The Pharma Innovation Journal 2018; 7(10): 63-70

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2018; 7(10): 63-70

www.thepharmajournal.com
Received: 04-08-2018
Accepted: 08-09-2018

**Kothapalli Rahul Chowdary**
Department of Pharmacy Practice, School of Pharmacy, Anurag Group of Institutions, Venkatapur, Ghatkesar, Telangana, India

**Gangavarapu Venkata Mounika**
Department of Pharmacy Practice, School of Pharmacy, Anurag Group of Institutions, Venkatapur, Ghatkesar, Telangana, India

**Chalapati Prasanth Chowdary**
Department of Pharmacy Practice, School of Pharmacy, Anurag Group of Institutions, Venkatapur, Ghatkesar, Telangana, India

**Rani Samyuktha Velamanakki**
Department of Pharmacy Practice, School of Pharmacy, Anurag Group of Institutions, Venkatapur, Ghatkesar, Telangana, India

**Vasudha Bakshi**
Department of Pharmacy Practice, School of Pharmacy, Anurag Group of Institutions, Venkatapur, Ghatkesar, Telangana, India

**Mounika Tejaswi Gorle**
Department of Pharmacy Practice, School of Pharmacy, Anurag Group of Institutions, Venkatapur, Ghatkesar, Telangana, India

**Correspondence**
**Mounika Tejaswi Gorle**
Department of Pharmacy Practice, School of Pharmacy, Anurag Group of Institutions, Venkatapur, Ghatkesar, Telangana, India

# Study on prognostic markers in chronic kidney disease patients as an independent risk factors and its management

**Kothapalli Rahul Chowdary, Gangavarapu Venkata Mounika, Chalapati Prasanth Chowdary, Rani Samyuktha Velamanakki, Vasudha Bakshi and Mounika Tejaswi Gorle**

**Abstract**
The relationship of CKD is bidirectionally linked and this association leads to the vicious circle contributing to premature death. There are several risk factors that cause promotion and progression of CKD. The progression of disease and response o the therapeutic interventions in the patients can be predicted by evaluating prognostic markers and traditional risk factors. A few traditional risk factors like age, male gender, older gender, dyslipidemia, smoking, diabetes and the levels of few prognostic markers like haemoglobin, uric acid, serum albumin, Neutrophil-Lymphocyte ratio, para-thyroid hormone can be considered to observe the risk in CKD patients. A total of 131 patients were included in the study. Around 38% of the patients suffered from End-stage renal disease i.e. CKD stage 5. Among Six traditional risk factors considered in the study, majority of patients have hypertension (100%), followed by dyslipidemia (85.5%), and diabetes (82.4%). Higher level of troponin 1 (cardiac biomarker) is seen in 91% of the patients. Considering patients with the end stages of CKD majority of the patients diagnosed with CKD it has have moderate abnormal levels of haemoglobin, severe hyperuricemia, severe albuminuria, severe Neutrophil-Lymphocyte ratio, moderate hypercalcemia, mild hyperphosphataemia, severe levels of parathyroid hormone. In our study, we observed that highly prevalent in the end stages of Chronic Kidney Disease. The prognostic markers included show impact on CKD patients. It seems to be intuitive that early detection and proper management may serve to reduce the risk renal complications.

**Keywords:** chronic kidney disease, hyperuricemia, hyperphosphatemia, troponin 1, torsemide

## Introduction
Chronic Kidney Disease, with its high prevalence, morbidity and mortality, is an important public health problem. Large number of patients below the poverty line, low gross domestic product, and low monetary allocations for health care has led to suboptimal outcomes. Moreover, CKD and other non-communicable diseases have often been ignored in the face of persistent challenges from and competition for resources for communicable diseases and high infant and maternal mortality [1]. The burden of CKD is very high in developing countries of South Asia, Eastern Europe and Latin America. Diabetes mellitus, hypertension, lower socioeconomic status, environmental factors and intrauterine growth retardation are among the predisposing factors for CKD in developing countries [2].
According to NKF KDOQI Guidelines, CKD is defined as either kidney damage or GFR for <60ml /min 1.73m$^2$ for greater than 3 months. Kidney damage is defines as pathologic abnormalities or Markers of kidney damage, including abnormalities in the composition of blood or urine, or abnormalities in imaging tests [3].
CKD usually develops in stages as the kidneys don't usually fail all at once. Instead, kidney disease often progresses slowly over a period of years. There are usually 5 stages, they are

- **Stage 1:** with normal or high GFR (GFR > 90 mL/min)
- **Stage 2:** Mild CKD (GFR = 60-89 mL/min)
- **Stage 3A:** Moderate CKD (GFR = 45-59 mL/min)
- **Stage 3B:** Moderate CKD (GFR = 30-44 mL/min)
- **Stage 4:** Severe CKD (GFR = 15-29 mL/min)
- **Stage 5:** End Stage CKD (GFR <15 mL/min)

**Epidemiology**

CKD is emerging to be an important chronic disease globally, and the reason of this is a multifactorial. CKD is a worldwide public health issue, the incidence and prevalence of which are increasing, resulting in high cost and poor outcomes. In the United States, the prevalence of earlier stages of CKD is approximately 100times greater than the prevalence of kidney failure, affecting almost 11% of adults in the United States. Its major cause is due to the Most of the people have inadequate health-care provision due to either lack of health education, lack of primary healthcare, inadequate funding on the part of the government and, most importantly, the increasing prevalence of risk factors for CKD such as diabetes and hypertension. In addition, other causes like glomerulonephritis and renal stones are prevalent due to infections and dry weather conditions [4].

