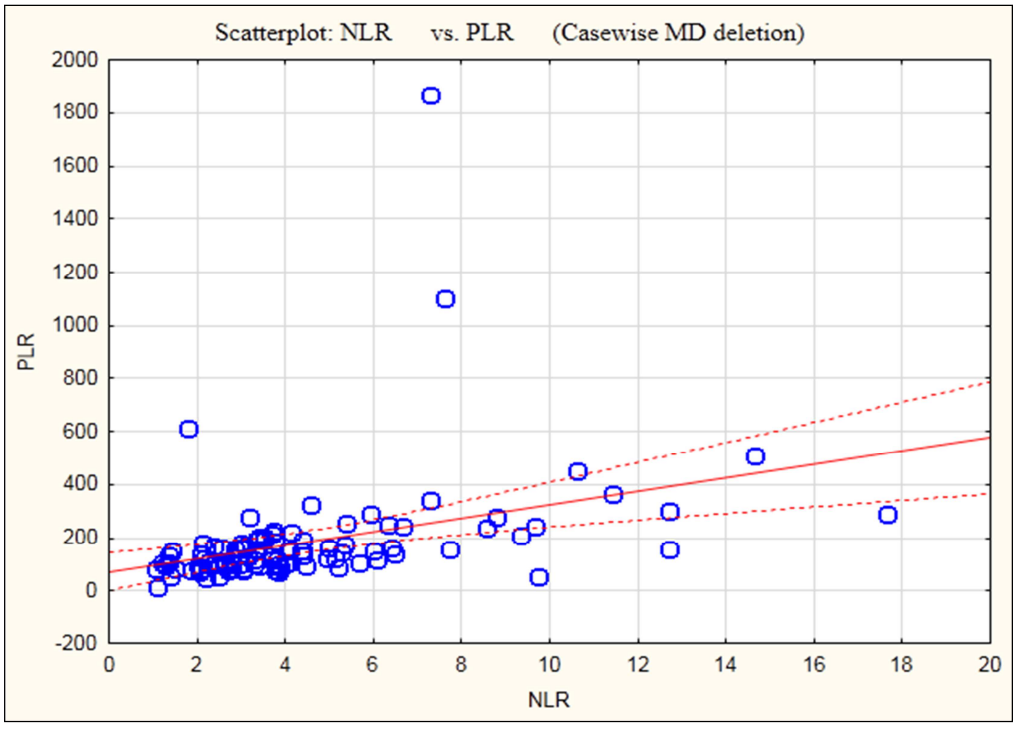
Table no.23 shows comparison between hemoglobin and eGFR and the results observed were depicted in above table.

Table no 24: Comparison between NLR and PLR by Spearman's rank method:

Correlation between	N	Spearman R	t-value	p-value
NLR & PLR	100	0.5496	6.5126	0.0001*

*p<0.05

Graph no. 17: Scatter diagram showing correlation between NLR and PLR scores

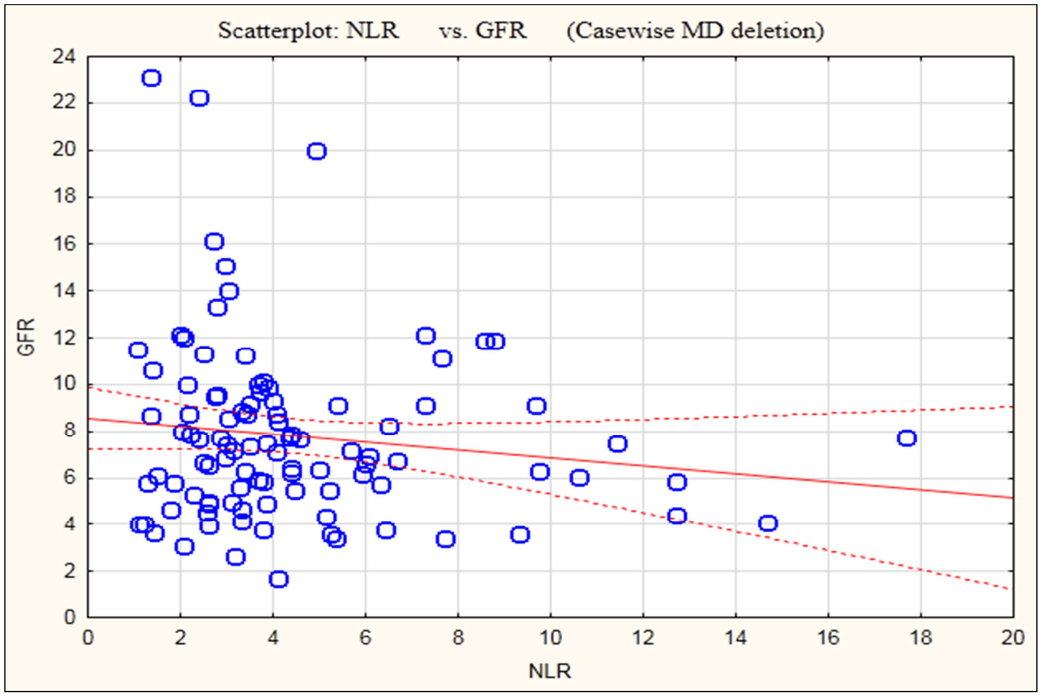


Above table reflects the comparison between NLR and PLR in 100 patients. Spearman R which was 0.5496, the t-value was 6.5126 and p value was statistically significant (0.0001)

Table no. 25: Comparison of NLR and eGFR by Spearman's rank method:

Correlation between	N	Spearman R	t-value	p-value
NLR & GFR	100	-0.1036	-1.0308	0.3052

Graph no. 18: Scatter diagram showing correlation between NLR and eGFR scores:

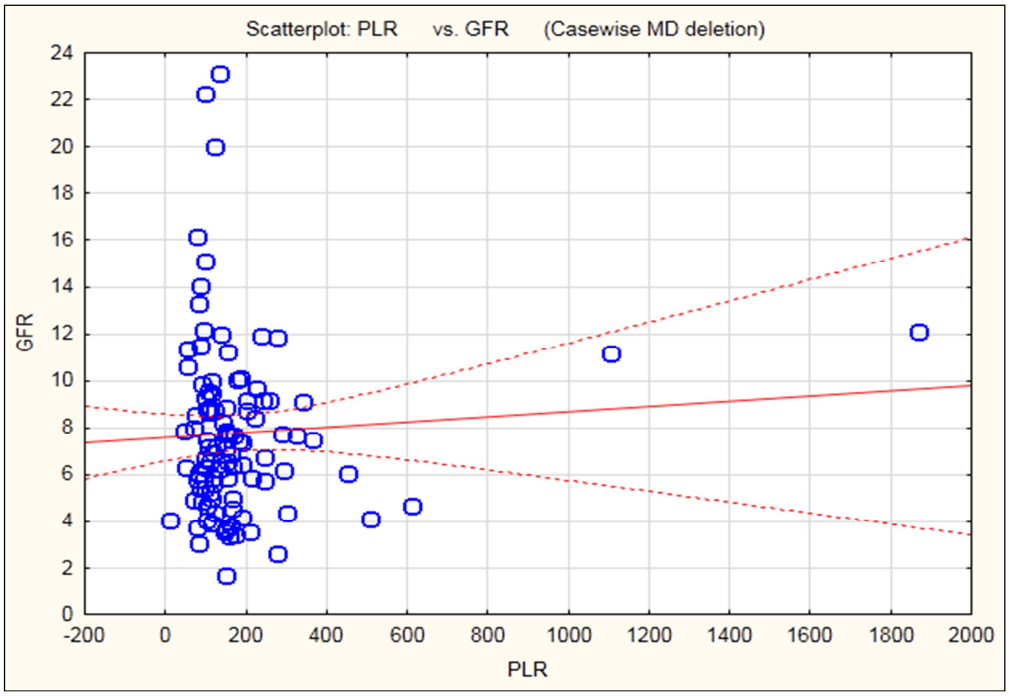


We correlated NLR to eGFR by spearman's rank method and above results were obtained. P-value was statistically insignificant.

