TITLE: HAEMATOLOGIC PROFILE IN PRE-DIALYSIS CHRONIC KIDNEY DISEASE PATIENTS IN A TERTIARY HOSPITAL IN SOUTHERN NIGERIA

IYAWE OI[1] , ADEJUMO OA[2]

[1] Department of Internal Medicine, University of Benin, Benin City, Edo State

[2] Department of Internal Medicine, Kidney Care Centre, University of Medical Sciences Ondo, Ondo State, Nigeria.

ABSTRACT

BACKGROUND: Chronic kidney disease (CKD) is associated with variable changes in the hematological parameters. Anemia is the most common abnormality, however, both number and function of white cells and platelets may be affected. These abnormalities are associated with overall poor clinical outcome. This study assessed the hematologic profile of pre-dialysis CKD subjects and associated factors.

MATERIALS AND METHODS: This was a cross-sectional analytical study that assessed and compared the hematologic profile in 100 pre-dialysis CKD subjects and 90 healthy controls. P value of < 0.05 was taken as significant

RESULTS: Mean age of the CKD and control subjects were 49.39±14.84 years and 52.66±13.90 years respectively. Ninety (90%) of CKD subjects had anaemia, significantly higher than 26(28.8%) in the control group (p=0.000). The proportion of CKD subjects with leukocytosis was significantly higher than the control subjects (p= 0.007). There was no significant difference in the proportion of CKD and control subjects with thrombocytopenia (p=0.64). The mean cell volume was significantly lower in the CKD group compared to the control subjects (p=0.000) . Severity of anaemia was significantly associated with CKD stage (p=0.000) but not with etiology (p=0.27).

CONCLUSION: Anaemia was highly prevalent in our pre-dialysis CKD patients and was significantly associated with CKD stage. White cell count was also significantly higher in the CKD subjects and this may reflect increased risk of cardiovascular morbidity and mortality

Key Words: haematological, profile, anaemia, pre-dialysis, chronic kidney disease.

INTRODUCTION

Chronic Kidney Disease (CKD) is a major health problem with a steady rise in its incidence and prevalence globally. Its burden is in epidemic proportions, affecting both developed and developing nations especially countries in the sub Saharan region.[1] The prevalence of CKD worldwide is estimated at 8-16% varying substantially across countries and regions[1]. Even within Nigeria there are variations in the reported prevalence of CKD, varying between 6-12 %.[2-4]

Anaemia is the most common reported hematological abnormality present in CKD. The prevalence of anemia in CKD patients varies between 77.5%-94%, depending on the stage of the disease.[5-8] The cardiovascular disease burden in CKD is further increased in the presence of anemia particularly in high risk populations, coupled with the higher risk of progression of CKD to end stage renal disease (ESRD) and frequent hospitalization.[9,10] The other detrimental effects of anemia include fatigue, depression, reduced exercise tolerance, and cardiovascular consequences, such as left ventricular hypertrophy (LVH) and left ventricular systolic dysfunction. These effects tend to worsen morbidity and lead to poor clinical outcome in the patients.[11-13]

Other blood cells such as platelets and white blood cells are also affected, but these have not been well studied. The number and function of platelets and white cells may also be affected in CKD resulting in attendant complications such as increase susceptibility to infections and bleeding tendencies. Reduced lymphocyte number may also be a marker of malnutrition in CKD.[14] Elevated total white cell counts and granulocyte counts are associated with increased

progression of CKD, cardiovascular morbidity and mortality.[15-17] This study assessed the hematologic profile of pre-dialysis CKD subjects and associated factors.

MATERIALS AND METHODS

STUDY DESIGN

This was a hospital-based cross sectional analytical study carried out in the University of Benin Teaching Hospital (UBTH). Consecutive pre-dialysis CKD patients who met the inclusion criteria were recruited over one year period from the nephrology clinic, medical wards and the emergency unit of the hospital.

SAMPLE SIZE

This was calculated using the Leslie Kish formula for sample size determination in a finite population. The prevalence of anemia in CKD patients used in the sample size calculation was 94% as reported by Shittu et al. [6]

STUDY POPULATION

A total of 100 pre-dialysis CKD subjects and 90 age and sex matched apparently healthy adults without CKD were included in the study

Inclusion criteria were newly diagnosed CKD patients, those on conservative management who were ≥ 18 years of age and who gave informed consent to participate in the study. Exclusion criteria were CKD patients on renal replacement therapy, those with urinary or respiratory tract infection, HIV infection, chronic hepatitis B and C infection, tuberculosis, haemoglobinopathies, malignancy, history of cigarette smoking, use of erythropoiesis stimulating agents and iron products for a period of 4 weeks to the time of evaluation or history of blood transfusion in the previous 4 weeks.