In India, given its population >1 billion, the rising incidence of CKD is likely to pose major problems for both healthcare and the economy in future years. Indeed, it has been recently estimated that the age-adjusted incidence rate of ESRD in India to be 229 per million population (pmp) and>100,000 new patients enter renal replacement programs annually in India. On the other hand, because of scarce resources, only 10% of the Indian ESRD patients receive any renal replacement therapy (RRT). The lack of community-based screening programs has led to patients being detected with CKD at an advanced stage. It is possible that early detection of kidney disease through community based screening programs might have an impact on this problem through earlier intervention. In USA the overall prevalence of CKD increased from 12 percent to 14 percent between 1988 and 1994 and from 1999 to 2004 but has remained relatively stable since 2004. The largest increase occurred in people with Stage 3 CKD, from 4.5 percent to 6.0 percent, since 1988.Women (15.93 percent) are more likely to have stages 1 to 4 CKD than men (13.52 percent). African Americans (17.01 percent) and Mexican Americans (15.29 percent) are more likely to have CKD than Caucasians (13.99 percent). The prevalence from 1999 to 2004 is higher than it was in 1988 to 1994. [5] US has seen a 30% increase in prevalence of CKD in the last decade.

In India, the CKD prevalence recorded as 17.2% with stage 1, 2, 3, 4, 5 as 7%, 4.3%, 4.3%, 0.8% and 0.8% respectively. 43.1% of their cohort had hypertension, and 18.8% had diabetes. In states like Karnataka prevalence of diabetes and 33.62% of hypertension, authors found 6.3% prevalence of CKD stage 3.In state of Andhra Pradesh the coastal regions of the Srikakulam district and Chimakurthy mandal (30–40 km from the coast) in the Prakasham district of Andhra Pradesh, India (known as the Uddanam area), 60% of the local population has been found to have CKD. Nearly 4000 villagers have died of CKD in the last decade, and almost a third of the population in Uddanam suffers from CKD.

**Aim**

The aim of the study is to evaluate various prognostic markers in chronic kidney disease patients and its management.

**Objectives**

**Primary objectives**

- To determine different prognostic markers in chronic kidney disease patients.
- To assess several approaches for management.

**Secondary objectives**

- To estimate various co-morbidities and complications.
- To evaluate traditional risk factors which are associated with chronic kidney disease according to Framingham heart study.

**Methodology**

**Study protocol**

It is a prospective observational study conducted for a period of 6 months. Patients who meet the study criteria will be included in the study. The required data will be collected from the case sheets.

**Study site**

The study was conducted at Yashoda Hospital, Secunderabad, and Telangana, India. It is a 600 bedded multi-disciplinary hospital. The study was approved by the Institutional Ethics & Research Committee of Yashoda Hospital, Secunderabad.

**Study design**

It is a prospective observational study.

**Study period**

Study period was about 6 months that is from November 2017 to April 2018.

**Study population**

Total 131 patients were included in the study.

**Study criteria**

**Inclusion criteria**

- Patients both male and female, above age 30 years are included.
- Patients diagnosed with chronic kidney disease from stage 1 to 5.
- Any cardiovascular disease patients with history of chronic kidney disease are also included.
- Patients who meet study criteria.

**Exclusion criteria**

- Patients both male and female below 30 years of age are excluded.
- Pregnant and lactating women are excluded.
- Patients with insufficient data.
- Patients who are undergoing dialysis.

**Study procedure**

- A prospective observational study was conducted at Yashoda Hospital, Secunderabad for a period of six months.
- Based on inclusion and exclusion criteria, Chronic kidney disease patients were included in the study
- All necessary and baseline information was collected using the patient data collection proforma which includes:
  - Patient demographic characteristics such as age, gender, personal history and habits
  - Present illness
  - Past medical history
  - Traditional risk factors
  - Prognostic markers
  - Cardiovascular complications associated with chronic kidney disease
  - Present medication chart

- The collected and documented data was analyzed by using the appropriate statistics based on following parameters:
  - Patient distribution based on age.
  - Patient distribution based on gender
  - Patient distribution based on Body Mass Index.
  - Patient distribution based on stages of chronic kidney disease.
  - Patient distribution based on significance between prognostic markers and observed abnormal lab investigations.

**Statistical analysis**

- Advanced statistical tests like Chi-square was used to rule out significance between the considered parameters like prognostic parameters and diagnostic tests.
- Software's like SPSS and MS EXCEL were used to arrange and evaluate the outcomes.

**Outcome measurements**

- Prognostic markers in chronic kidney disease are believed to be the independent risk factors for causing cardiovascular complications.
- These markers may worsen the existing cardiovascular disease or increase the risk of development of cardiovascular diseases in patients with chronic kidney disease and it seems intuitive that early detection and more aggressive intervention may serve to reduce the risk in effected individuals.
- Proper management of these prognostic markers may reduce the severity and progression of cardiovascular complications in chronic kidney disease patients, and can improve the quality of life of the patients.

**Results**

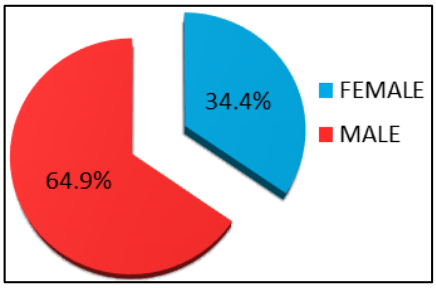


**Fig 1:** Gender wise distribution

The study population comprised of total 131 patients. Among them 64.9% of the patients are male and 34.4% of the patients are female.

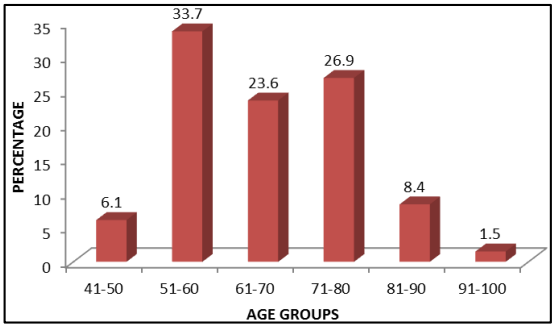


**Fig 2:** Age groups

Majority of the patients in our study belong to the age group of 51-60 years (33.7%) followed by 71-80 years (26.9%). Around 23% of the patients belong to the age group of 61-70 years.