Table no.26: Comparison of PLR and eGFR by Spearman's rank method

Correlation between	N	Spearman R	t-value	p-value
PLR & GFR	100	-0.0576	-0.5712	0.5692

Graph no.19: Scatter diagram showing correlation between PLR and eGFR scores:



Similarly, PLR was compared with eGFR and above result was obtained and P-value was statistically insignificant.

Table no. 27: Comparison of gender wise the lab parameters by Mann-Whitney U test method:

Parameters	Male			Female			U-value	Z-value	p-value
	Mean	SD	Mean rank	Mean	SD	Mean rank			
Hb	9.21	1.63	53.91	8.21	1.83	36.88	527.50	2.3439	0.0191*
WBC counts	6600.75	2145.62	49.29	7207.50	2309.59	55.35	703.00	-0.8316	0.4057
Platelet counts	181.94	76.18	50.59	168.85	63.62	50.15	793.00	0.0560	0.9553
Neutrophil counts	67.74	9.92	48.33	72.15	11.62	59.20	626.00	-1.4951	0.1349
Lymphocyte	20.81	7.94	53.18	16.85	9.21	39.78	585.50	1.8441	0.0652
Creatinine	10.07	4.08	51.75	9.14	3.91	45.50	700.00	0.8574	0.3912
ANC	4503.94	1757.31	48.48	5266.74	2064.55	58.60	638.00	-1.3917	0.1640
ALC	1348.34	681.72	51.91	1190.81	679.44	44.85	687.00	0.9694	0.3323
NLR	4.02	2.45	47.69	6.25	4.32	61.73	575.50	-1.9303	0.0536
PLR	186.48	236.92	49.04	182.57	103.71	56.35	683.00	-1.0039	0.3154
GFR	8.05	3.74	53.33	6.75	3.87	39.20	574.00	1.9432	0.0520

*$p<0.05$

We compared various parameters in terms of percentage of variables like hemoglobin, total count, platelet count, neutrophil count and leucocyte count and same was compared with absolute counts of neutrophil, lymphocytes and platelets as well we compared the ratio between Neutrophil to lymphocyte (NLR) and the ratio between platelet to lymphocyte (PLR) and also the comparison was done with creatinine and eGFR.

Table no. 28: Comparison of eGFR with all the variables by Spearman's rank method:

Correlation between	N	Spearman R	t-value	p-value
GFR & Hb	100	-0.0028	-0.0281	0.9776
GFR & WBC counts	100	-0.0297	-0.2939	0.7694
GFR & Platelet counts	100	0.0663	0.6576	0.5123
GFR & ANC	100	-0.0945	-0.9401	0.3495
GFR & ALC	100	0.1255	1.2525	0.2134
GFR & NLR	100	-0.1036	-1.0308	0.3052
GFR & PLR	100	-0.0576	-0.5712	0.5692

Table 28 shows the comparison of various parameters and results obtained were tabulated.

Table 29: Comparison of variables based on clinical staging of CKD by Mann-Whitney U test method:

Variables	Grade 4			Grade 5			U-value	Z-value	p-value
	Mean	SD	Mean Rank	Mean	SD	Mean rank			
Age in yrs.	56.00	9.67	57.90	52.24	15.29	50.11	200.50	0.5773	0.5638
Hb	9.46	0.99	57.20	8.99	1.74	50.15	204.00	0.5219	0.6017
WBC counts	6880.00	2896.03	51.50	6713.79	2156.76	50.45	232.50	0.0712	0.9433
Platelet counts	166.60	59.85	48.40	179.99	74.59	50.61	227.00	-0.1582	0.8743
ANC	4452.40	2391.29	45.30	4667.24	1819.41	50.77	211.50	-0.4033	0.6867
ALC	1578.80	476.40	68.20	1303.04	688.92	49.57	149.00	1.3918	0.1640
NLR	2.87	1.31	32.20	4.55	3.07	51.46	146.00	-1.4392	0.1501
PLR	105.40	21.49	30.50	189.92	221.29	51.55	137.50	-1.5736	0.1156

Table 29 shows comparison of eGFR with various variables with clinical staging of CKD (stage 4 and stage 5, since all our patients were in either stage 4 or stage 5 of CKD).

Table 30: Comparison of gender with age and weight of patient by Mann-Whitney U test method:

Variables	Male			Female			U-value	Z-value	p-value
	Mean	SD	Mean rank	Mean	SD	Mean rank			
Age in yrs.	52.34	14.67	51.98	52.80	16.88	50.13	770.50	0.2499	0.8027
Weight in kg	57.51	8.43	30.98	50.10	7.49	55.38	409.50	-3.3607	0.0008*

*p<0.05

Graph no. 20: Comparison of male and females with age and weight:

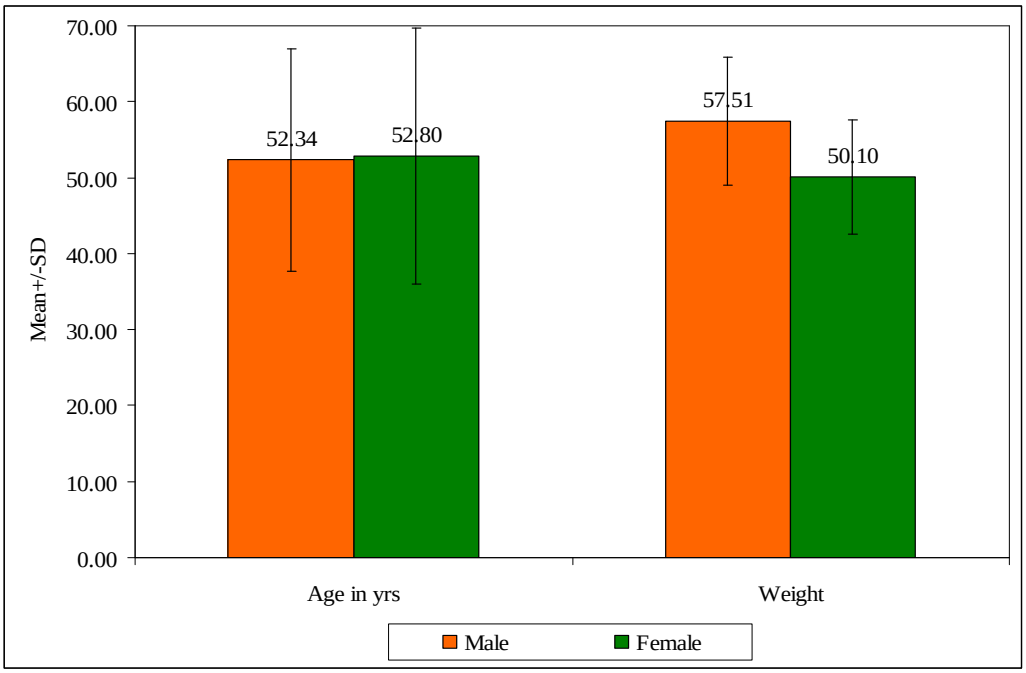


Table 30 shows no significant correlation between gender and age comparison in our 100 patients but statistically significant correlation was seen between gender and weight (p value 0.0008).

Table no. 31: comparison of age with variables (Hb, TC, N, L, etc.) by spearman rank method:

Correlation between	N	Spearman R	t-value	p-value
Age in yrs. & Hb	100	0.1502	1.5036	0.1359
Age in yrs. & WBC counts	100	0.1310	1.3077	0.1940
Age in yrs. & Platelet counts	100	0.0426	0.4221	0.6739
Age in yrs. & Neutrophil counts	100	0.0192	0.1902	0.8495
Age in yrs. & Lymphocyte	100	0.1005	1.0002	0.3197
Age in yrs. & Creatinine	100	-0.2595	-2.6600	0.0091*
Age in yrs. & ANC	100	0.1050	1.0451	0.2985
Age in yrs. & ALC	100	0.1825	1.8378	0.0691
Age in yrs. & NLR	100	-0.0693	-0.6880	0.4930
Age in yrs. & PLR	100	-0.1030	-1.0255	0.3076
Age in yrs. & GFR	100	-0.1857	-1.8706	0.0644

*$p<0.05$

Table 31 shows comparison of age with various lab variables and observations made are showed in above table.

