



Prevalence of Anemia and Associated Factors in Non-Dialysis Chronic Kidney Disease Patients, Saint Paul Hospital Millennium Medical College

St. Paul's Hospital Millennium Medical College

Addis Ababa, Ethiopia

August, 2019

Done By- Anteneh Getachew (MD, Internal Medicine Resident)



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Research Thesis Submitted to the Department of Internal
Medicine in Partial Fulfillment of Internal Medicine Specialty

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Abbreviations

ACEi	Angiotensin converting enzyme inhibitor
CCB	Calcium channel blocker
CGN	Chronic Glomerulonephritis
CKD	Chronic Kidney Disease
D-CKD	CKD On Dialysis
DN	Diabetic Nephropathy
eGFR	Estimated Glomerular Filtration Rate
ESA	Erythropoiesis Stimulating Agent
Hgb	Hemoglobin
IDA	Iron Deficiency Anemia
KDIGO	Kidney Disease: Improving Global Outcomes
KNOW-CKD	Korean Cohort Study For Outcome In Patients With Chronic Kidney Disease
MDRD	Modification Of Diet In Renal Disease
ND-CKD	CKD Not On Dialysis
PI	Principal Investigator
RBC	Red Blood Cells
SPHMMC	Saint Paul hospital millennium medical college
TSAT	Transferring Saturation Percentage
WBC	White Blood Cells

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Abstract

Background: Anemia is common and serious complication of Chronic Kidney Disease that presents during the early phase of the disease and worsens as the kidney function deteriorates. It contributes considerably to reduced quality of life of patients with Chronic Kidney Disease and has been associated with a number of adverse clinical outcomes. Early identification and treatment of anemia improves cardiovascular morbidity and mortality in Chronic Kidney Disease patients. But usually it's under diagnosed and under treated even in best setups.

Objective: to determine the prevalence of anemia and associated factors among Chronic Kidney Disease patients on follow up at st Paul hospital millennium medical college, renal clinic.

Methodology: hospital based cross-sectional study to assess the prevalence, clinical characteristics and associated factors of anemia in all stages of non-dialysis Chronic Kidney Disease patients. The sample size was 198 as calculated by single population proportion formula and systematic random sampling technique was used. The study uses both primary and secondary data. Data is analyzed using SPSS computer software version 25.

Results: The overall prevalence of anemia is 60.6% among non-dialysis Chronic Kidney Disease patients. The magnitude of anemia and its severity increases with the stages of Chronic Kidney Disease. Anemia was seen in 0%, 33.3%, 23.7%, 54.5%, and 91.3% of stage 1 to 5 patients respectively. The proportion of patients with severe anemia at each Chronic kidney disease stages 1-5 is 0%, 16.7%, 0%, 9.1%, and 34.8% respectively. The stages of Chronic Kidney Disease, diabetic nephropathy, Chronic Kidney Disease with unknown cause and diuretics use are positively associated while family support, co morbid disease and Calcium channel blocker use are negatively associated with presence of anemia. Age, sex, Body mass index and Angiotensin converting enzyme inhibitors use are not associated with anemia.

Conclusion: The prevalence of anemia in our Chronic Kidney Disease patients is 60.6%. More than half (51.4%) of our patients are not getting any treatment for their anemia. The baseline laboratory workups recommended by Kidney disease: improving global outcome are not done for all anemic patients.

Key words; Anemia, chronic kidney disease, iron deficiency, erythropoietin, SPHMMC

1 Introduction

1.1 Background of the study

Anemia is a global public health problem affecting both developing and developed countries with major consequences for human health as well as social and economic development. It occurs at all stages of the life, but is more prevalent in pregnant women, young children and individuals with co morbidity (1, 2). Some of common co morbid conditions that increase the chance of anemia include chronic kidney disease (CKD), diabetes mellitus (DM), and retroviral infection (RVI).

Anemia is serious complication of CKD that presents during the early phase of the disease and worsens as the kidney function deteriorates. The primary cause of anemia in CKD is a reduced ability of the failing kidneys to produce erythropoietin (EPO). Iron deficiency and inflammation are additional etiological factors that may contribute to anemia in CKD (2-6).

1.2 Statement of the problem

Anemia is common complication of CKD and can increase the risk of several co morbidities, including cardiovascular disease, and is associated with activity impairment, reduced quality of life and work productivity. Furthermore, untreated anemia has been shown to result in negative effects on cardiac, cognitive, and immune functions, as well as survival, while appropriate treatment can significantly improve quality of life and slow disease progression (2,3,6).

There are a number of studies about prevalence of anemia worldwide. There is significant difference in prevalence between the studies because of the difference in population under study. It is as low as 15.4% in USA and as high as 77.5 % in Nigerian studies. Prevalence of anemia increase as kidney function decreases (2, 4, 7, 11, 14, and 15).

1.3 Significance of the study

Anemia is one of the co morbid conditions affecting patients with CKD. There is no study addressing the prevalence of anemia in Ethiopia so far. So the main significant of this study is to fill this knowledge gap. Knowing the magnitude of anemia will make the clinicians to anticipate and treat patients earlier. This will improve quality of life to the patient, increases adherence and decrease overall cost of medical care. Early anemia correction will also decrease the need for blood transfusion and associated complications specially blood borne infections and graft rejection after transplant.

The result of this study will determine the exact prevalence of anemia in CKD patients and common contributing factors. It will build physicians knowledge about status of their patients suffering from anemia with CKD and gaps in their treatment. It will also assist nephrology unit and department of internal medicine to focus on common contributing factors and propose possible solutions to the college and aid organizations.