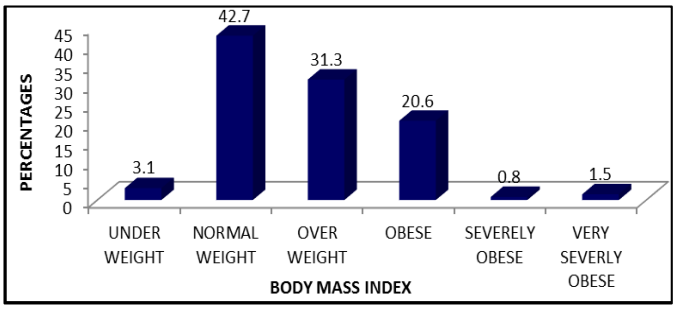


**Fig 3:** Distribution of population based on body mass index

The graph depicts that among the total study population 42.7% patients had healthy weight, while 31.3% were overweight and 20.6% patients were obese.

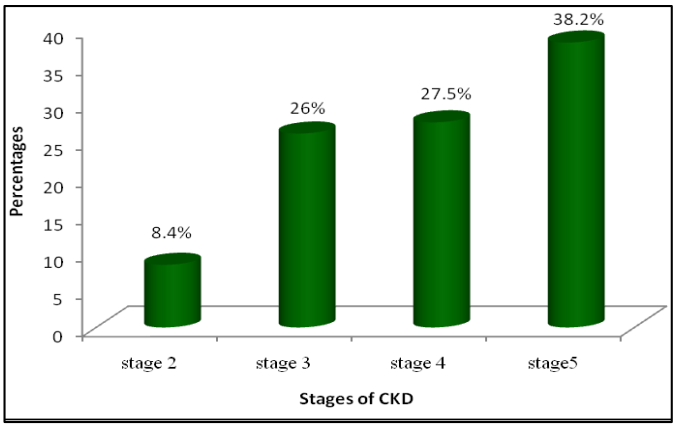


**Fig 4:** Distribution of population in different stages of CKD

The chart gives information about the distribution of population in various stages of chronic kidney disease. Majority of the population (38.2%) are suffering from the end-stage renal disease i.e. stage 5 CKD. Around 27.5% of the patients are in stage 4 CKD, followed by 26% who are in stage 3 CKD. The least number of patients belong to the early stage of the disease.

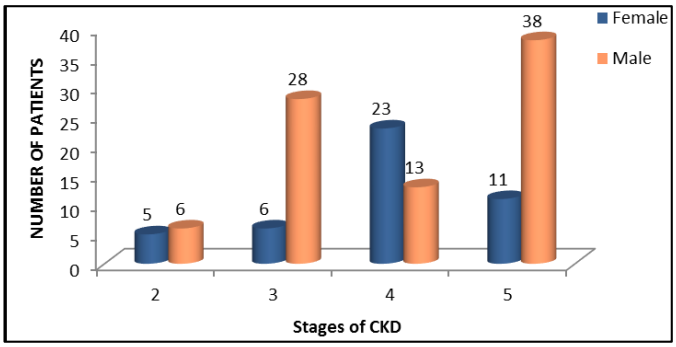


**Fig 5:** Gender wise distribution of population in five stages of CKD

The bar chart depicts information about the Number of patients in both male and female population in various stages of CKD. Overall, least number of patients of both the genders is in stage 2 of CKD. Majority of male patients are in the 3rd and 5th stages making up to 28 and 38 members respectively. The Highest number of female patients 23 belongs to the 4th stage of CKD.

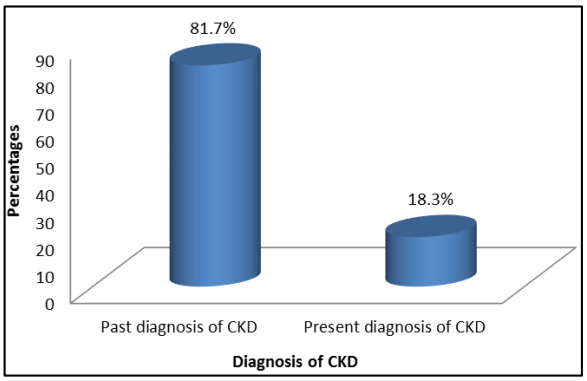


**Fig 6:** Diagnosis of Chronic Kidney Disease

The chart shows the onset of CKD. Among 131 patients, 81.7% of the population had past history of CKD while 18.3% are presently diagnosed with CKD.

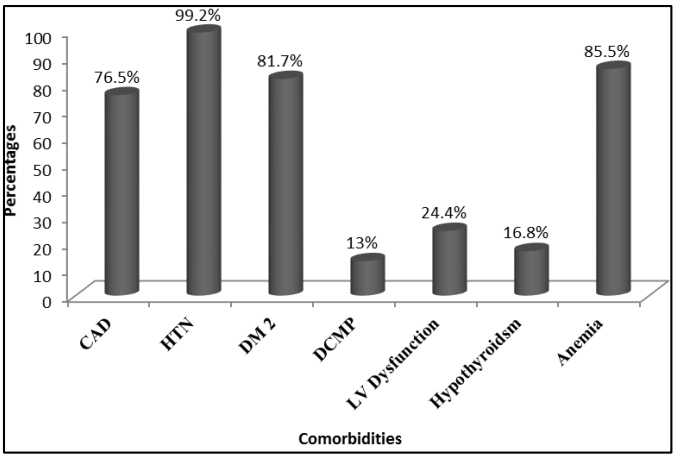


**Fig 7:** Comorbidities

The bar chart depicts information about the different comorbidities were seen in the CKD population. Majority of the population (99.2%) have hypertension followed by 85.5% suffering from anaemia. 81.7% of the patients have diabetes mellitus. 75.6% of the population were affected by Coronary Artery Disease. In the population least number of patients suffered from dilated cardiac myopathy (13%), Left ventricular hypertrophy (24.4%) and hypothyroidism (16.8%)