Table no.32: Comparison between Hb and Creatinine scores by Spearman's rank method:

Correlation between	N	Spearman R	t-value	p-value
Hb & Creatinine	100	-0.0045	-0.0447	0.9644

Graph no.21: Scatter diagram showing correlation between Hb and Creatinine scores:

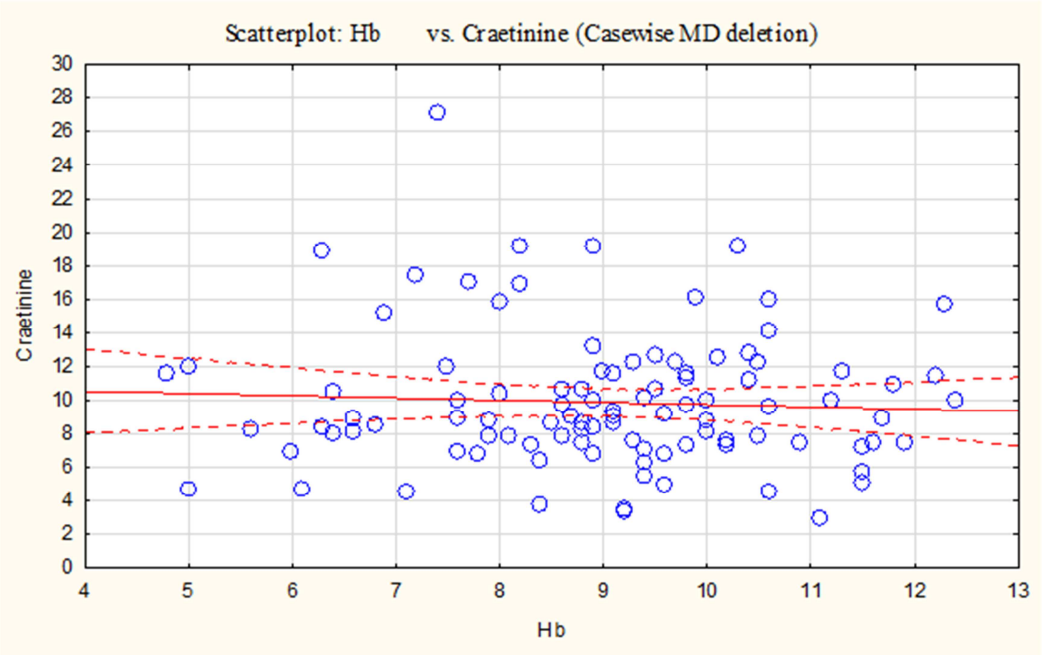


Table 32 reflects the comparison between Hb and creatinine by spearman rank method which does not show significant correlation.

Table no. 33: comparison of all lab variables by Kolmogorov Smirnov test:

Variables	Z-value	p-value
Age	0.1140	0.0030*
Hb	0.0710	0.2000
WBC	0.0370	0.2000
PLATELET	0.0790	0.1300
NEUTROPHIL	0.1040	0.0500*
LYMPHOCYTE	0.0760	0.1640
CREATININE	0.1100	0.0040*
ANC	0.0790	0.1300
ALC	0.0900	0.0440*
NLR	0.1890	0.0001*
PLR	0.2500	0.0001*
GFR	0.1090	0.0050

*$p<0.05$

(Note that, most of the variables do not follow normal distribution. Therefore, the non-parametric tests were applied)

The above table no.33 shows various lab variables when compared by Kolmogorov Smirnov test method and the results obtained are shown in above table.

DISCUSSION

In our present study of 100 patients with CKD (stage 4 and stage 5) of various etiologies were studied and subjected to NLR and PLR to see whether these markers help in patient of CKD which is being used off late in patients of CKD.

In our study of 100 patients the age of patients ranged from 20 to 81 years, the youngest was 20 years and the oldest was 81 years old. There were 66 patients between the age group of 40 to 69 years, 23 patients were in age group of 20 to 39 years and 11 patients were in age group of more than 70 years. The mean age of our patients was 52.43 ± 15.05 (table 5). This is almost similar to a study done by Vijoy Kumar Jha Et.al.[83] In their study the youngest was 14 years old and oldest was 82 years of age. This is in sharp contrast with Erhan Tatar et.al., they observed the mean age of their patient was 73.8 ± 6.1. Their most of the patients were in age group of 65 to 90 years. [80]

When gender was taken into account, we found male preponderance in our study with ratio of male: female - 4:1. 80 were males and 20 were female. Study by Erhan Tatar et.al also observed a slight male preponderance in their study population. [80] Study by Vijoy Kumar Jha Et.al also found a male preponderance in their study with the ratio of male: female 3.2:1. [83]

We subjected all our patients for weight measurement and found patients weight range from 40 to 60 kgs that is 62 patients, 32 patients weight between 60 to 80 kgs, only one patient was weighing more than 80 kgs. A study by Joel D. Kopple et.al. found in their study population weight ranging from 65 to 85 Kgs in their patients.[84]

We studied symptomatology of our patients with chronic kidney disease. Most of our patients presented with generalized weakness and easy fatiguability 86 (86%), edema 67 (67%) (Pedal edema, facial edema or generalized edema), oliguria 65(65%) patients, gastrointestinal symptoms (anorexia, nausea, vomiting) 57 (57%) patients, Breathlessness 41(41%) patients. 2 patients presented with altered sensorium because of uremic encephalopathy. Most of our patients had overlapping symptoms. This is similar to study by Ravi Kumar U., Shashank J. & Narayana Swamy. [85] In their study population they also found generalized weakness is the most common symptom in almost all their patients. Though this was a non-specific symptom, did not reflect much significance.

In our study majority of our patients had pallor as a presenting sign (79%) followed by edema (pedal-61, facial- 13, generalized edema –7). Ascites was seen in 14 patients. Most of our patients had overlapping signs. Yet again our observation is similar to study by Ravi Kumar U., Shashank J.& Narayana Swamy who observed pallor in almost 100% of their patients. Pedal edema was seen in 75%, hypertension in 64%, generalized edema was seen only in 2% of their patients.[85]

In our present study we observed hypertension in 73(73%) patients, 57 (57%) diabetics, both hypertension and diabetes were seen in 37 patients, 34(34%) patients had cardiovascular disease (IHD -18, left ventricular dysfunction- 11, DCM – 5), 8 patients had chronic obstructive pulmonary disease, 5 patients had benign prostate hypertrophy, 2 patients had multiple myeloma. A study by Karolina et.al. found in their study population hypertension being most common finding followed by diabetes.[86] Another study by Erhan Tatar et. Al. found diabetes was a commonest in their study population followed by hypertension.[80] Study by Vijoy Kumar Jha

Et.al[83] observed in the study population hypertension as a commonest finding followed by diabetes. This is almost similar to study by Suresh Chandra Dash and Sanjay K. Agarwal, conducted in AIIMS. They found hypertension in more than 70% of their study population.[87]

We attempted to find etiology of our patients for chronic kidney disease and found to have diabetic nephropathy as a commonest cause that is 46(46%), Hypertensive nephropathy 24 (24%), chronic-tubulo interstitial disease 15(15%), 7 patients' chronic glomerulonephritis, 5 patients polycystic kidney disease, 3 patients had reflux nephropathy. Most of our patient etiology of chronic kidney disease was based on clinical basis. Few patients were diagnosed with renal biopsy, most of them were CGN and CTID. Vivek Kumar and Ashok Yadav et.al. have studied more than 4000 patients in their study and they also found diabetic kidney disease as a commonest cause followed by hypertensive nephrosclerosis as the cause of chronic kidney disease.[88] The other etiologies in their study population were CTID, polycystic kidney disease and undetermined etiologies. Vijoy Kumar Jha in their study population found diabetes a commonest cause of chronic kidney disease followed by CTID.[83]

We categorized all over 100 patients by doing eGFR (KDIGO criteria) and staged them clinically from stage 1 to stage 5. Study by Vijoy Kumar Jha and Shashibhushan subjected their study population to MDRD criteria and majority of their patients were in stage 3 and 4 together followed by stage 5[83]. In our study population all our patients were either in stage 4 or 5 of chronic kidney disease. Study by Ravi Kumar U., Shashank J. & Narayana Swamy deployed clinical staging and they too observed most of their patients in stage four and five of chronic kidney

disease.[85] In our study most of our patients were in stage 5 chronic kidney disease 95(95%), only five were in stage 4 (table no. 12).