Ten milliliters of blood were collected from participants for serum creatinine, erythrocyte sedimentation rate (ESR), full blood count, reticulocyte count. Estimated glomerular filtration rate (eGFR) was calculated using Modification of Diet in Renal Disease (MDRD) that has been previously validated in Nigerians.[18]

Definition of Terms

Anaemia was defined using the World Health Organization (WHO) definition Hb concentration < 12g/dl (females), < 13g/dl (males).Severity of anaemia was classified as mild anaemia (Hb concentration<11-12.9g/dl for males and 11-11.9g/dl for females); moderate anaemia (Hb concentration< 8-10.9g/dl) and severe anaemia (Hb concentration< 8g/dl).[19]

CKD was defined as presence of markers of kidney damage and or estimated GFR of less than 60 ml/min/1.73 m^2 for at least three months.[20] Pre-dialysis CKD patients were those patients who fulfilled the criteria for the definition of CKD and had not been dialyzed.

CKD stages were defined according to Kidney Disease Improving Global Outcome (KDIGO) as follows: stage 1, eGFR greater than 90 ml/min/1.73 m^2 and/or persistent proteinuria; stage 2, eGFR of 60 to 89 ml/min/1.73 m^2 and/or persistent proteinuria; stage 3, eGFR of 30 to 59 ml/min/1.73 m^2; stage 4, eGFR of 15 to 29 ml/min/1.73 m^2; and stage 5, eGFR less than 15 ml/min/1.73m^2.[20]

Thrombocytopenia was defined as platelet count of $<90\times10^9$ cells/L. [21]

Leukocytosis was defined as White blood cell count > 8.2×10^9 cells/L [21]

Ethical clearance for this study was gotten from the Ethics and Research Committee of University of Benin Teaching Hospital.

Data Analysis

Data entry and analysis was performed using International Business Machines Statistical Product and Service Solution (IBM-SPSS) Version 21. Data was presented as frequencies, percentages and means (standard deviation). Frequencies were compared using chi-square test. Continuous data were compared using students t-test, Pearson's correlation test was used to find association between continuous variables. A p-value ≤ 0.05 was considered as statistically significant for all test conducted.

RESULTS

One hundred pre-dialysis CKD patients and ninety aged matched controls participated in the study with a mean age of 49.39±14.84 years and 52.66±13.90 years respectively. There were 56 (56%) male and 44(44%) female CKD subjects. The controls had 39 (43.3%) males and 51(56.7%) female controls. Sixty-two (62%) of the CKD subjects were young or middle aged. Fourteen (14%) of the CKD subjects were in stage 1, 8(8%) in stage 2, 29(29%) in stage 3, 14(14%) in stage 4 and the remaining 16(16%) were in stage 5. The etiology of CKD in the patients recruited were hypertension (32%); diabetes mellitus (31%); CGN (25%) and obstructive uropathy (12%). (Table 1)

Ninety (90%) of the CKD subjects had anaemia which was significantly higher than 26(28.8%) of the control with anemia (p= 0.000). Among the anemic CKD subjects, it was severe in 46 (51.1%), moderate in 35(38.8%) and mild in 9(10%). In the control group, 24(92.3%) of those with anemia had mild form.(Fig 1)

Leukocytosis was significantly higher in the CKD subjects compared to the control group(24% versus 7.8%) p= 0.007 There was no significant difference in thrombocytopenia between the two groups (3% versus 1.1%) p=0.64. (Fig 2)

The red blood cell count, haemoglobin concentration, packed cell volume and mean cell volume were significantly lower in the CKD patients compared to the controls (p=0.000). The reticulocyte count of the pre-dialysis CKD patients (1.62±2.80%) was higher than the controls (1.31±0.67%) p=0.297. The total white cell count was significantly different between both groups ($6.75\pm3.26\times10^9$ cells/L versus $5.82\pm1.72\times10^9$ cells/L) p= 0.017. The mean ESR value was higher in the CKD subjects with p values of 0.000 (Table 2)