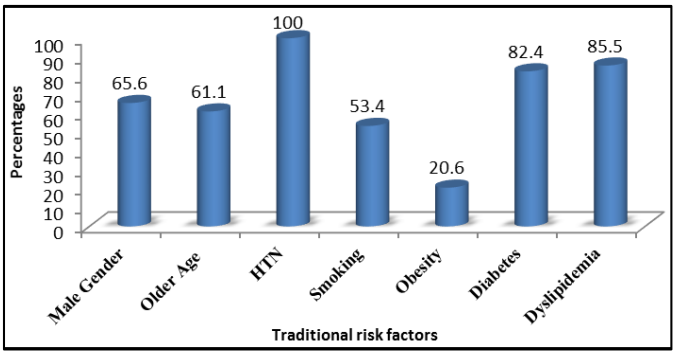


**Fig 8:** Traditional risk factors

The bar chart illustrates various traditional risk factors that are commonly associated with chronic kidney disease and cardiovascular diseases. From the study conducted 100% of patients have hypertension. 85.5% of the patients are with dyslipidemia and 82.4% of the patients are diabetic. Only 20.6% of the patients are obese.

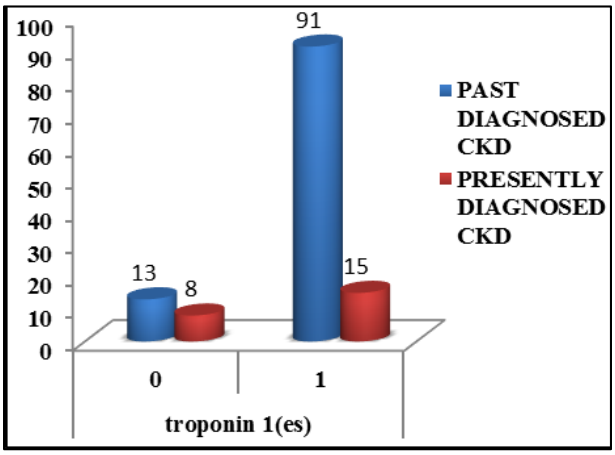


**Fig 9:** Levels of troponin 1 in past and presently diagnosed CKD patients

The graph compares the levels of troponin 1 in the patients with past history of CKD and the patients who were diagnosed with CKD in the present. In contrast, higher level of troponin 1 (es) is seen in 91% of the patients who were diagnosed with CKD in the past.

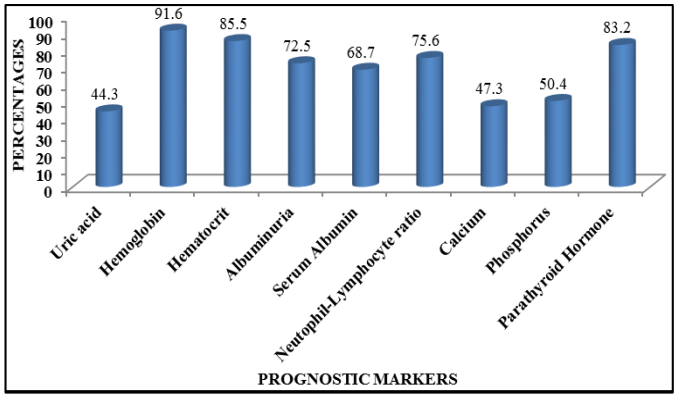


**Fig 10:** Prevalence of various prognostic markers.

The graph depicts the prevalence of different prognostic markers which were included in our study. These markers were seen in patients with CKD. Around 91% of the patients have abnormal haemoglobin levels followed by 85.5% patients with abnormal hematocrit values. Out of the total population 83.2% have abnormal levels of parathyroid hormone, 75.6% have abnormal Neutrophil-Lymphocyte ratio, 72.5% have Albuminuria, and 68.7% have abnormal serum albumin. Around half of the study population has abnormal phosphorous levels while the population with abnormal calcium and uric acid levels made up to 47.3% and 44.3% respectively.

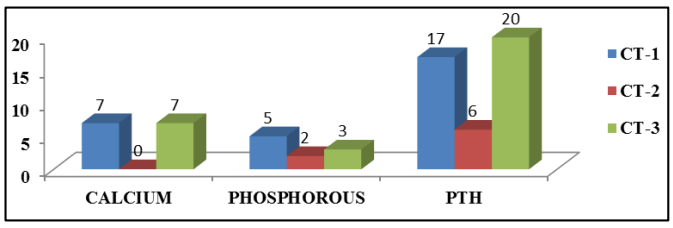


**Fig 11:** Association between different prognostic markers and CT scan interpretations

The bar graph gives information about the relation between different markers and CT scan interpretations. Majority of the

patients with high PTH levels showed fibrotic calcifications i.e. CT-1(17 patients) and atheromatous calcifications of aorta and coronary artery i.e.CT-3 (20 patients).

**Table 1:** Chi-square test for phosphorous and CT scan interpretations

| | Pearson's Chi-Square | | |
|---|---|---|---|
| | **Chi-square** | **Differential factor** | **Significance** |
| Clustered calcifications in kidney | 3.239 | 1 | .050 |
| Aorta and coronary arteries show atheromatous calcifications | .666 | 1 | .041 |
| Aorta calcifications | 2.617 | 1 | .106 |
| Fibro calcifications plaque noted in CCA | 2.777 | 1 | .036 |
| Vascular calcification in abdominal arteries | .006 | 1 | .939 |
| Pleural thickening with pleural calcifications | 2.260 | 1 | .133 |

The table below shows that there is significance between phosphorous and atheromatous calcifications of aorta and coronary artery, aorta calcifications, fibro calcific plaques and clustered calcifications in kidneys.