This research is a gateway for further study on CKD complications and will add to evidence based medicine in Ethiopia.

2. Literature review

Anemia is an almost universal complication of CKD. It contributes considerably to reduced quality of life and has been associated with a number of adverse clinical outcomes. Anemia in CKD is associated with cognitive impairment, sleep disturbances, CKD progression, cardiovascular co morbidities, and higher overall mortality (2, 3, 11 and 12). The cost of anemia management is considerable, and it has also become apparent that full anemia correction may cause harm; therefore a rational and careful consideration of the risks and benefits is mandatory (13).

2.1 prevalence of anemia and associated factors in CKD patients

There are a number of studies about prevalence of anemia worldwide. There is significant difference in prevalence between the studies mainly due to the difference in population under study. It is as low as 15.4% in USA and as high as 77.5 % in Nigerian studies. Prevalence of anemia increase as kidney function decreases (2, 4, 7, 11, 14, and 15).

The KoreaN Cohort Study for Outcome in Patients with Chronic Kidney Disease (KNOW-CKD) is a prospective nationwide cohort study to investigate natural courses and risk factors for progression of Korean CKD. 2,198 non-dialysis CKD patients stage 1–5 non-dialysis patients were enrolled from 9 hospitals throughout Korea between June 2011 and February 2016. Overall prevalence of anemia was 45.0%. More than half (51.8%) of female CKD patients had anemia. Diabetic nephropathy (DN) as a cause, CKD stages, body mass index (BMI), smoking, leukocyte count, serum albumin, iron markers, calcium, and phosphorus concentration were identified as independent risk factors for anemia. DN had the highest overall prevalence of anemia (75.9%) than other etiologic subgroups. The lower BMI of 18.5–22.9 was associated with elevated risk of anemia compared with BMI between 23.0 and 24.9 as the reference. Current smoker showed 42.0% reduction of risk for anemia compared with non-smoker (11).

In Catalonia study involving 504 patients (56.4% male, mean age of 67.8 ± 15.5 years): 61.5% had stage 3 CKD, 30.2% stage 4 and 8.3% stage 5. The prevalence of anemia was 58.5% (n=295), however, only 14.9% of patients had hemoglobin levels <11 g/dl. Among the patients with anemia (n=295), 36.3% (n=107) had iron deficiency and only 53.3% of these patients were treated with iron supplements (15)

In another study done by William McClellan et al in USA anemia was present in 47.7% of 5222 predialysis patients with chronic kidney disease. Blacks are found to have 3 times increased risk for anemia than white counterpart (13, 14).

The prevalence of anemia in CKD is even higher in African studies. For example Chinwuba Ijoma studied 364 patients (mean age 44.8 ± 14.8 years) and 143 control subjects (mean age 43.52 ± 12.00 years, $P=0.35$) in Enugu Nigerian. Overall 77.5% of CKD patients and 11.9% ($P<0.001$) of control subjects had anemia defined as hemoglobin less than 12 g/dL. Anemia increased progressively with declining GFR with mean hemoglobin concentration of 12.91 ± 1.35 g/dl, 12.14 ± 1.96 , 10.57 ± 2.42 , 8.84 ± 2.19 and 7.33 ± 1.74 for CKD stages 1 to 5, respectively. Chronic glomerulonephritis (CGN), human immunodeficiency/retroviral disease, collagen vascular disease and chronic pyelonephritis were predictor of anemia in CKD (14).

There is no similar study in Ethiopia but one study was done in Tikur Anbessa specialized hospital nephrology unit and pharmacy department primarily to assess medication adherence. In that study done by Belayneh Kefale, Yewondwossen Tadesse et al involving 256 CKD patients, 30% of patients are reported to have anemia out of which 92% are on iron therapy (16). The prevalence seems underestimated and further characterization of the result is difficult due to the aim of the study.

In another Ethiopian study involving other co morbidities the prevalence of anemia is even higher than most available studies. A retrospective cohort study was done by temesgen fiseha et al on 373 patients from ART clinic in Dessie Referral hospital, South Wollo from September 2010 to August 2013. The prevalence of anemia at the time of ART initiation was 34.4%; with 20.5, 12.3 and 1.6% mild, moderate and severe anemia, respectively. Renal insufficiency was present in 27.9% of patients and was associated with a high prevalence of

anemia (74%). The prevalence of anemia increased with stage of insufficiency, from 23.7% in stage 1 to 100% in stage 4. Impaired renal function (eGFR < 60 mL/min/1.73 m²) was associated with a higher risk of all forms of anemia; i.e., mild (AOR = 3.96; 95% CI: 2.76–5.69), moderate (AOR = 2.21; 95% CI: 1.16–4.19) and severe anemia (AOR = 5.89; 95% CI: 1.02–12.03) (8).

2.2 clinical management of anemia

Despite high prevalence of anemia in CKD patients, it is usually under diagnosed and under treated condition. Most patients don't have proper work up for their anemia. The proportion of CKD patients being treated for their anemia is strikingly very low. This is also true even in high income countries and tertiary centers. Among 2,125 CKD patients with anemia in USA total of 22.8% of reported being treated for it. Treatment frequencies were similar at stages 1 and 2 (12.1% and 16.2%; $P = 0.57$; weighted mean 14.6%) and stages 3 and 4 (26.5% and 20.7%; $P = 0.76$; weighted mean 26.4%) (12).