The prevalence of anaemia increased from 64.2% at stage 1 to 87.5% at stage 2, 89.6% at stage 3, 96.9% and 100% at stage 4 and 5 CKD respectively (p= 0.000). There was a significant association between the severity of anaemia and stage of CKD (p= 0.000) (Table 3).There was no significant difference between haemoglobin concentration of the various aetiologies of CKD (p= 0.27). (Table 5)

DISCUSSION

This study showed a high prevalence of anaemia among our pre-dialysis CKD patients (90%). This finding is comparable to studies by Shittu et al [6] and Arun et al [22] who reported prevalence of anaemia to be 94% and 98% respectively. A lower prevalence of 77.5% was reported by Ijoma et al [7] in a study done in Southeastern Nigeria. The findings from this present study is at variance with studies done in Spain and United States of America which showed that prevalence of anemia were 58.5% and 15.4 % respectively.[23,24] Anaemia is more prevalent among patients with CKD in developing nations than developed nations. Possible reasons include the presence of factors that are not directly due to kidney disease such as high burden of infections like hookworm infestation, poor nutrition, racial and ethnic factors. Also, aetiology of CKD and time of presentation of these patients to nephrologist may also be partly responsible.

The prevalence of anaemia in the control group was 28.8% with majority having a mild form of anaemia. This is similar to the prevalence of anaemia in the general population reported by McLean et al as 24.8%.[25] Anaemia is known to be relatively common among apparently healthy population in the Sub Saharan region. [25,26] The prevalence of anaemia in the control subjects is also similar to 21.7% reported in apparently healthy Nigerian adults by Ugwuja et al.[27]

Severity of anaemia was shown to be significantly associated with the stage of CKD. This is consistent with the fact that as the glomerular filtration rate declines, there is a corresponding decline in the haemoglobin concentration which is mostly due to reduced synthesis of erythropoietin.[7,28,29]

Comparison of the mean red cell indices between the CKD and control groups showed that only the mean cell volume was significantly lower in the CKD subjects. There was no significant

difference with the other red cell indices. A similar finding was observed in the study by Shittu et al.[6] There was no association between these red cell indices and the degree of renal impairment in this study. This also agreed with report of work done in Nigeria.[6]

Chronic glomerulonephritis accounted for the lowest mean haemoglobin concentration (7.86±2.74%), closely followed by hypertension (8.76±2.66%), then diabetes mellitus (9.07±2.73%) and obstructive uropathy (9.41±2.49%). There was no significant association between the aetiology of CKD and anemia similar to an earlier report.[29] However, in variance to our finding, Loutradis et al[30] reported anaemia is more common in diabetic kidney disease patients compared to other kidney disease.

About a quarter of the CKD subjects had leukocytosis compared to 7.8% in the control group. The mean total white cell count and granulocyte count were significantly higher in the CKD group compared to control. This finding is similar to report by Shittu et al[6] but different from report by Suresh et al[31] and Islam et al.[32] Suresh et al[31] reported no significant difference in the mean white cell count and granulocyte count between their CKD patients and controls, however Islam et al[32] reported a significantly lower white cell count in their CKD patients compared to controls. This elevated white cell count and erythrocyte sedimentation rate may be associated with inflammation in the absence of infection which was excluded in our study. Coronary heart disease risk ratio is associated with high white blood cell count which is comparable with other inflammatory markers such as C-reactive protein.[33]

White blood cells play key role in the initiation and progression of atherosclerosis; these cells release cytokines that cause macrophage recruitment and proliferation of vascular smooth muscle.[33] Elevated white cell count and granulocyte have been associated with rapid progression

to ESRD, cardiovascular morbidity and mortality.[15-17] This may therefore imply that our CKD subjects are at increased risk of developing cardiovascular disease, hence there is need for aggressive cardiovascular risk factor modification and treatment.