**Table 2:** Chi-square test for phosphorous and atheromatous calcifications

| | Pearson Chi-square | | |
|---|---|---|---|
| | **Chi-square** | **Differential factor** | **Significance** |
| Clustered calcifications in kidney | 3.693 | 1 | .005 |
| Aorta and coronary arteries show atheromatous calcifications | 0.39 | 1 | 0.05 |
| Aorta calcifications | 4.696 | 1 | .030 |
| Fibro calcific plaques | 2.051 | 1 | 0.035 |

**Assessment of prognostic markers**

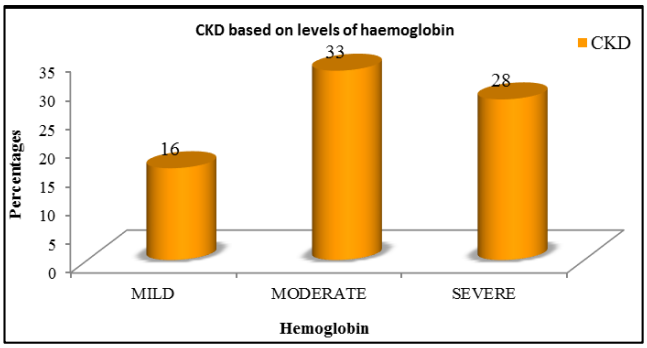


**Fig 12:** Distribution of patients with CKD based on levels of haemoglobin

The above bar graph gives information about the patients with abnormal haemoglobin values suffering from CKD. Overall, majority of the patients diagnosed with CKD (33) have moderate abnormal levels of haemoglobin.

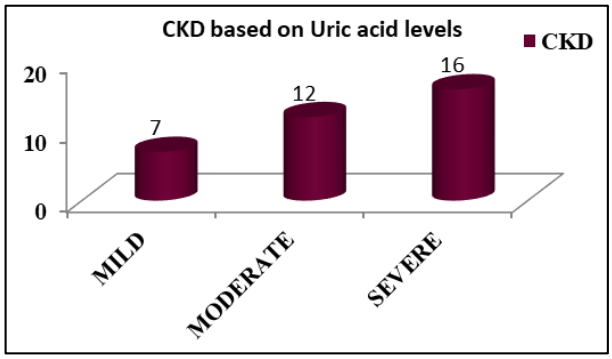


**Fig 13:** Distribution of patients with CKD based on levels of uric acid

The bar graph gives information about the distribution of patients diagnosed with CKD based on the levels of uric acid. Overall, the graph shows an increasing trend. Most of the patients suffering from CKD (16) have severe hyperuricemia.

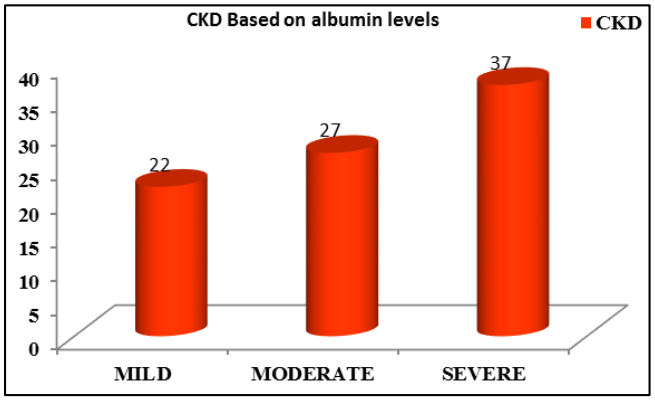


**Fig 14:** Distribution of patients with CKD based on albumin levels

The above bar graph gives information about the distribution of patients diagnosed with CKD based on the levels of albumin. Majority of the patients with CKD (37) seems to have severe albuminuria.

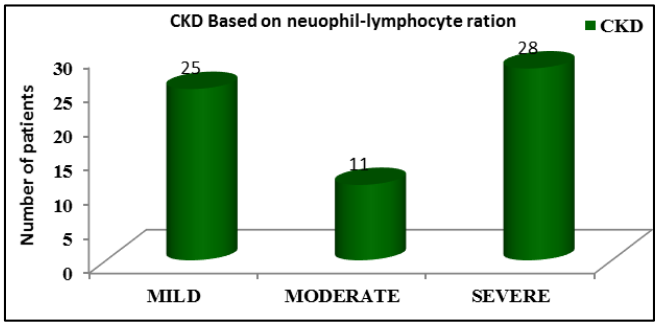


**Fig 15:** Distribution of patients with CKD based on neutrophil-lymphocyte ratio

The above bar graph gives information about the distribution of patients suffering from CKD and CAD based on Neutrophil-Lymphocyte ratio. Majority of the patients with CKD (28) (24) have severe Neutrophil-Lymphocyte ratio.

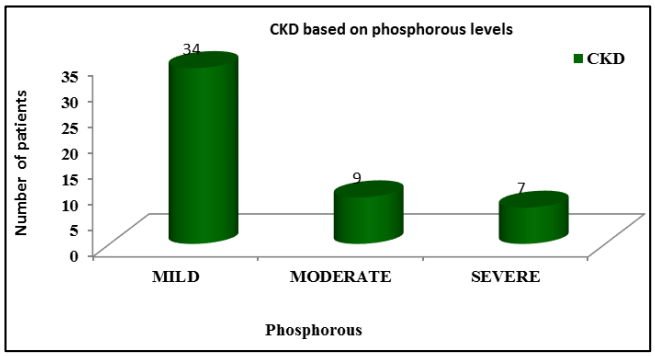


**Fig 16:** Distribution of patients with CKD based on phosphorous levels

The bar graph gives information about the distribution of patients with CKD based on the levels of phosphorous. Majority of the patients suffering with CKD (34) have mild hyperphosphatemia.