Among 2,127 Korean subjects with CKD stage 1–5 (KNOW-CKD study above) with TSAT and ferritin levels available at enrollment, 297 patients (14.0%) had TSAT less than 20.0% and 1,070 (50.3%) had ferritin less than 100 ng/mL. The proportion of patients having TSAT less than 20.0% was higher in patients with anemia than without anemia (20.0% vs. 9.2%; respectively, $P < 0.001$). Of 938 patients with anemia, 44.3% showed TSAT more than 20.0% and ferritin more than 100 ng/mL. Among patients with anemia, the prescription rate of iron agents was 28.7% when TSAT was less than 20.0% and 27.5% when TSAT was higher than 20.0%. Only 6 (1.2%) out of 520 patients applicable intravenous iron supplement according to KDIGO guidelines were managed by intravenous iron. The number of patients having hemoglobin level less than 10 g/dL was 177 (8.1%) out of 2,198 subjects. Among them, 59 (33.3%) received ESAs (11).

In another prospective study on anemia management in two visits, performed 6 months apart, in 755 ND-CKD stage 3b-5 patients followed in 19 nephrology clinics. Prevalence of severe (hgb < 11 gm/dl) and mild (hgb > 11 gm/dl) anemia was 18.0 and 44.0% at baseline and remained unchanged at Month 6 (19.3 and 43.2%). Iron deficiency was prevalent at both visits

(60.1 and 60.9%). There is significant Clinical inertia among physicians to start ESA at baseline and at Month 6 (39.6 and 34.2%, respectively, $P = 0.487$) and it was less frequent than clinical inertia to iron therapy (75.7 and 72.0%, respectively) (4).

3. Objective of the study

3.1 General objective

- ✓ To determine the prevalence of anemia and associated factors in patients with ND-CKD in SPHMMC.

3.2 Specific objective

- ✓ Determine prevalence of anemia among ND-CKD
- ✓ Describe factors associated with prevalence of anemia.
- ✓ Describe characteristics of anemia in apatients with CKD.

4. Study population and Methods

4.1 Study area

The study took place in St. Paul hospital which is located in Addis Ababa, Gullele sub city, Swaziland Street around 4 km from Piassa. St Paul hospital is built in 1969 by Emperor Haile Selassie I in collaboration with the German evangelical church, as medical center to serve the poor population. It is currently the second largest hospital in the country with 700 beds, average 200,000 patients annual visit and a catchment population of over 5 million. Approximately 75% of the patients receive medical services free of charge. There are over 2800 clinical and non-clinical staffs in over 13 departments.

Department of internal medicine has significant share from this outpatient visits and more than 48 beds for inpatient care. The department teaches more than 90 residents. It started fellowship program in 3 fields; nephrology, cardiology, and gastroenterology. Nephrology unit is the first unit to be established.

The hospital is a pioneer in the country for hemodialysis and renal transplantation. There are thousands of CKD patients who come from all over the country for these services. These peculiarities make the hospital a unique place to perform researches especially involving renal diseases.

4.2 Study design

This is a cross sectional analytic study to determine the prevalence and associated factors of anemia in ND-CKD patients who have follow up at SPHMMC renal clinic.

4.3 Study period

The study period was two months from May 1 to June 30, 2019. This will catch most patients since average follow up period from the clinic was about two months.

4.4 Population

4.4.1 Source population

The source population is all CKD patients who are on follow up at SPHMMC, renal clinic.

4.4.2 Study population

The study population is all ND-CKD patients on follow up at SPHMMC, renal clinic in study time.

4.5 Sample Size Estimation

The sample size is calculated by Single population proportion formula. The total population size is considered to be all patients with CKD who come to the clinic in the study period. This number is predicted from average number of CKD patients seen every month. According to data from HMIS log book registry 270 CKD patients visit the clinic monthly. Since the study is planned to take two months total number of CKD patients is 540.

The prevalence of anemia in ND-CKD patients is 77.5% from Nigerian study (8). So P-value of 0.7 is taken by the investigator since there is no similar study done in the country and better related setup. A confidence interval of 95% ($Z=1.96$) and margin of error (w) of 5% are taken.

$$\text{Single population proportion formula (m)} = \frac{z^2 p(1-p)}{w^2} ;$$

Where: m = sample size necessary for estimating the proportion

P = prevalence of anemia in CKD

W = margin of error

That means $m = \frac{1.96^2 0.7(1-0.7)}{0.05^2} = 271.$

The calculated sample size is 271 using single population proportion formula above.

This number is corrected by correction formula for small finite population.

$$\text{Sample size after correction (n)} = \frac{m}{1 + \frac{m-1}{N}},$$

Where, m = calculated sample size

n = sample size after correction

N = is total number of CKD patients in renal clinic in study period

The sample size will be 180.

Then 10% contingency was added on 180:

$$\text{Sample size after correction (n)} = \frac{271}{1 + \frac{271-1}{540}} = 180.$$

From this number 10% contingency is added;

$$180 \times 10\% = 18$$

$$180 + \text{contingency} = 198.$$

So, the study participants are 198 ND-CKD patients on follow up at renal clinic in SPHMMC.

4.6 Sampling Procedure and Data Collection

The type of data is both primary and secondary data. The data collectors filled all socio-demographic data by patient interview. The remaining data involving clinical characteristics and laboratory results are collected from the patient's medical record card. eGFR is calculated from last creatinine level using CKD-EPI 2009 formula. PI checked all filled questionnaires for completeness and accuracy.

During study period data collectors revised all patients cards quickly early in each morning. Patients who fulfill inclusion criteria are eligible patients. Patients are selected by systematic random sampling method each day of the data collection. The sampling is taken from HMIS log book which contains the card number of patients appointed for that specific day. From the list every forth patient was taken after choosing a random number from 1-3 by lottery method.