In our present study of 100 patients all our patients were on MHD but duration varied. Majority of patients i.e., 47 (47%) were on MHD between 13 to 36 moths followed by 23 between 37 to 60 months, 16 patients <12 months and only 14 patients >60 months. Study by Christopher et. Al. observed in their study population of 134 more than half i.e., 68 patients were on hemodialysis (PD 28 + HD 60) who were in clinical staging of stage 4 of CKD.[89]

We observed various degree of anemia in our study population ranging from mild to severe. All our patients either had mild, moderate or severe anemia. None had normal hemoglobin percentage. Majority of our patients had moderate anemia 62 (62%), 25 (25%) had severe anemia and only 13(13%) had mild anemia. This severity of anemia was based on WHO criteria (table no. 14). A study by Ravi Kumar U. Shashank J., Narayana Swamy observed in all their patient's anemia as a sign ranging from moderate to severe.[85] Majority of their patients had moderate anemia 73% and only 1.8% had severe anemia (Hb<6%). Study by Vijoy Kumar Jha Et.al observed in their population anemia as a most common finding.[83] Study by Vivek Kumar and Ashok Yadav et.al. also observed anemia in their patient ranging from mild to severe.[88] In their study population majority of them (45.5%) had moderate anemia, mild in 25.8% and severe in 1.9%. Anemia is observed more often than not in patients of chronic kidney disease. The three studies quoted above including our, anemia is most common observed clinical sign in patients of chronic kidney disease. Though there is no satisfactory definition of anemia in these patients with chronic kidney disease and there are no acceptable guidelines for normal hemoglobin in these patients

with chronic kidney disease, this could be because of low production of erythropoietin, also the reflection of severity of anemia depends on duration of chronic kidney disease.

All our patients were subjected to total WBC count estimation and results observed were, in 87% total WBC count ranged from 4500 to 11,000 and remaining 13% had less than 4500. Study by Erhan Tatar et al. found total WBC count in most of their patients around 7000 ± 1902.[80] A study by Yohei Arai et al. in their study population the count varied from 6400 ± 3500.[90] In most of our patients though whole blood count neither was very high (>11000) or neither very low (<3500). the explanation offered for high WBC count in study by Yohei Arai et al., either inflammation associated which could lead to fast progression of chronic kidney disease and carrying poor prognosis and low WBC count observed could be a risk factor for chronic kidney disease progression. They could not offer a significant positive correlation for low WBC count in their study.

Similarly, all our patients were subjected to neutrophil count estimation and results observed were, in 86 patients it ranged between 1500 to 7000 and in 12 patients more than 7000 and only two patients had less than 1500. Though we could not ascertain in 12 patient who had absolute neutrophil count more than 7000 the cause, as well those two patients who had absolute neutrophil count less than 1500, most of the studies have not taken only absolute neutrophil count alone into consideration, they have taken neutrophilic to lymphocytic ratio into account.

We subjected all our patient to absolute lymphocytic count and results observed are shown in table 17. Again, no author has taken absolute lymphocytic

count alone in their study, they have taken neutrophil to lymphocytic ratio for prognosis of chronic kidney disease patients.

Similarly, we subjected all our patients for absolute platelet count estimation and found to have majority of our patients the count varied between 1,50,000 to 4,50,000 i.e., 63 patients (63%), 36 patients (36%) had count below 1,50,000, only one patient had more than 4,50, 000. Most of the authors have not taken either total count, neutrophil count, lymphocyte count and platelet count in their study of these counts the absolute value. They have either compared neutrophilic to lymphocyte ratio or platelet to lymphocytic ratio. One study by Erhan Tatar et al. has taken platelet count alone as well as neutrophil to lymphocyte ratio and in their study the platelet count ranged between 2,46,000 ± 84000.[80]

Our main aim of study was to see the difference in neutrophil to lymphocyte ratio (NLR) and platelet to lymphocytic ratio (PLR), whether the ratio is altered, is it more or less and to our observation when we subjected all our patients to NLR, the ratio was not only altered and it was more in 29 patients and remaining 71 patients the ratio was below 4.99 as shown in table no. 19. Most of the authors have taken a ratio of 0.78 to 3.53 as a reference ratio. This is very well reflected in a study by Forget P. et al. i.e. normal ratio as a cut off for NLR is between 0.78 to 3.53[62]. A study by Wadgaonkar Udit Rajendra et al. and Erhan Tater et al. who observed the ratio was altered and it was more in their study population also.[81][80] This is because of end stage renal disease i.e., stage four and stage five. Many authors have also found altered ratio and ratio being more in chronic kidney disease as the disease is progressing. To quote studies by Han li et al.[4] and study by Kocyigit et al.[91]and study by Okyay GU et al.[92] who also observed the difference and increased

neutrophil to lymphocyte ratio in their study population of chronic kidney disease. All these studies quoted above had a positive correlation of altered ratio i.e., increasing NLR and the p-value was statistically significant in all their studies. Similarly in our study the ratio is not only altered and was found to be more, though it was not statistically much significant. But we found a correlation of increasing trend of NLR in our patients.

The probable explanation of this altered ratio of NLR with increasing trend reflects chronic inflammation. Another explanation could be because of chronic inflammation there is increased oxidative stress as a result there might be higher levels of neutrophil to lymphocyte ratio which is attributed to chronic kidney disease progression. It has been found that NLR is an important marker/indicator of inflammation, increase morbidity and mortality in patients of cardiovascular disease and various malignancy which is a result of chronic inflammation, which may contribute to the pathogenesis of the disease process as well as progression of the disease. Same may be extrapolated to patients of chronic kidney disease. This NLR is important marker in predicting the progression in patients with chronic kidney disease. It is an important observation in most of the studies that altered ration of neutrophil to lymphocyte (increased ratio) not only reflects poor outcomes of patients with chronic kidney disease also showed the need for renal replacement therapy (hemodialysis) in these patients, because most of these patients where in the stage four and five CKD. In our study population all our patients were on maintenance hemodialysis as they were in stage 4/stage 5 CKD.

Similarly, we subjected all our patients to PLR estimation and results found were tabulated in table no 20. We observed almost 96 patients whose PLR was <499

however one each in ratio of 1500-2000 and 1000-1499 were found. Only 2 patients were found in ratio of 500-999. Most of the authors with special reference to Jesse Fest et al. who have defined a cut off value of 120 ranging from 61 to 239.[72] In our study further analyzing we found 57 patients whose ratio was >120 remaining 43 had less than 120. In our study we could not say precisely PLR ratio whether has significance in patients of CKD. The results obtained were little indifferent as compared to studies by other workers. A study by Turkmen et.al who found in their study population a PLR as a strong indicator of inflammation in patients of ESRD, they observed an increase in PLR in their study population.[12] However, they could not find a direct correlation of PLR as a marker of either increased mortality or RRT requirement. This could be explained on the basis of the platelet function decline with aging of patients. As we observed most of our patients i.e., 77 patients were beyond 40 years, only 23 patients were below 40 years of age (table 5). Study by Erhan Tatar et al. were also of the same opinion as far as PLR was concern.[80]

We attempted comparison of NLR by Mann-Whitney U test with various etiologies in our patients and results obtained were not statistically significant (table 21). To best of our knowledge many authors have not compared NLR with etiologies. Similarly, comparison of PLR with various etiologies by same method (Mann-Whitney U test) did not reflect positive correlation.