There was no significant difference between platelet count of CKD and control groups in this present study. This is similar to report by van Blade et al[34] but differs from other reports where CKD patients had significantly lower platelet count.[9,30,31] Only 3% of the CKD subjects in our study had thrombocytopenia unlike 7.7% and 52% reported by Akinsola et al[5] and Talwar et al[8] respectively. The difference in the prevalence of thrombocytopenia in these studies may be related to differences in the cut off value of platelet count used to define thrombocytopenia and severity of CKD of the studied subjects. Akinsola et al[5] used a higher cut off of less than 10×10^9 cells/L unlike our study that used a lower count of less than 9×10^9 cells/L. Also, Talwar et al[8] who reported a high prevalence of thrombocytopenia studied patients on maintenance HD unlike our study which involved pre-dialysis patients only. The effect of heparin, dialyzer membrane and extracorporeal circulation on platelet during HD may account for the very high prevalence of thrombocytopenia in the previous study compared to our study. Abnormal platelet function has been reported in CKD patients even when the platelet count is normal as reported by van Blade et al.[34]

This study revealed a high prevalence of anaemia among our CKD subjects pronounced in the later stages of CKD. White cell count was also significantly higher in the CKD subjects which may reflect increased cardiovascular morbidity and mortality in our patients, hence the need for prompt and aggressive intervention.

REFERENCES

1. Arogundade F, Barsoum R. CKD prevention in Sub-Saharan Africa: A call for governmental, nongovernmental, and community support. Am J Kidney Dis. 2008;51(3):515–23.

2. Kadiri S, Arije A. Temporal variations and meteorological factors in hospital admissions of chronic renal failure in south west Nigeria. West Afr J Med. 1999;18(1):49–51.

3. Akinsola W, Odesanmi WO, Ogunniyi JO, Ladipo GO. Diseases causing chronic renal failure in Nigerians--a prospective study of 100 cases. Afr J Med Med Sci. 1989;18(2):131–7.

4. Ulasi II, Ijoma CK, Onodugo OD, Arodiwe EB, Ifebunandu NA, Okoye JU. Towards prevention of chronic kidney disease in Nigeria: a community-based study in Southeast Nigeria. Kidney Int Suppl. 2013;3(2):195–201.

5. Akinsola A, Durosinmi MO, Akinola NO. The haematological profile of Nigerians with chronic renal failure. Afr J Med Med Sci 2000; 29:13-6

6. Shittu AO, Chijioke A, Biliaminu SA, Makusidi AM, Sanni MA, Abdul-Rahman MB A-AM. Haematologic profile of patients with chronic kidney disease in Nigeria. J Nephrol Ren Transplant. 2013;5(1):2–10.

7. Ijoma C, Ulasi I, Ijoma U, Ifebunandu N. High prevalence of anemia in predialysis patients in Enugu, Nigeria. Nephrology Research and Review 2010; 2(1): 61 - 65

8. Talwar VK, Gupta HL, Shashinarayan. Clinicohaematological Profile in chronic renal failure. J Assoc Physicians India 2002;50:228-233

9. Silverberg DS, Wexler D, Iaina A, Schwartz D. The correction of anemia in patients with the combination of chronic kidney disease and congestive heart failure may prevent progression of both conditions. Clin Exp Nephrol. 2009;13(2):101–6.

10. Keane WF, Brenner BM, de Zeeuw D, Grunfeld J-P, McGill J, Mitch WE et al. The risk of developing end-stage renal disease in patients with type 2 diabetes and nephropathy: the RENAAL study. Kidney Int. 2003;63(4):1499–507.

11. Review E, National Kidney Foundation. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. Am J Kidney Dis. 2006 ;47(5 Suppl 3):S11–145.

12. Levin A, Foley RN. Cardiovascular disease in chronic renal insufficiency. Am J Kid Dis. 2000;36(6 Suppl 3):S24–30.

13. Levin A, Thompson CR, Ethier J, Carlisle EJ, Tobe S, Mendelssohn D et al. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. Am J Kidney Dis. 1999;34(1):125–34.

14 Kovesdy CP, George SM, Anderson JE,Kalantar-Zadeh K. Outcome predictability of biomarker of Protein Energy Wasting and Inflammation in moderate and advance chronic kidney disease. Am J Clin Nutr 2009;90(2):407-414

15. Reddan DN, Klassen PS, Szczech LA, Coladonato JA, O'Shea S,Owen WF et al. White blood cells as a novel mortality predictor in hemodialysis patients. Nephrol Dial Transpl 2003;18(6):1167-73

16. Bash LD, Erlinger TP, Coresh J, Marsh-Manji J,. FolsomAR, Astor BC. Inflammation, hemostasis and the risk of kidney function decline in Atherosclerosis Risk In Community (ARIC) study. Am J Kidney Dis 2009;53(4):596-605

17. Fried L, Solomon C, Shlipak M, Seliger S, Stehman-Breen C, Bleyer AJ et al. Inflammatory and prothrombotic markers and the progression of renal disease in elderly individuals. J Am Soc Nephrol. 2004;15(12):3184-91.