Selected patients were asked about their background socioeconomic data (questionnaire part-1) after data collectors took verbal consent. Clinical characteristics and laboratory values were filled by principal investigator (PI) from patient card. Patient medication lists were also collected from the patient card (questionnaire part -2&3).

4.7 Study Variable

4.7.1 Independent Variables

- age – in years
- sex – male/female
- address
- educational status
- monthly income
- religion
- BMI
- history of smoking and pack years
- number of years after CKD diagnosis
- cause of CKD

- WBC and platelet count
- RBC indices (MCV, MCH, RDW)
- peripheral morphology
- iron study
- current medications

4.7.2 Dependent Variable

- Hemoglobin concentration within 1 year of the study period. The minimum frequency of Hgb determination is every one year according to KDIGO-2012 guideline.

4.8 Questionnaire design

The questionnaire has three parts. The first section is about the socio-demographic characteristics of the patients. The second part contains questions about CKD and anemia associated characteristics of respondents. Last portion is data entry check list for important laboratory findings and drugs list.

4.9 Method of data processing and analysis

The completeness of the questionnaires was manually checked by PI. The data was entered to the computer and analyzed using SPSS version 25 software program. Descriptive statistics Such as frequencies, percentage and appropriate graphic presentation are used for analysis. Chi square test, Odds ratio, 95% confidence interval and p-value <0.05 is used to check significant association between dependent & independent variables. The data was also analyzed using binary and multinomial logistic regression analysis to control cofounders.

4.10 Inclusion and Exclusion criteria

The inclusion criteria were

- all Stages of CKD patients who came to renal clinic SPHMMC during the study period
- CBC done in the past 1 year of the study period
- Age>18 years.

The exclusion criteria

- Patients with known malignancies
- Pregnant patients
- Patients on hemodialysis

4.11 Data quality assurance

The PI made pretest on 20 patients about a month before actual data collection. Physicians working in the clinic commented on questionnaire and little modification was made. The data collectors took onsite training about proper data collection by PI. The data quality was assured by adhering to the inclusion and exclusion criteria and the study protocol. The data were collected by a well-structured questionnaire and check list. Incomplete data which lack sociodemographic characteristics, last creatinine and CBC were rejected.

4.12 Ethical clearance

Ethical clearance and approval of the study protocols were obtained from the institutional Review Board (IRB) of SPHMMC. In addition, permission was taken from the respective heads of Department of Internal Medicine and renal clinic to conduct the study in the clinic. Prior to data collection, individual patients were informed about the study and verbal consent was obtained from the study participants. Each patient was informed about the objective of the study, procedures of selection, and assurance of confidentiality and their right to refuse was maintained. No identifiers were used except card number to minimize social desirability bias and enhance anonymity.

4.13 Data Dissemination

The findings of the study will be discussed with the staff of the internal medicine and renal unit. It will also be presented on defense thesis presentation and annual research conference of

the college. Local and international medical/non medical journals will be communicated for publication.

5 Operational Definitions

Anemia was diagnosed in this study when hgb concentration is below 12gm/dl for both male and female.

WHO severity classification of anemia ,1999

Hgb<8gm/dl-----severe anemia

Hgb 8-10.9gm/dl----- moderate anemia

Hgb ≥11gm/dl-----mild anemia

Anemia of CKD is an isolated normochromic, normocytic anemia occurring due to reduced production of erythropoietin from diseased kidneys.

Co morbidities are all diagnosed illnesses other than CKD.

Iron study is a combination of lab parameters to asses iron store of the patient.

Iron deficiency is when a patient has inadequate iron store in the body. The gold standard is to have bone marrow biopsy but is rarely indicated in CKD patients. If the patient has TSAT $\leq 30\%$ and ferritin ≤ 500 ng/ml (≤ 500 mg/l) , patient might have iron deficiency and benefit with iron therapy. Absolute iron deficiency is likely when ferritin < 100 ng/ml and TSAT $< 20\%$, functional/relative iron deficiency assumed when TSAT $\leq 30\%$ with normal or high ferritin.

RBC indices are laboratory measures of structure and function of red cells.

Transferring saturation (TSAT) = (serum iron /total iron binding capacity) X 100

6. Results

6.1 Sociodemographic characteristics

A total of 220 patients were selected for the study. Out of these 22 patients were excluded by principal investigator for incomplete data (3 patients), inappropriate patient specifically patients on hemodialysis (8 patients), no update CBC in the last 1 year (5 patients) and patient card can't be retrieved for secondary data (6 patients). Finally data from 198 patients were used for analysis, with the response rate of 90%. Among these 103(52%) are male, age ranges 18-92 years with mean age of 49.5($\pm$ 16). Majority (59.1%) of patients live in Addis Ababa but about a fifth of patients travel above 200km from Addis Ababa which is likely to take more than one day to attend their follow up.

More than half of patients attain at least secondary education (56.5%) but most (89.4%) earn less than 5000ETB/month and 76(38.4%) of them depend on their family support for their living and medical care. One hundred thirty six (68.7%) of patients had healthy BMI, but 28(14.1%) of patients are underweight and 6 patients are obese. All patients reported no history of smoking.

Table 1= Sociodemographic characteristics of 198 ND-CKD patients who had follow up at SPHMMC, renal clinic on month of May1-June30/2019.