We tried to correlate with hemoglobin percentage (Hb%) and eGFR by Spearman's rank method and found no direct correlation between Hb% and eGFR. Majority of patients had Hb% ranging between 8 to 10.9 gm% (62 patients) and had moderate anemia, 25 patients had severe anemia the Hb% was below 8 gm% (table 14/23). A study by Vijoy Kumar Jha et al. found anemia as a most common

observation in their study population.[83] This could be a reflection of CKD as there is no definite quantitative definition of anemia in patients of CKD and also there is no fixed levels of Hb% which is ideal for these patients of CKD. This may happen as a result of low production EPO in these patients or it could be because of inhibition of erythropoiesis. The severity of anemia reflects the duration of CKD.

We attempted correlation between NLR and PLR by Spearman's rank method (table 24) and found to have positive correlation between NLR and PLR. These two markers suggest a chronic inflammation in these patients. In our study NLR alone though there was an increasing trend in our study population but there was no statistical significance observed as discussed earlier. PLR alone was also not reflecting any positive correlation in our study population. But when we attempted to compare between NLR and PLR we found significant positive correlation. P-value being statistically significant (P=0.0001). Study by Turkmen et.al. found a positive correlation in their study population in patients of CKD especially in patients of ESRD.[12] They also observed a PLR was significantly elevated in their study population as a sign of inflammation. A study by Peiyuan Li et al. found NLR and PLR were increased, also comparison showed a positive correlation in their patients.[78] Various studies have shown in the past the NLR and PLR as a marker of inflammation in patients of CKD. One study has also demonstrated a positive correlation between NLR and TNF-alpha as a sign of inflammation.

We attempted to compare NLR with eGFR by applying Spearman's rank method and we did not find any positive correlation for same. One study by Erhan Tatar et al. also quoted in their study population no direct correlation between NLR and eGFR.[80] Similarly, comparison between PLR and eGFR by same method also

did not reflect any direct correlation. Study by Erhan Tatar et al. also did not find any direct correlation between PLR and eGFR.[80]

In our study we considered the comparison of gender with lab parameters by Mann Whitney U test and there was no comparison of lab parameters with the gender except for hemoglobin percentage, which was slightly more in male gender compared to their counterpart as depicted in table no. 27. The p-value was statistically significant (p value- 0.0191). Study by Vivek Kumar et al. have compared the lab parameters like hemoglobin percentage, creatinine, albumin, uric acid, total cholesterol and triglycerides and eGFR.[88] Their study also depicted a correlation of anemia with gender which was slightly more in female compared to male. However, in our study we did not subject patients to estimation of albumin, uric acid, cholesterol and triglycerides.

In our study we subjected all our patients for comparison with eGFR with other lab variables with Spearman's rank method and there was no correlation with eGFR and lab parameters (hemoglobin percentage, whole blood count, platelet, absolute neutrophil count, absolute leukocyte count, NLR and PLR). Studies quoted in our earlier discussion have also not found any correlation with this lab parameters and eGFR. One study by Erhan Tatar et al. in fact found negative correlation between NLR and PLR with eGFR.[80]

We took comparison of clinical staging of chronic kidney disease that is stage four and stage five in our study with various variables by Mann Whitney U test and we found no correlation of these variables with clinical staging of chronic kidney disease (table 29). Most of the studies quoted in our discussion have not compared the variables with clinical stages of chronic kidney disease.

We compared gender of the patients with age and weight by Mann Whitney U test and found no correlation of gender with age or weight in our study group. P-values were statistically insignificant in all these variables (age, weight and gender). Most of the authors we have compared our study with theirs have not compared the gender with age and weight in their study population.

We attempted comparison of age of all our patients with lab variables by Spearman's rank method as shown in table no. 31 and found to have no correlation of age with other parameters except for age and serum creatinine which was correlated. P-value was statistically significant (p value- 0.0091). Probable explanation for this rising level of serum creatinine maybe because of older age, clinical staging of chronic kidney disease or duration of the disease. Studies we quoted have not compared age with different lab parameters. One study by Li Quingping and Wei Ribao et al. have found some correlation with age and eGFR who have found decreasing trend of eGFR with older age. Also, they have found a slightly better eGFR in female as compared to male gender.[93]

Comparison of hemoglobin with serum creatinine levels by Spearman's rank method revealed there was no correlation. Most of the studies we have quoted comparison of either hemoglobin or eGFR with clinical staging of chronic kidney disease and they have found low levels of hemoglobin and rising levels of serum creatinine in advancing renal disease, less hemoglobin percentage in female gender and more creatinine in patients with end stage renal disease (table 32). Same have been depicted by scattered diagram depicting correlation between serum creatinine and hemoglobin percentage.

Finally, we took all the parameters into consideration, applying the Kolmogorov Smirnov test method as the normal distribution of this parameters by usual testing methods did not reflect any correlation. Hence, we applied non parametric tests and found to have some correlation with age, neutrophil, serum creatinine, absolute lymphocyte count, neutrophil to lymphocyte ratio, and platelet to lymphocyte ratio (table 33). However, it did not have any positive correlation in our study. However, it did reflect some variables may be contributing in these patients of chronic kidney disease. Since study population was small (number of patients 100) to address all these issues we need a larger sample size and take into consideration all these variables and compare. In our study only we could find some correlation when taken into account variables like hemoglobin percentage, serum creatinine, neutrophil to lymphocyte ratio which did not reflect a positive correlation and P values were not statistically significant. However, there was a positive correlation when PLR and NLR taken into consideration which most of the studies have quoted.

SUMMARY

In the present study of 100 patient titled "A study of correlation between neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in patients of chronic kidney disease" during the study period from January 2021 to December 2021 in department of General Medicine KLE's Dr. Prabhakar Kore Hospital and medical research Centre Belagavi.

The finding of the study summarized as below:

1. There were 100 cases of chronic kidney disease either in stage four or stage five disease.
2. There were 80 percentage of male patients and 20 percentage of female patients (M: F- 4:1).
3. Most of our patients presented with generalized weakness and easy fatiguability.
4. The most observed clinical finding was pallor and edema.
5. In most of our patient's diabetes was commonest etiological factor followed by hypertension and CTIN.
6. We took noninvasive parameters neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in our study group which reflected a positive correlation in this patient.
7. NLR alone though reflected an altered ratio but did not have positive correlation in our patients.
8. Similarly, PLR was also altered and again did not show positive correlation.

9. In most of our patients we observed low hemoglobin percentage (slightly more hemoglobin percentage in males compared to females).
10. The serum creatinine levels were raised in patients of older age group.
11. As our patients were either stage four or stage five chronic kidney disease and all were on maintenance hemodialysis.

CONCLUSION

In our present study 100 patients with chronic kidney disease who were on maintenance hemodialysis (clinical staging 4 and 5)

- The commonest etiological factor for chronic kidney disease was diabetes followed by hypertension and chronic tubulo-interstitial nephritis.
- There is a positive correlation between NLR and PLR.
- Comparison of lab parameters did not have significant correlation.
- Gender did not influence in these patients of chronic kidney disease.
- There was no correlation with neutrophil to lymphocyte ratio alone similarly PLR alone.
- These simple cost effective, non-invasive parameters could help in this patient of chronic kidney disease.
- In future these ratios with large sample size can be made used in these patients to stage them, to see whether they require hemodialysis as maintenance therapy.
- These simple markers which can be done in all the lab including periphery can be used as a marker of inflammation in these patients.
- Owing to small sample size of 100 a bigger sample size is required to address these issues.

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ANNEXURE I – INFORMED CONSENT FORM

Dear Mr./Mrs./Dr. _____, you are kindly requested to enroll yourself in a research study tilted, **"A STUDY OF CORRELATION BETWEEN NEUTROPHIL TO LYMPHOCYTE RATIO AND PLATELET TO LYMPHOCYTE RATIO IN PATIENTS OF CHRONIC KIDNEY DISEASE AT KLE'S Dr. PRABHAKAR KORE HOSPITAL AND MRC, BELAGAVI."** being conducted by _____, a post graduate student in M.D. General Medicine and the study will be carried out under the direct supervision and guidance of _____, Professor and Unit Chief, Department of General Medicine, Jawaharlal Nehru Medical College, Belgaum.

You have been requested to participate in this as you fit into the laid-out criteria for a study 'subject'/ participant.