18. Abefe SA, Abiola AF, Olubunmi AA, Adewale A. Utility of predicted creatinine clearance using MDRD formula compared with other predictive formulas in Nigerian patients. Saudi J Kidney Dis Transpl 2009;20:86-90

19. Chan M. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. World Health Organisation 2011;1–6

20. Kidney Disease Improving Global Outcome (KDIGO) 2012 Clinical Practice Guideline of evaluation and management of CKD. Kidney Int Supplements 2013;3:1-150

21. Halim NKD, Famodu AA. Textbook of clinical haematology. AMBIK Press, Benin City, Edo State, Nigeria.1997:6

22. Arun S, Prabhu MV, Chowta KN, Bengre ML. The Haematological Pattern of the Patients with Chronic Kidney Disease in a Tertiary Care Setup in South India. J Clin diagnostic Res. 2012;6(6):1003–6

23. Cases-Amenós A, Martínez-Castelao A, Fort-Ros J, Bonal-Bastons J, Ruiz MP, Vallés-Prats M, et al. Prevalence of anaemia and its clinical management in patients with stages 3-5 chronic kidney disease not on dialysis in Catalonia: MICENAS I study. Nefrologia. 2014;34(2):189–98.

24. Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. PLoS One 2014;9(1):e84943.

25. McLean E, Cogswell M, Egli I, Wojdyla D, de Benoist B. Worldwide prevalence of anaemia, WHO Vitamin and Mineral Nutrition Information System, 1993–2005. Public Health Nutr .2009;12(04):444–54.

26. Miller LJ. Iron Deficiency Anemia: A Common and Curable Disease. Cold Spring Harb Perspect Med. 2013;3(7) doi:10.1101/cshperspect.a011866 accessed on 20th October, 2017

27. Ugwuja EI, Ogbonnaya LU, Obuna AJ, Awelegbe F, Uro-Chukwu H. Anaemia in Relation to Body Mass Index (BMI) and Socio-Demographic Characteristics in Adult Nigerians in Ebonyi State. J Clin Diagn Res. 2015;9(1):4–7

28. McClellan W, Aronoff SL, Bolton WK, Hood S, Lorber DL, Tang KL, et al. The prevalence of anemia in patients with chronic kidney disease. Curr Med Res Opin. 2004;20(9):1501–10

29. Asfar R, Sanavi S, Salimi I, Ahmadzadeh M. Hematological profile of chronic kidney disease in Iran, in predialysis stages and after initiation of hemodialsysis. Saudi J Kid Dis Transpl 2010;21(2):368-371

30. Loutradis C, Skodra A, Georgianos P, Tolika P, Alexandrou D, Avdelidou A et al. Diabetes mellitus increases the prevalence of anemia in patients with chronic kidney disease: A nested case-control study. World J Nephrol. 2016 Jul 6; 5(4): 358–366.

31. Suresh M, Mallikarjuna RN, Sharan SM, Hari KB, Shravya KG, Chandrasekhar M. Heamatological changes in chronic renal failure. Int J Sci R Pub 2012;2(9)

32. Islam MN, Ferdous A, Zahid AZ, Alam M. Islam MN. Hematological profile of patients with chronic kidney disease in Northern Bangladesh. Dinajpur Med Col J 2015;8(1):21-27

33. Madjid M, Fatemi O. Components of complete blood count as a risk predictor for coronary heart disease. Text Heart Inst J 2013;40(1):17-29

34. Van Blade RE, de Jager RL, Walter D, Cornelissen L, Gaillard CA, Broven LA et al. Plateletsof patients with chronic kidney disease demonstrate deficient platelet reactivity in vitro. BMC Nephrol. 2012; 13: 127.doi: 10.1186/1471-2369-13-127

Table 1: CHARACTERISTICS OF STUDY POPULATION

PARAMETERS	CKD subject n=100 n(%)/mean(SD)	Control n=90 n(%)/mean(SD)	p-value
Age (years)			
Mean age	49.39(14.8)	52.66(13.90)	0.120
≤45	42(60.0)	30(40.0)	
46-65	20(47.6)	22(52.4)	0.350
>65	38(50)	38(50.0)	
Gender			
Male	56(58.9)	39(41.1)	0.080
Female	44(46.3)	51(53.7)	
Stage of CKD			
1	14(14)		
2	8(8)		
3	29(29)		
4	33(33)		
5	16(16)		
Aetiology of CKD			
Diabetes mellitus	31(31%)		
Hypertension	32(32%)		
Chronic Glomerulonephritis	25(25%)		
Obstructive Nephropathy	12(12%)		