Variable	Category	Frequency(n=198)	Percent (%)
Sex	Male	103	52.0
	Female	95	48.0
Address	Addis Ababa	117	59.1
	Out Of Addis But In 200km	43	21.7
	Out Of Addis And Above 200 Km	38	19.2
Educational Status	Illiterate	29	14.6
	Elementary School	57	28.8
	High School	65	32.8
	College And Above	47	23.7
Monthly Income in ETB	<1000	83	41.9
	1000-5000	94	47.5
	5000-10,000	20	10.1
	>10,000	1	.5
Source Of Income	Self support	122	61.6
	Family Support	76	38.4
BMI	BMI<18.5	28	14.1
	BMI 18.5-24.9	136	68.7
	BMI 25-29.9	26	13.1
	BMI>=30	6	3.0
	BMI Can't Be Assessed	2	1.0
Religion	Orthodox Christian	127	64.1
	Muslim	50	25.3
	Protestant Christian	20	10.1
	Other	1	0.5

6.2 Clinical Characteristics

The estimated GFR was calculated by CKD-EPI 2009 method using computer program from the last stable creatinine value. More than 85% of patients had stage 3 or above CKD. The cause of CKD was taken from the card (taking more than 2 similar documents) and the most common cause of CKD was hypertensive nephrosclerosis (32.3%), followed by unknown (23.7%), glomerular disease/chronic glomerulonephritis(16.2%) and diabetic nephropathy (15.2%).

Close to half (48.5%) of patients were known to have CKD for 1-5 years and about 40% patients know their diagnosis for less than 1 year. Ninety three(47%) patients had history of hypertension before they were diagnosed to have CKD with the mean duration of 7 years (ranges 6 month – 27 years) and 35 (17.7%) patents reported history of DM before CKD with the mean duration of 7.2 years (range 1-17 years).

Fifty nine (29.8%) patients reported any of symptoms of anemia. Twenty (10.1%) patients required transfusion to correct their anemia. The common co morbid diagnoses were hypertensive heart disease (44% of hypertensive/23.9% of all CKD patients) dyslipidemia and dyspepsia but 8 patients has hepatitis B virus infection and 3 are RVI patients.

Table 2- clinical characteristics of 198 ND-CKD patients who had follow up at SPHMMC, renal clinic on month of May 1-June 30/2019

Variable	Category	Frequency(n=198)	Percent (%)
Stage of CKD	eGFR>=90	14	7.1
	eGFR 60-89	12	6.1
	eGFR 30-59	59	29.8
	eGFR 15-29	44	22.2
	eGFR <15	69	34.8
Cause of CKD	DM	30	15.2
	HTN	64	32.3
	GLOMERULAR DISEASE	32	16.2
	OBSTRUCTIVE UROPATHY	5	2.5
	ADPKD	14	7.1
	INTERSTITIAL DS	6	3.0
	UNKNOWN	47	23.7
Duration of CKD	<6month	40	20.2
	6 month-1 yr	42	21.2
	01 yr-5 yrs	96	48.5
	>5 yrs	20	10.1
Co morbidity	History of DM	35	17.7
	History of HTN	93	47
Anemia related	Symptoms of anemia	59	29.8
	History of transfusion	20	10.1

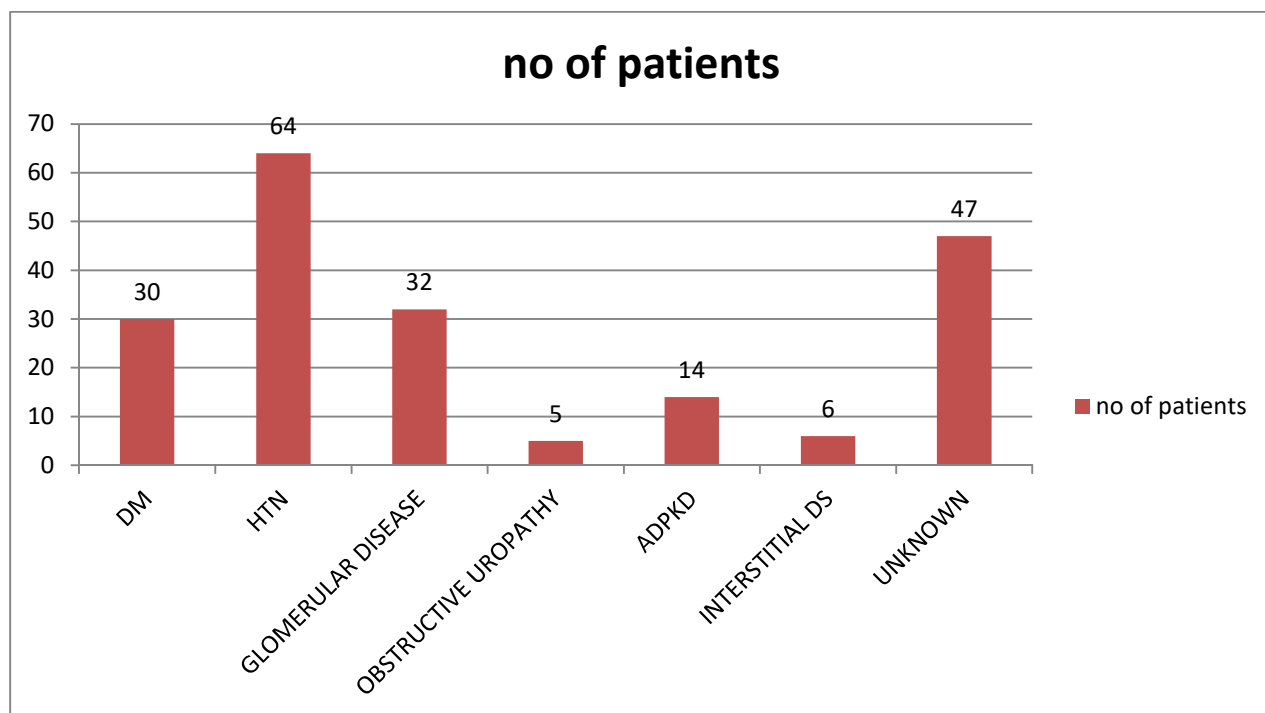


Fig 1- possible causes of ND-CKD among 198 patients who had follow up at SPHMMC, renal clinic on month of May 1-June 30/2019