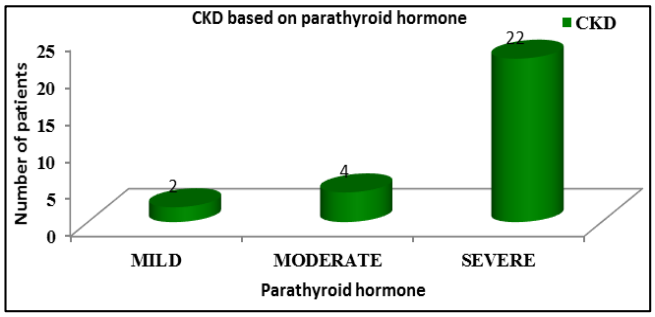


**Fig 17:** Distribution of patients with CKD based on parathyroid hormone

The bar graph explains about the distribution of patients with CKD based on the levels of parathyroid hormone. Majority of the patients with CKD (22) have severe levels of parathyroid hormone.

## Treatment

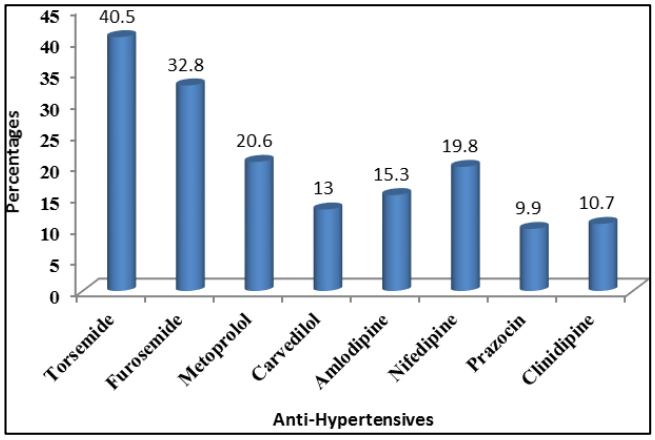


**Fig 18**: Percentage of anti-hypertensive's prescribed

The graph illustrates information about the preferred Anti-Hypertensive's given to the patients with chronic kidney disease diuretics were the most prescribed drugs. Among them Torsemide was given to around 40% of the patients and 32.5% were prescribed Furosemide.

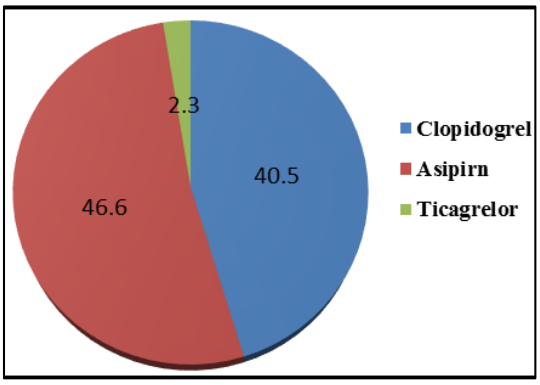


**Fig 19:** Percentages of anti-platelets prescribed

The pie chart above illustrates the information about the prescription pattern of anti-platelets. Among the three anti-platelets given Aspirin was prescribed to 46.6% patients making it the most prescribed drug. 40.5% of the patients were prescribed Clopidogrel, Ticagrelor was given to only 2.3% of the patients.

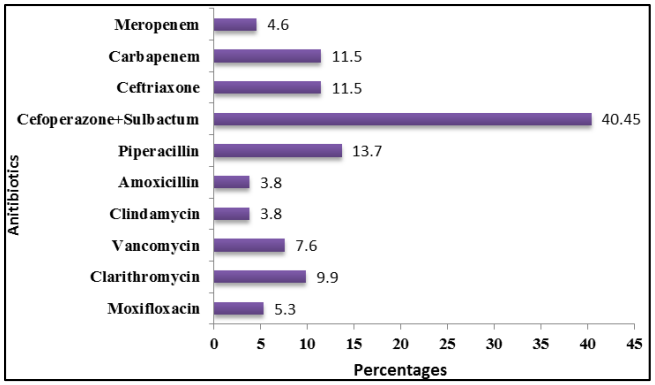


**Fig 20:** Percentages of antibiotics prescribed

The above bar chart gives information about the percentages of various antibiotics prescribed to the patients. Cefoperazone in combination with Sulbactam was given to 40.45% of the patients.

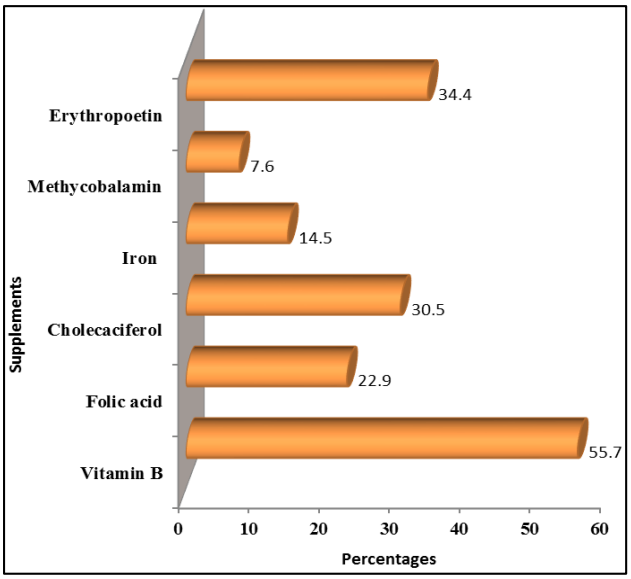


**Fig 21:** Percentages of supplements prescribed

The bar graph gives information about the supplements which were given to the patients. 55.7% of the patients were

prescribed vitamin-B complex supplement and 34.4% were prescribed Erythropoetin, Cholecalciferol was given to only 30.5% patients.