TITLE OF THE STUDY:

"A STUDY OF CORRELATION BETWEEN NEUTROPHIL TO LYMPHOCYTE RATIO AND PLATELET TO LYMPHOCYTE RATIO IN PATIENTS OF CHRONIC KIDNEY DISEASE AT KLE'S Dr. PRABHAKAR KORE HOSPITAL AND MRC, BELAGAVI."

PURPOSE OF THE STUDY:

To study of correlation between neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in chronic kidney disease patient.

PROCEDURES INVOLVED:

If you agree to enroll yourself in my study, you will be clinically examined in detail and investigated for the below said investigations accordingly.

Sr. Creatinine.

Neutrophils

Lymphocytes

Platelets

Hemoglobin

RISKS AND BENEFITS:

There are no potential risks involved in this study.

Benefits of taking part in this research:

To establish a proven relationship between neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in chronic kidney disease patient.

VOLUNTARY PARTICIPATION / WITHDRAWAL FROM THE STUDY:

Taking part in the study is voluntary. You may choose not to enroll yourself in this study and may choose to leave the study anytime in between.

ALTERNATIVES:

Your decision regarding participation in study will not change present or future health care services offered to you at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. You would simply be excluded from the study if you wish to, and all your details shall be kept confidential and you will get the routine line of management.

PRIVACY AND CONFIDENTIALITY:

All data collected or disclosed by you during the course of participation of study, will be kept fully confidential. If, however during the course it becomes necessary for the progress of the course to disclose the identity, it would be done so only after your informed & written consent.

The only people to know that you are a research subject are members of the research team. No information about you will be disclosed to other without your written permission except:

- In emergency to protect your rights AND welfare.
- If required by law.

AUTHORIZATION TO PUBLISH RESULT:

The results of the study may be used to publish an article. When the results of research published or discussed, in a conference, no information will be displayed that would disclose your identity. Any information obtained in connection with this study and that can be identified with you will remain confidential.

FINANCIAL INCENTIVES FOR PARTICIPATION:

No additional costs shall be incurred upon you for the purpose of this study.

It is purely being done with the idea of research and all the cost of study will be borne by the investigator.

COMPENSATION:

In the event that you become injured as a result of taking part in this study, treatment will be offered to you at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum, or you will be given information about where to receive medical care. However, no reimbursement, compensation or free medical care will be given.

QUESTIONS/CONTACT DETAILS:

You shall be free to contact the below mentioned name & addresses anytime during the study period for any clarification or help as you may desire for. In case of the queries during study or in future you may contact following persons,

Dr. HARSHA HEGDE
Chairperson, JNMC, IEC & Scientist D, ICMR
National Institute of Traditional Medicine
Belagavi. -94804225001

CONSENT FORM

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read this consent form, or it has been read to me, this consent form and have had all the questions answered

Signature / Left Thumb print of the Participant or legally authorized representative

Participant's name ……...

Signature / Left thumb impression ……...

of the participant

Name of the legally authorized ……...

representative / guardian

Signature / Left thumb impression ……...

Witness name ……...

Signature / Left thumb impression …….

Investigator's name and signature ……...

Date:

Place:

ANNEXURE II - PROFORMA

"A STUDY OF CORRELATION BETWEEN NEUTROPHIL TO LYMPHOCYTE RATIO AND PLATELET TO LYMPHOCYTE RATIO IN PATIENTS OF CHRONIC KIDNEY DISEASE AT KLE'S Dr. PRABHAKAR KORE HOSPITAL AND MRC, BELAGAVI."

CASE NO: **IP NO.:**

DATE:

NAME:	
AGE/SEX:	
ADDRESS:	
OCCUPATION	

BREIF HISTORY:

CHIEF COMPLAINTS AT PRESENTATION:

Generalized weakness, easy fatiguability	
Anorexia, Nausea, Vomiting,	
Edema (facial, pedal or generalized edema)	
Breathlessness	
CNS manifestation (confusion, drowsiness, seizure)	
Oliguria	
Other	

PAST HISTORY AND COMORBIDITIES:

Duration of CKD

Comorbidities:

1. Diabetes Mellitus
2. Hypertension
3. Cardiovascular disease
4. COPD
5. BPH
6. Others

History of acute kidney injury

History of drug intake/pain killers

History of chronic liver disease

History of cardiovascular disease

History of diseases causing thrombocytopenia

History of tuberculosis/bacterial infection

History of blood/platelet transfusion

FAMILY HISTORY:

CKD- T2DM- HTN- IHD- OTHER-

PERSONAL HISTORY:

Diet: Appetite: Sleep:

Bowel/Bladder: Habits: Alcohol/smoking

TREATMENT HISTORY:

Duration on MHD:

Medications:

PHYSICAL EXAMINATION:

GENERAL CONDITION/BUILT:	
WEIGHT (kgs)	
PALLOR	
ICTERUS	
CYANOSIS/CLUBBING/ LYMPHADENOPATHY	
BLOOD PRESSURE	
TEMPERATURE	
PULSE	
RESPIRATORY RATE	

SENSORIUM	
EDEMA- PEDAL EDEMA FACIAL EDEMA GENERALIZED SWELLING ASCITES	
JVP	

SYSTEMIC EXAMINATION:

Respiratory system:

Breath Sounds

Crepitations

Rales

Cardiovascular system:

Apical impulse / Parasternal impulse

Heart sounds / Murmurs

Per abdomen:

Hepatomegaly / Splenomegaly

Ascites

Central nervous system:

Higher Mental Functions:

Cranial Nerves:

Motor system:

Sensory system:

INVESTIGATIONS:

Serum Creatinine	
Neutrophils	
Lymphocytes	
Platelets	
Hemoglobin	
Other investigations	

DIAGNOSIS:

Date:

Signature of the Guide: Signature of the investigator

ANNEXURE III - KEY TO MASTER CHART

GENDER	-	M- MALE F- FEMALE
HTN	-	HYPERTENSION
BPH	-	BENIGN PROSTATE HYPERTROPHY
COPD	-	CHRONIC OBSTRUCTIVE PULMONARY DISEASE
GFR	-	GLOMERULAR FILTRATION RATE
MHD	-	MAINTENANCE HEMODIALYSIS
CVD	-	CARDIOVASCULAR DISEASE
L	-	LEFT VENTRICULAR DYSFUNCTION
I	-	ISCHEMIC HEART DISEASE
D	-	DILATED CARDIOMYOPATHY
CGN	-	CHRONIC GLOMERULONEPHRITIS
CKD	-	CHRONIC KIDNEY DISEASE
CTID	-	CHRONIC TUBULOINTERSTITIAL DISEASE
GFR	-	GLOMERULAR FILTRATION RATE
HB	-	HEMOGLOBIN
KDIGO	-	KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES
MDRD	-	MODIFICATION OF DIET IN RENAL DISEASE
MHD	-	MAINTENANCE HEMODIALYSIS
NLR	-	NEUTROPHIL TO LYMPHOCYTE RATIO
PLR	-	PLATELET TO LYMPHOCYTE RATIO
P,F,G	-	PEDAL, FACIAL OR GENERALIZED EDEMA
WBC	-	WHOLE BLOOD COUNT