6.3 Laboratory results of patients

The overall mean hgb value for both male and female is 11.7gm/dl (± 3.0239) and ranges from 4.9-18. According to WHO criteria 120 (60.6%) patients have anemia and 14 patients qualify laboratory criteria for polycythemia. Among anemic patients only 10 had documented peripheral morphology patients all suggesting possibility of iron deficiency; 4 had anisocytosis, 4 showed normocytic hypochromic and 2 microcytic hypochromic.

At least one component of iron study was done for 24 patients (20 % of anemic). According to KDIGO 2012 guideline, 20 of 24 patients (83.3%) had absolute or relative iron deficiency. But Serum vitamin B12 level and folate level was determined for 1 and 3 patients respectively.

Table 3 – proportion and severity of anemia (WHO criteria) among 198 ND-CKD patients who had follow up at SPHMMC, renal clinic on month of May 1-June 30/2019

Category	Frequency(n=198)	Percent (%)
No anemia	78	39.4
Mild anemia	75	37.9
Moderate anemia	15	7.6
Severe anemia	30	15.2

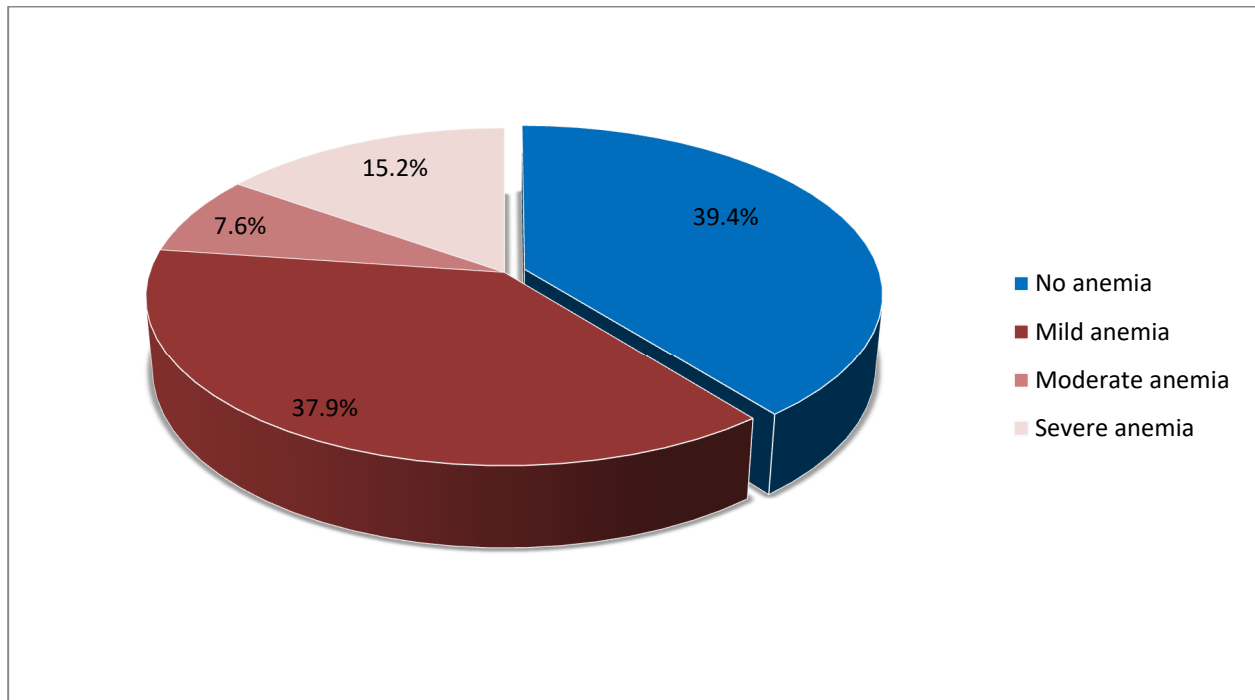


Fig 2 = proportion and severity of anemia (WHO criteria) among 198 CKD patients who had follow up at SPHMMC, renal clinic on month of May-June/2019

The proportion and severity of anemia increases with the stages of CKD. Anemia was seen in 0%, 33.3%, 23.7%, 54.5%, 91.3% of stage 1,2,3,4 and 5 patients respectively (with p-value of <0.001). The same wise the proportion of patients with severe anemia at each CKD stages 1-5 is 0%, 16.7%, 0%, 9.1%, and 34.8% respectively. The main portion (80%) of severely anemic patients are in stage 5 CKD. Subsequently cross tabulation was done for Hgb, MCV, MCH and RDW against stages of CKD. Hgb and MCV categories shows significant

association (with p-value <0.001 and 0.048 respectively) while MCH and RDW doesn't have any association with CKD stage.