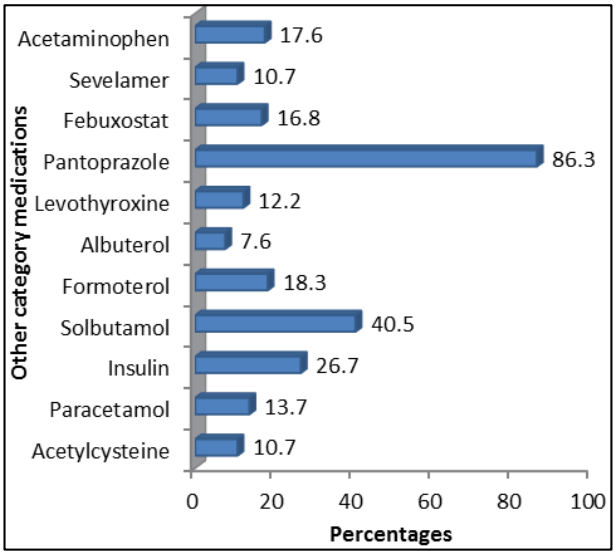


**Fig 22:** Other category medications

The above graph illustrates information about the other category of drugs which were given to the patients. In comparison, pantoprazole was the most prescribed drug. 86.3% of the patients were prescribed pantoprazole.

**Discussion**

A total of 131 CKD patients were included in our study. The population was screened for cardiovascular complications and the significance between prognostic markers and observed complications was determined. About 3/5$^{th}$ of the population (64.9%) were males and 2/5$^{th}$ of the population (35.1%) were females. Males are more prone for developing CKD when compared to females**.** This might be due to the factors like Smoking and alcohol. Smoking has been the paramount risk factor which initiates and progress major diseases like CKD. Other risk factors like Diabetes and Hypertension may progress the risk of developing CKD complications or increase the severity of the existing complications. The least affecting factors include Systemic Infections and nephrotoxic agents, cardiovascular complications.

Most of the patients are suffering from ESRD. Among them most of the patients are males when compared to females. When a patient is diagnosed with CKD, several factors like hypertension, diabetes, persistent proteinuria, hyperlipidemia, smoking and/or any existing cardiovascular complications play a vital role in progression of disease from stage 1 to stage 5. CKD may cause dyslipidemia which is considered to be the key factor for development of atherosclerosis. It was observed that 85.5% of the patients are reported to have dyslipidemia. In patients who were diagnosed with CKD in the past because of the prolonged duration of the disease when compared to the patients who are presently diagnosed with CKD. This shows that the patients who are already suffering with CKD are at a higher risk of developing cardiovascular diseases.

Albuminuria is considered as a marker of renal injury, as well as it is accepted as an independent risk factor for cardiovascular morbidity and mortality. It is also the marker for the sub clinical vascular damage in the kidney and for the vascular beds and it signify the systemic endothelial dysfunction that predisposes the further Cardiovascular events. But in our study we did not had the significance for any of the complication. In this case further studies to be needed in large population to evaluate the exact role. Hyperuricemia is another considerable prognostic marker. It is defined as elevated levels of uric acid in the body. Significance was observed between abnormal uric acid levels hypoalbuminemia is considered as a marker for underlying inflammation and malnutrition. Albumin is known to increase blood viscosity and cause vascular dysfunction by impairing vasodilatory response. Hypoalbuminemia is also considered as a cardiac marker. Albumin effects cholesterol transport thus causing left ventricle dysfunction and heart failure.

Anti-hypertensives are prescribed to treat hypertension which is a common complication that develops due to CKD. Generally, Diuretics is the most preferred class in patients with CKD and CVD. Anti platelets are prescribed commonly in patients with any vascular diseases. In this, aspirin (46.6%) and clopidogrel (40.8%) are highly prescribed. Antibiotics are prophylactically given because underlying infections are common. In our population Cefoperazone (40.45%) is highly prescribed. Piperacillin, Ceftriaxone, Amoxicillin, Clindamycin, Clarithromycin are the other choice of drugs. Majorly vitamin B complex is prescribed in supplements category. Reason behind this is, CKD patients are mostly on fluids so they do not reach the nutrition requirement. Other supplements like folic acid, iron supplements are also prescribed. In other medication category pantoprazole is highly prescribed, and other drugs like Salbutamol, Formoterol, Insulin, Paracetamol are also prescribed. For hyperuricaemia, Febuxostat is prescribed in about 16.8% cases. Sevelamer is prescribed in about 10.7% cases for hyperphosphatemia.

**Conclusion**

- In our study we observed that coronary artery disease is highly prevalent in the end stages of chronic kidney disease.
- Risk factors like hypertension, dyslipidemia and diabetes are commonly observed in chronic kidney disease patients.
- Left Ventricular hypertrophy is observed more in patients with low hemoglobin levels.
- Myocardial Infarction is observed in patients with low hemoglobin levels and albuminuria.
- Left ventricular dysfunction and left ventricular hypertrophy were observed more in patients with anemia and albuminuria.
- Coronary artery disease, severe LV dysfunction and Myocardial Infarction are significant with increased uric acid levels.
- Dilated Cardiomyopathy and Coronary artery disease are seen in patients with high Neutrophil-lymphocyte ratio.
- Vascular calcification markers like high serum calcium, high serum phosphorous and high PTH have shown significance with clustered calcifications in kidney, aorta and coronary artery calcifications, fibro calcifications in common carotid artery, fibro calcific plaques, tracheobranchial wall calcifications and aortic knuckle calcifications.
- Low serum albumin levels have shown significance with severe LV dysfunction and LV hypertrophy.
- According to our study, the prognostic markers included show impact on cardiovascular complications in CKD patients.

- Diuretics are the most preferred class of drugs in chronic kidney patients with cardiovascular complications. Atorvastatin is the highly prescribed anti-hyperlipidemic drug and aspirin is the most prescribed anti-platelet drug.
- It seems to be intuitive that early detection and proper management may severe to reduce the risk of cardiovascular complications in chronic kidney disease patients.