																		SYMPTOMS						COMORBIDITIES						ETIOLOGY						CLINICAL OBSERVATION						
SERIAL NO.	IP NO	AGE(yrs)	SEX	WEIGHT(kgs)	Hb(gm/dl)	WBC(cell/mm3)	PLATELET(10e/L)	NEUTROPHIL(%)	LYMPHOCYTE(%)	CREATININE(mg/dl)	ANC (cell/mm3)	ALC(cell/mm3)	NLR	PLR	GFR (ml/min)	MHD since (months)	Generalised weakness and easy fatiguability	Anorexia,Nausea,Vomiting.	EDEMA(P.F.G)	BREATHLESSNESS	Oliguria	DIABETES MELLITUS	HYPERTENSION	CVD	COPD	BPH	Multiple Myeloma	DIABETIC NEPHROPATHY	HYPERTENSIVE NEPHROPATHY	CTID	POLYCYSTIC KIDNEY DISEASE	CGN	REFLUX NEPHROPATHY	PALLOR	PULMONARY EDEMA	PEDAL EDEMA	FACIAL EDEMA	ASCITES	GENERALIZED SWELLING	ALTERED SENSORIUM
1	4532867	76	F	47	7.1	7400	200	79	18	4.53	5846	1332	4.39	150.2	7.8	26	1			1			1	L						1			1	1						
2	545344	63	M	51	9.2	7600	142	65	24	3.38	4940	1824	2.71	77.9	16.1	8	1	1	1	1	1	1											1	1	1		1		
3	1111910	72	M	49	7.4	4300	109	70	17	27.05	3010	731	4.12	149.1	1.7	77	1	1			1	1	1	I	1			1					1						
4	6283378	48	F	54	8.6	4100	148	85	8	9.71	3485	328	10.63	451.2	6.0	51	1	1	1				1									1		1					
5	3890811	62	M	54	10.6	4900	268	52	36	15.96	2548	1764	1.44	151.9	3.7	62	1		1	1	1						1			1			1	1	1	1	1	1	
6	1054700	39	M	60	8.4	7600	194	62	26	3.78	4712	1976	2.38	98.2	22.3	7						1						1					1						
7	1086317	29	M	56	10.2	7100	87	55	22	7.61	3905	1562	2.50	55.7	11.3	9	1	1	1	1	1		1									1		1		1			
8	1120535	47	M	54	9.6	7900	350	62	26	9.11	4898	2054	2.38	170.4	7.7	13	1		1		1		1	L					1				1		1				
9	996708	36	F	47	11.2	6500	193	76	12	10.03	4940	780	6.33	247.4	5.8	56	1	1	1		1		1						1						1		1		
10	1076753	67	M	52	8.8	7600	247	75	17	8.19	5700	1292	4.41	191.2	6.4	14	1	1	1	1	1	1						1					1		1				
11	1059698	31	M	39	6.4	5400	128	66	20	10.53	3564	1080	3.30	118.5	5.6	38	1	1	1	1	1		1						1				1	1	1				
12	5953152	60	M	56	9.1	8400	116	74	13	8.66	6216	1092	5.69	106.2	7.2	31		1	1			1	1	I					1					1			1			
13	1115174	23	M	46	8.6	5600	145	63	23	7.86	3528	1288	2.74	112.6	9.5	28			1	1	1		1						1					1		1				
14	1113737	59	F	51	9	5300	213	70	21	11.69	3710	1113	3.33	191.4	4.2	5	1		1		1	1						1					1		1		1		
15	1081928	52	M	65	7.9	3100	109	72	19	7.84	2232	589	3.79	185.1	10.1	15	1		1		1	1	1					1					1		1				
16	5262522	48	M	59	9.4	700	144	80	11	6.23	560	77	7.27	1870.1	12.1	37		1		1	1	1	1					1					1	1					
17	3334297	76	F	48	9.4	9700	183	84	9	10.13	8148	873	9.33	209.6	3.6	74	1	1			1	1	1	I		1		1					1						
18	1098698	25	F	41	6.6	6800	28	78	8	8.86	5304	544	9.75	51.5	6.3	13				1	1		1									1		1					
19	4954014	61	M	63	8.9	6800	105	79	13	9.98	5372	884	6.08	118.8	6.9	15	1		1	1		1	1	D				1					1	1	1	1	1	1	
20	1061268	39	M	54	8.1	5100	206	67	18	7.82	3417	918	3.72	224.4	9.7	25	1	1			1	1	1						1				1						
21	5102942	64	F	61	6	9900	128	62	28	6.95	6138	2772	2.21	46.2	7.9	18	1		1	1	1	1	1	I						1			1	1	1				
22	1054763	58	M	71	9.2	5000	225	46	34	3.50	2300	1700	1.35	132.4	23.1	41	1	1		1	1		1						1				1						
23	6354075	50	M	47	8.8	7200	213	80	12	8.70	5760	864	6.67	246.5	6.8	34	1	1	1	1	1	1		L				1					1	1	1				
24	6020556	62	M	51	10.9	8400	214	80	7	7.41	6720	588	11.43	363.9	7.5	32	1	1	1								1		1						1				
25	6250995	60	M	43	10.6	8600	151	85	11	14.12	7310	946	7.73	159.6	3.4	82					1		1	I							1								
26	1108143	23	M	55	8.7	9300	149	70	18	9.04	6510	1674	3.89	89.0	9.9	22	1	1	1	1	1		1									1	1	1					
27	4376898	42	M	39	12.2	1300	263	59	33	11.37	767	429	1.79	613.1	4.7	69	1		1			1	1							1					1		1		
28	4881180	41	F	61	7.6	8800	236	66	21	9.91	5808	1848	3.14	127.7	7.2	30	1	1	1	1	1		1						1				1	1	1				
29	6052714	61	M	58	10.6	6800	172	65	26	9.56	4420	1768	2.50	97.3	6.7	31	1	1				1		L	1			1					1						
30	1106834	33	M	54	9.8	7900	179	61	15	11.27	4819	1185	4.07	151.1	7.1	19	1		1	1	1		1						1				1	1	1				
31	4802190	28	F	42	9.5	7400	156	89	7	12.65	6586	518	12.71	301.2	4.4	5	1	1			1		1									1	1						
32	2464481	41	M	65	9.8	5800	141	70	16	11.53	4060	928	4.38	151.9	7.8	16	1	1	1	1	1	1	1	I					1					1	1	1	1	1	1	
33	803400	47	M	53	10.3	8300	182	79	15	19.18	6557	1245	5.27	146.2	3.6	81	1		1		1		1								1			1					
34	1079104	56	M	65	8.4	7200	259	54	26	6.33	3888	1872	2.08	138.4	12.0	37	1	1	1		1											1	1		1				
35	1062169	20	M	57	7.2	5900	73	73	14	17.41	4307	826	5.21	88.4	5.5	49	1	1	1	1			1						1				1	1	1				
36	6135959	49	M	64	9.4	6000	195	41	38	7.04	2460	2280	1.08	85.5	11.5	46	1	1	1		1	1	1						1				1		1				
37	1080513	58	F	43	9.5	7200	205	65	25	10.58	4680	1800	2.60	113.9	3.9	72	1	1	1		1	1	1	L				1					1		1				
38	2001850	35	M	63	12.3	10200	111	89	7	15.74	9078	714	12.71	155.5	5.8	47	1	1	1		1		1							1						1			
39	876727	63	M	45	11.3	9100	277	88	6	11.71	8008	546	14.67	507.3	4.1	68	1	1	1	1		1	1	D				1							1				
40	1096638	41	M	69	8	6600	269	70	20	10.36	4620	1320	3.50	203.8	9.2	21	1	1		1	1	1	1					1					1	1					
41	1120853	44	M	48	8.2	5300	103	77	12	16.92	4081	636	6.42	161.9	3.8	68	1		1		1	1	1					1					1		1		1		
42	5641567	63	M	61	10	6400	117	72	12	9.92	4608	768	6.00	152.3	6.6	23	1		1		1	1	1	I				1							1				
43	654928	23	F	54	6.6	4900	107	87	9	8.16	4263	441	9.67	242.6	9.1	18	1	1		1		1	1						1					1	1				
44	1053790	20	M	67	12.4	10100	329	71	21	9.95	7171	2121	3.38	155.1	11.2	9	1		1		1		1						1						1				
45	1094345	81	M	57	9.3	9200	349	77	13	7.55	7084	1196	5.92	291.8	6.2	45		1			1	1	1	I				1					1						
46	799314	60	F	61	11.1	10900	198	74	15	2.88	8066	1635	4.93	121.1	20.0	10	1		1	1		1		L				1							1				
47	1113674	59	M	47	8.6	4000	147	68	22	10.64	2720	880	3.09	167.0	5.0	54	1				1				1					1			1						
48	1108087	30	M	43	6.1	4400	86	70	23	4.68	3080	1012	3.04	85.0	14.0	39		1	1				1						1				1		1		1		
49	987236	53	M	58	5	6700	156	76	20	12.00	5092	1340	3.80	116.4	5.8	64	1	1	1		1		1						1				1		1				
50	1103887	56	M	56	8.9	8300	203	75	14	19.08	6225	1162	5.36	174.7	3.4	8	1	1	1	1		1	1					1					1	1	1				
51	6443864	71	F	53	7.9	9100	122	73	19	8.75	6643	1729	3.84	70.6	4.9	46	1		1		1	1	1	I				1					1		1				
52	3917720	50	M	48	10	7200	258	65	22	8.77	4680	1584	2.95	162.9	6.8	28	1				1		1						1				1						
53	1578716	69	F	47	8.9	5680	217	52	40	6.82	2953.6	2272	1.30	95.5	5.8	57	1	1	1	1	1	1	1	L		1		1						1	1	1	1	1	1	
54	1100923	54	M	68	11.7	8200	274	70	13	8.88	5740	1066	5.38	257.0	9.1	25	1	1	1		1	1	1						1						1				
55	6103532	63	M	39	11.5	6100	152	60	32	7.21	3660	1952	1.88	77.9	5.8	58	1				1							1											
56	1675517	68	M	59	9.6	10900	204	73	18	6.73	7957	1962	4.06	104.0	8.8	35	1	1				1	1	I	1			1						1						
57	1055193	63	M	72	10	6200	161	67	24	8.05	4154	1488	2.79	108.2	9.6	25	1		1		1		1							1						1			
58	1070030	57	M	62	8.2	10200	153	72	19	19.06	7344	1938	3.79	78.9	3.7	81	1		1	1		1		L				1					1	1		1			
59	1040163	60	M	74	9.4	3300	74	68	23	5.45	2244	759	2.96	97.5	15.1	41	1	1	1		1	1		I				1					1		1				
60	6412860	37	M	69	8	4000	90	75	17	15.83	3000	680	4.41	132.4	6.2	14	1		1	1										1			1	1	1				
61	1061321	50	M	58	10.4	5800	160	65	25	11.11	3770	1450	2.60	110.3	6.5	28	1				1	1	1						1					1						
62	6263875	40	M	61	6.8	8600	188	70	19	8.50	6020	1634	3.68	115.1	10.0	26	1	1					1							1				1						
63	5690554	49	M	71	9.8	5560	155	60	30	7.38	3336	1668	2.00	92.9	12.2	8	1	1	1			1	1						1					1		1		1		
64	1099993	55	M	59	7.6	4900	273	66	31	6.95	3234	1519	2.13	179.7	10.0	29	1		1		1	1			1			1						1		1				
65	1117064	63	M	52	7.5	6100	118	63	19	11.91	3843	1159	3.32	101.8	4.7	38	1	1				1	1					1						1						
66	1039773	68	M	65	8.9	8800	486	78	17	8.44	6864	1496	4.59	324.9	7.7	16	1		1	1	1	1	1	D		1		1						1	1	1	1	1	1	
67	1102407	64	M	57	11.5	7700	157	50	36	5.66	3850	2772	1.39	56.6	10.6	17		1	1			1	1	I								1			1					
68	1115745	27	M	51	6.9	4600	127	57	25	15.20	2622	1150	2.28	110.4	5.3	53	1		1		1							1				1		1		1			
69	1102329	78	M	62	9.3	4500	83	77	15	12.28	3465	675	5.13	123.0	4.3	63	1	1			1	1		I		1		1						1						
70	6154008	57	F	53	7.7	4600	107	58	28	16.97	2668	1288	2.07	83.1	3.1	11	1		1	1	1		1							1				1	1	1				
71	4886054	41	M	63	10.2	8900	189	77	9	7.28	6853	801	8.56	236.0	11.9	11	1	1	1			1						1						1		1				
72	1063580	69	M	61	10.6	4600	89	67	24	4.52	3082	1104	2.79	80.6	13.3	10	1	1			1		1	L					1						1					
73	3465177	69	M	58	9.8	7200	293	70	19	9.70	5040	1368	3.68	214.2	5.9	57	1	1		1		1	1	I	1			1						1	1					
74	1114547	56	M	59	11.6	6700	120	72	18	7.39	4824	1206	4.00	99.5	9.3	14	1		1		1		1							1						1				
75	6180079	57	F	43	11.5	10600	179	78	12	5.10	8268	1272	6.50	140.7	8.3	27	1				1	1	1					1												
76	1114394	56	F	56	5	10300	287	88	10	4.68	9064	1030	8.80	278.6	11.9	9	1	1	1		1		1								1			1		1				
77	4867182	31	M	64	9.1	5100	181	66	16	11.54	3366	816	4.13	221.8	8.4	30	1	1	1	1										1				1	1	1	1	1	1	1
78	1094004	50	M	63	7.6	7700	242	70	21	8.89	5390	1617	3.33	149.7	8.9	16	1	1				1	1	I				1						1	1					
79	1102117	60	M	56	10.1	9900	279	65	25	12.52	6435	2475	2.60	112.7	5.0	68	1	1	1		1	1		L				1							1					
80	1107109	65	M	48	7.8	3800	144	70	20	6.77	2660	760	3.50	189.5	7.4	19		1	1				1					1						1		1				
81	888323	50	F	61	6.3	5670	49	53	3	8.37	3005.1	170.1	17.67	288.1	7.7	25	1	1	1		1	1	1					1							1		1			
82	6018351	34	M	58	4.8	5000	201	66	22	11.50	3300	1100	3.00	182.7	7.4	29	1	1		1											1			1	1					
83	5706728	61	M	51	11.9	8000	153	73	19	7.50	5840	1520	3.84	100.7	7.5	20					1	1	1	D				1												
84	1095957	59	M	67	5.6	6300	236	80	11	8.25	5040	693	7.27	340.5	9.1	33	1		1	1		1	1					1						1		1				
85	987338	70	F	40	8.3	5900	224	59	23	7.29	3481	1357	2.57	165.1	4.5	40	1	1	1	1	1	1	1	I	1	1		1						1	1		1			