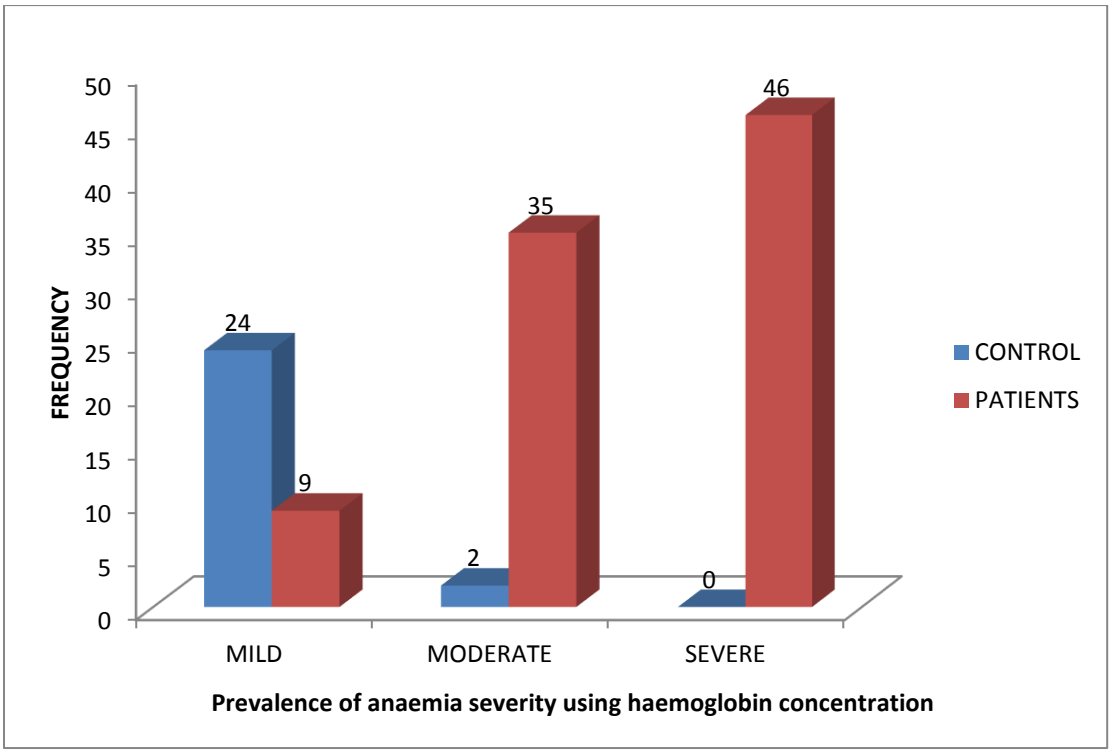

Figure 1: Classification of anaemia (n=190)