**Acknowledgement**
We wish to thank the management of School of Pharmacy, Anurag Group of Institutions, Venkatapur, Ghatkesar, and Telangana, India for providing necessary equipment for research, constant encouragement, praiseworthy inspiration, facilities and support.

**Conflict of interest**
Author declares that there is no conflict of interest to disclose.

**Sponsorship**
Nil.

**References**

1. Georgi Abraham, Santosh Varughese, Thiagarajan Thandavan Arpana Iyengar, Edwin Fernando, Jaffar Naqvi SA, Rezvi Sheriff, *et al*. Chronic kidney disease hotspots in south Asia. Clinical Kidney Journal. 2016; 9(1):135-141.
2. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002; 399(2, 1):1-266.
3. Ajay K Singh, Youssef MK Farag, Bharati V Mittal, Kuyilan Karai Subramanian, Sai Ram Keithi Reddy, Vidya N Acharya, Alan F Almeida, *et al*. Epidemiology and risk factors of chronic kidney disease in India – results from the SEEK (Screening and Early Evaluation of Kidney Disease) study. BMC Nephrology, 2013; 14:114.
4. Ritz E, Ogata H, Orth SR. Smoking a factor promoting onset and progression of diabetic nephropathy. Diabetes Metab. 2000; 26(4):54-63
5. Wang P, Lau J, Chalmers T. Meta-analysis of the effects of intensive blood-glucose control on late complications of type I diabetes. Lancet. 1993; 341:1306-1309.
6. Malvinder S Parmar. Director of dialysis Chronic renal disease; BMJ. 2002; 325(7355):85-90.
7. Mora-Fernández C, Domínguez-Pimentel V, de Fuentes MM. "Diabetic kidney disease: from physiology to therapeutics". J. Physiol. 2014; 592(18):3997-4012.
8. Paolo Cravedi, Giuseppe Remuzzi. Pathophysiology of proteinuria and its value as an outcome measure in chronic kidney disease, Br J Clin Pharmacol. 2013; 76(4):516-523.
9. Harsh Mohan. Textbook of pathology, The Heart, chapter 16:417.
10. Joseph T, DiPiro Robert, Talbert L, *et al*. Pharmacotherapy – A Pathophysiologic Approach; ischemic heart disease Chapter. 17:217.
11. Gerard J. Tortora Bryan Derrickson, Principles of Anatomy and Physiology; chapter 20, The Cardiovascular System: The Heart; 13th Edition. 757.
12. Sun R, Liu M, Lu L, Zheng Y, Zhang P. Congenital Heart Disease: Causes, Diagnosis, Symptoms, and Treatments, Cell Biochem Biophys. 2015; 72(3):857-60.
13. Dr. Carlos Valladares. Acute Pericarditis, ESC Council for Cardiology. 2014; 18(1):29-40.
14. Roth, Gregory A. Demographic and epidemiologic drivers of global cardiovascular mortality. New England Journal of Medicine. 2015; 372(14):1333-1341.
15. Dorairaj Prabhakaran, Panniyammakal Jeemon, Ambuj Roy. Cardiovascular Diseases in India, Circulation. 2016; 133:1605-1620.
16. Foley RN, Parfrey PS, Sarnak MJ. Epidemiology of cardiovascular disease in chronic renal disease. J Am Soc Nephrol. 1998; 9:16–S23.
17. Suguru Yamamoto, ValentinaKon. Mechanisms for increased cardiovascular disease in chronic kidney dysfunction, Curr Opin Nephrol Hypertens. 2009; 18(3):181–188.
18. Arun Kumar Subbiah, Yogesh K Chhabra, Sandeep Mahajan. Cardiovascular disease in patients with chronic kidney disease: a neglected subgroup, Heart Asia. 2016; 8(2): 56–61.
19. Foley RN, Wang C, Collins AJ. Cardiovascular risk factor profiles and kidney function stage in the US general population: the NHANES III study. Mayo Clin Proc. 2005; 80(10):1270-7.
20. Amaresan MS. Cardiovascular disease in chronic kidney disease. Indian J Nephrol. 2005; 15:1-7.
21. Levin A. Clinical epidemiology of cardiovascular disease in chronic kidney disease prior to dialysis. Semin Dial. 2003; 16(2):101-5.
22. Fujiwara N. Osanai T. Kamada T. Study on the relationship between plasma nitrite and nitrate level and salt sensitivity in human hypertension. Modulation of nitric oxide synthesis by salt intake. Circulation. 2000; 101:856-861.
23. Leopold A. Aldosterone, mineralocorticoid receptor activation, and cardiovascular remodeling. Circulation. 2011; 124:466-468
24. Foley RN, Parfrey PS, Harnett JD, *et.al*. The impact of anemia on cardiomyopathy, morbidity, and mortality in end-stage renal disease. J Am Soc Nephrol. 2005; 16:529-538.
25. London GM. Cardiovascular calcifications in uremic patients: clinical impact on cardiovascular function. J Am Soc Nephrol, 2003; 14(4):305-309.
26. Obrador GT. Macdougall IC. Effect of red cell transfusions on future kidney transplantation. CJASN. 2012; 8:3409.
27. Parham WA, Mehdirad AA, Biermann KM, Fredman CS. Hyperkalemia revisited Tex Heart Inst J. 2006; 33:40-47.
28. Vanholder R. Glorieux G. Lamiere N. Uraemic toxins and CVD Nephrol Dial Transplant. 2006; 18:463-466.
29. Herzog CA, Asinger RW, Berger AK, Charytan DM, Díez J, Hart RG, Eckardt KU, *et al*. Cardiovascular disease in chronic kidney disease Kidney Int. 2011; 80(6):572-86.
30. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004; 351(13):1296-305.
31. Manjunath G, Tighiouart H, Coresh J, Macleod B, Salem DN, Griffith JL, Levey AS, *et al*. Level of kidney function as a risk factor for cardiovascular outcomes in the elderly. Kidney Int. 2003; 63(3):1121-9.