86	1093083	56	M	64	8.5	5100	188	46	34	8.60	2346	1734	1.35	108.4	8.7	32	1		1	1		1					1					1	1	1				1
87	1060764	54	M	56	10.5	10600	174	76	17	12.26	8056	1802	4.47	96.6	5.5	49		1	1		1		1						1				1		1					
88	1077753	80	M	59	10.5	7000	136	68	20	7.78	4760	1400	3.40	97.1	6.3	21	1						1	I					1				1							
89	1095669	63	M	65	6.4	5700	169	52	24	7.96	2964	1368	2.17	123.5	8.7	15	1	1	1			1			1			1					1		1					
90	4923051	38	M	58	8.8	5400	186	63	22	10.60	3402	1188	2.86	156.6	7.8	28	1			1			1						1				1	1						
91	6144288	47	M	67	11.8	8300	174	59	29	10.85	4897	2407	2.03	72.3	8.0	31	1		1		1		1							1					1					
92	1058865	38	M	46	9.9	7400	285	45	37	16.06	3330	2738	1.22	104.1	4.1	70		1	1	1	1	1									1			1						
93	3446239	39	M	58	9.1	7000	269	65	19	9.31	4550	1330	3.42	202.3	8.7	18		1			1		1					1				1							
94	958730	57	M	56	8.9	7700	170	63	24	13.18	4851	1848	2.63	92.0	4.9	50	1		1	1		1		D				1				1	1	1					
95	1055579	49	M	83	9.7	5200	85	67	22	12.23	3484	1144	3.05	74.3	8.6	20	1		1	1	1	1	1							1				1	1	1	1	1		
96	5208970	32	F	39	6.3	3400	197	67	21	18.83	2278	714	3.19	275.9	2.6	8	1	1	1		1		1						1				1		1					
98	6011963	59	M	49	9.6	2000	243	84	11	4.95	1680	220	7.64	1104.5	11.1	8	1			1	1		1					1				1	1						
99	1099327	74	M	56	10.4	10900	58	50	45	12.72	5450	4905	1.11	11.8	4.0	7	1		1		1	1	1					1						1						
100	1774533	72	M	61	9.1	6300	156	75	15	9.08	4725	945	5.00	165.1	6.3	27	1	1	1	1	1	1		L				1				1	1	1					