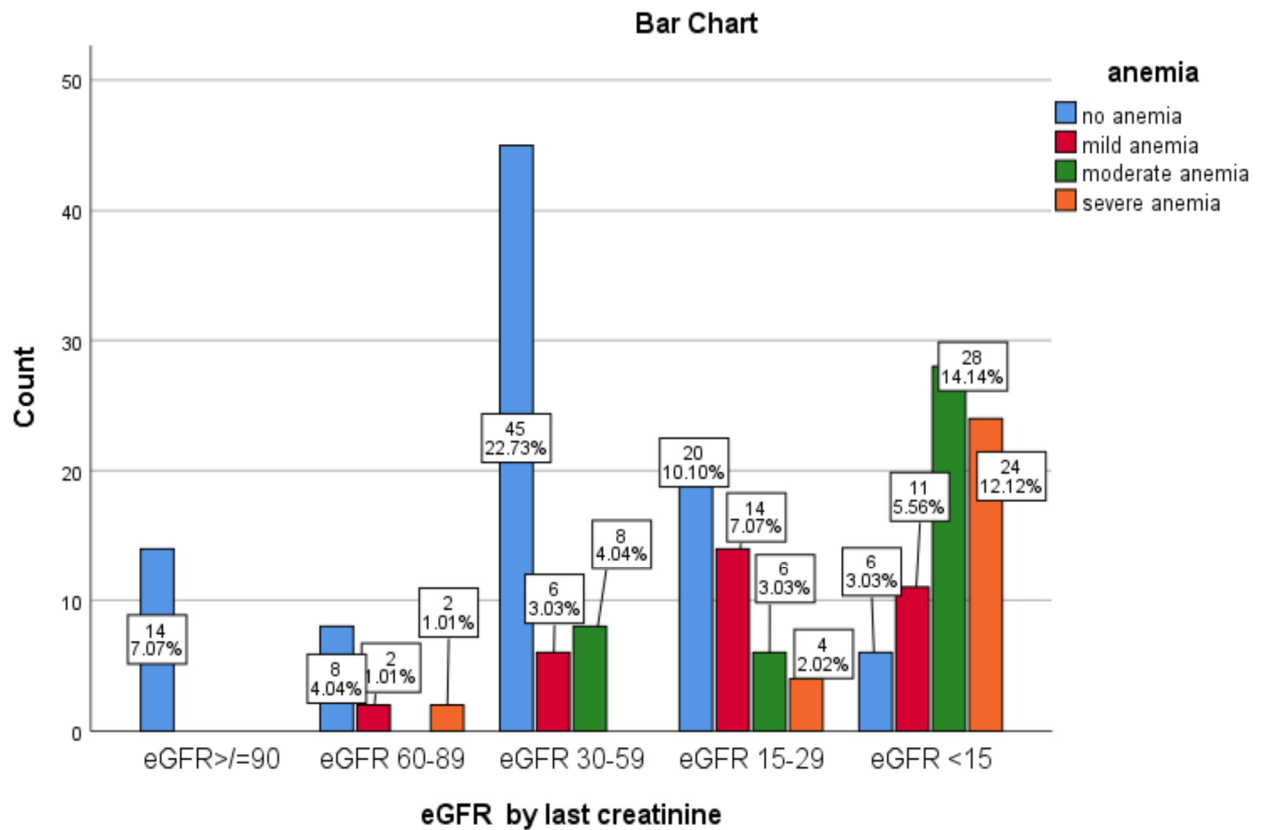


Fig -3 Proportion and severity of anemia according to **eGFR** for 198 ND-CKD patients who had follow up at SPHMMC, renal clinic on month of May 1-June 30/2019.

			anemia				
			No anemia	Mild anemia	Moderate anemia	Severe anemia	
			No anemia	Mild anemia	Moderate anemia	Severe anemia	Total
eGFR by last creatinine	eGFR>=90	Count	14 _a	0 _b	0 _{a, b}	0 _{a, b}	14
		% within eGFR by last creatinine	100.0%	0.0%	0.0%	0.0%	100.0%
		% within anemia	15.1%	0.0%	0.0%	0.0%	7.1%
		% of Total	7.1%	0.0%	0.0%	0.0%	7.1%
	eGFR 60-89	Count	8 _a	2 _a	0 _a	2 _a	12
		% within eGFR by last creatinine	66.7%	16.7%	0.0%	16.7%	100.0%
		% within anemia	8.6%	3.3%	0.0%	6.7%	6.1%
		% of Total	4.0%	1.0%	0.0%	1.0%	6.1%
	eGFR 30-59	Count	45 _a	12 _b	2 _{a, b}	0 _b	59
		% within eGFR by last creatinine	76.3%	20.3%	3.4%	0.0%	100.0%
		% within anemia	48.4%	20.0%	13.3%	0.0%	29.8%
		% of Total	22.7%	6.1%	1.0%	0.0%	29.8%
	eGFR 15-29	Count	20 _a	16 _a	4 _a	4 _a	44
		% within eGFR by last creatinine	45.5%	36.4%	9.1%	9.1%	100.0%
		% within anemia	21.5%	26.7%	26.7%	13.3%	22.2%
		% of Total	10.1%	8.1%	2.0%	2.0%	22.2%
	eGFR <15	Count	6 _a	30 _b	9 _{b, c}	24 _c	69
		% within eGFR by last creatinine	8.7%	43.5%	13.0%	34.8%	100.0%
		% within anemia	6.5%	50.0%	60.0%	80.0%	34.8%
		% of Total	3.0%	15.2%	4.5%	12.1%	34.8%
Total		Count	93	60	15	30	198
		% within eGFR by last creatinine	47.0%	30.3%	7.6%	15.2%	100.0%
		% within anemia	100.0%	100.0%	100.0%	100.0%	100.0%
		% of Total	47.0%	30.3%	7.6%	15.2%	100.0%

Each subscript letter denotes a subset of anemia categories whose column proportions do not differ significantly from each other at the .05 level.