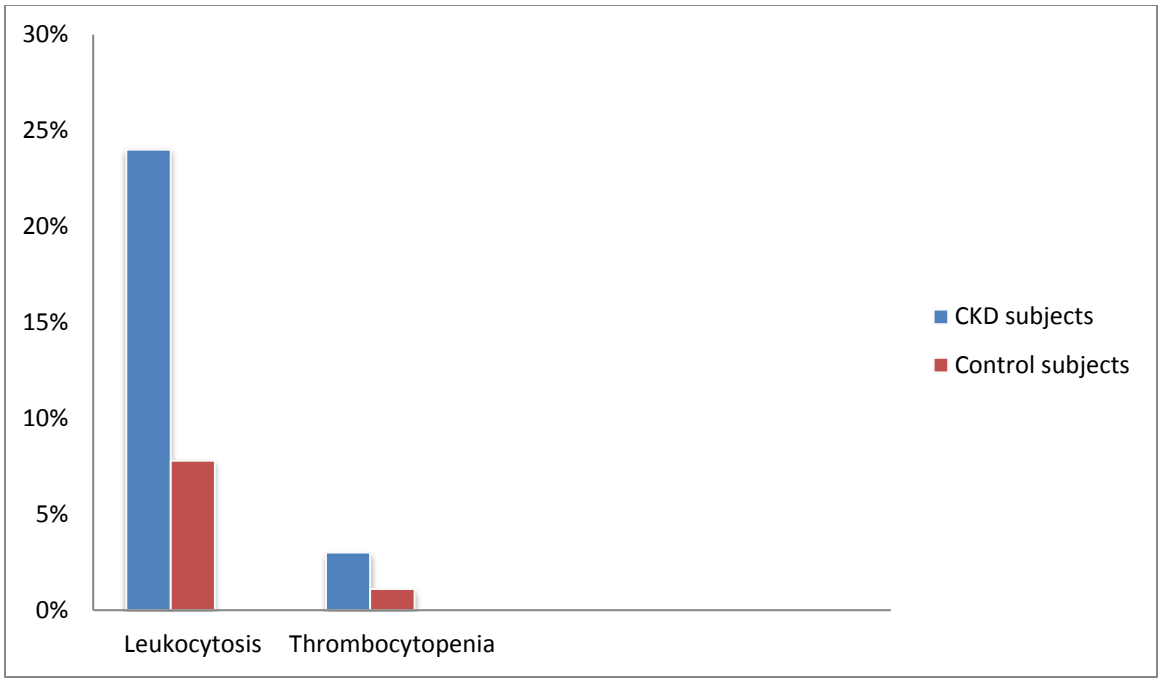

Fig 2: Prevalence of leukocytosis and thrombocytopenia among Study subjects

Table 2: HAEMATOLOGICAL INDICIES OF PREDIALYIS SUBJECTS AND CONTROLS (N=190)

	Subject n=100 mean(SD)	Control n=90 mean(SD)	T	p-value
Red cell count($X10^{12}$/L)	3.48(0.97)	4.40(0.51)	8.06	0.000
Hb concentration (g/dl)	8.71(2.70)	12.93(8.7)	4.01	0.000
Packed cell volume (%)	26.64(12.17)	38.05(6.11)	8.03	0.000
Mean cell volume (fl)	73.11(11.11)	82.69(6.55)	5.65	0.000
MCHC (g/dl)	32..03(2.97)	35.48(32.06)	1.07	0.285
MCH (pg)	28.38(31.03)	28.35(2.49)	-0.01	0.993
Reticulocyte count (%)	1.62(2.80)	1.31 (0.67)	-1.05	0.297
WBC count ($X10^9$/L)	6.75(3.26)	5.82(1.72)	-2.92	0.017
Granulocyte ($X10^9$/L)	11.37(20.22)	4.73(7.98)	-2.91	0.004
Lymphocyte ($X10^9$/L)	4.98(9.06)	3.98(7.98)	-0.73	0.420
Monocyte ($X10^9$/L)	1.34(2.69)	1.06(2.56)	-0.73	0.467
Platelet count ($X10^9$/L)	200.79(82.97)	219.18(62.26)	1.71	0.088
ESR (mm/hr)	51.99(32.74)	17.50(8.59)	-9.70	0.000

Hb(haemoglobin), MCHC(mean cell haemoglobin concentration), MCH(mean cell haemoglobin), ESR(erythrocyte sedimentation rate)

Table 3: ASSOCIATION BETWEEN THE SEVERITY OF ANAEMIA AND STAGE OF CKD

		CKD STAGE					
		1 n=14 n(%)	**2 n=8 n(%)**	**3 n=29 n(%)**	**4 n=33 n(%)**	**5 n=16 n(%)**	**Test Statistic**
Severity of Anaemia	Mild	0(0.0)	4(44.4)	3(33.3)	2(22.2)	0(0.0)	$\chi 2=29.7$ df=8 P = 0.000
	Moderate	2(5.7)	2(5.7)	15(42.9)	12(34.3)	4(11.1)	
	Severe	7(15.2)	1(2.2)	8(17.4)	18(39.1)	12(26.1)	

Table 4: COMPARISON BETWEEN HAEMOGLOBIN CONCENTRATION OF THE VARIOUS AETIOLOGIES OF CKD

		Aetiology of CKD				
		CGN n=25	**Diabetes Mellitus n=31**	**Hypertension n=32**	**Obstructive Uropathy n=12**	**Test Statistic (ANOVA)**
Haemoglobin Concentration (g/dl)	Mean SD	7.86 2.74	9.07 2.73	8.76 2.66	9.41 2.49	F=3.63 p=0.27