Table 4 - **eGFR by last creatinine * anemia cross tabulation** for 198 CKD patients who had follow up at SPHMMC, renal clinic on month of May-June/2019.

Table 5= Hgb concentration according to the different stages of CKD in 198 ND-CKD patients who had follow up at SPHMMC, renal clinic on month of May 1 –June 30/2019.

Hemoglobin concentration (gm/dl)	All patients	stage 1 patients	stage 2 patients	stage 3 patients	stage 4 patients	stage 5 patients
n	198	14	12	59	44	69
Mean	11.732	14.4000	12.6417	13.5729	11.6795	9.4925
Median	11.900	14.2000	14.0000	13.5000	11.9000	10.0000
Std. Deviation	3.0239	1.73027	3.29641	2.32897	2.50001	2.43714
Minimum	4.9	12.80	6.50	8.60	5.30	4.90
Maximum	18.0	18.00	16.40	17.80	15.20	15.30

6.3.1 Sub-group analysis for patients with severe anemia and ESRD

Among severely anemic patients 19 of 30 (63%) have MCV value of <80fl (normal 80-94fl). The overall mean MCV for severely anemic patients were 80.2fl compared with 87.5fl in the non -anemic group. Similarly mean MCH value for severely anemic patients is 26.6 below normal for laboratory(28-33 pg/cell). The mean RDW value for these group of patients is 17 well above normal value(normal 11.5-14.5%). These findings suggests that, in the absence of peripheral morphology and iron study, most severely anemic patients have microcytic hypochromic anemia and anisocytosis signifying iron deficiency pattern rather than normocytic normochromic anemia which is typical of anemia of CKD. To strengthen this 7 of 12 severely anemic patients who had iron study show iron deficiency pattern.

Table 6- RBC indices comparison between anemic and non-anemic CKD patients

who had follow up at SPHMMC, renal clinic on month of May 1-June 30/2019

RBC indices - mean values	no anemia	Moderate anemia	Severe anemia	Normal lab ranges
MCV(fl)	87.5	86.3	80.2	80-94fl
MCH(pg/cell)	28.9	27.0	26.6	28-33 pg/cell
RDW(%)	13.8	14.9	17.8	11.5-14.5%

In sub-group analysis among ESRD (CKD stage 5) patients linear regression analysis was done for MCV, MCH, and RDW with Hgb concentration. MCV and MCH level shows significant association with Hgb but RDW didn't with p-values of 0.019, 0.001 and 0.07 respectively.

6.4 Treatments of study patients

Among patients with anemia 51(48.6%) are on either oral or intravenous iron therapy of which 20 of them have laboratory evidence for iron deficiency. Sixteen (15.2% of all anemic or 35.5% of those with Hgb<10gm/dl) of patients are getting ESA. Eight (7.6% of anemic) were taking folate but none of them had serum or RBC folate level determined. No patient was taking cyanocobalamin during the study period.

Most patients 169(85.3%) were taking some form of antihypertensive. The most commonly used antihypertensive medications are calcium channel blockers in 115(58% of all patients), followed by diuretics in 96(48.5%) and ACE inhibitors in 59(29.8%). Two patients were taking TDF and 3 patients were on AZT (all 3 have Hgb above 10) for their RVI and chronic hepatitis B virus infection.

Table 7 – drugs used by 198 CKD patients who had follow up at SPHMMC, renal clinic on month of May 1 - June 30/2019

Drug		Frequency(n=198)	Percent (%)
Iron	Oral	29	14.6
	intravenous	22	11.1
ESA		16	8.1
Folate		8	4
Diuretics		96	48.5
ACEi		59	29.8
CCB		115	58
Phosphate binder		58	29.3
Insulin		30	15.2
Statins		36	18.2
Beta blockers		38	19.2
Aspirin		23	11.6

6.5 Binary and multinomial logistic regression analysis

After descriptive statistics were done, binary regression analysis was done to identify any association between independent variables and dependent variable. Specifically Age ,sex, BMI educational status, religion, address, amount of income, source of income, duration of CKD, any history of underlying DM or HTN before diagnosis of CKD, presence of other known comorbid illnesses, symptoms of anemia, history of transfusion, stage and possible cause of CKD and commonly used drugs (diuretics, ACEi, CCB, phosphate binders, insulin and statins) are used. We took cut point of < 0.2 for significance on binary regression analysis and significant independent variables are analysed using multivariate linear regression analysis using p value of <0.05 and 95%confidence interval.

According to the result age, sex, BMI, address, religion and educational status didn't affect prevalence of anemia but CKD stage, cause of CKD and some drugs are associated with anemia. The amount of income doesn't affect prevalence of anemia but source of income affects. Patients who support themselves have increased risk of anemia when compared with patients who live with family support (p=0.02, OR=4.7,95 %CI 1.2-17.4).

The presence of hypertension and diabetes per se didn't affect prevalence of anemia but other co morbid diagnosis was negatively associated with risk of anemia. Diabetic nephropathy and CKD patients with unknown cause have increased risk of anemia. ACE inhibitor use didn't affect anemia prevalence but diuretics and CCB use was found to have positive and negative association with anemia respectively.

Table 8- Multivariate regression analysis for selected variables among 198 CKD patients who had follow up at SPHMMC, renal clinic on month of May 1 - June 30/2019.

Characteristics		p-value	AOR	95% C.I.	
				Lower	Upper
Social and clinical background data	source of income-self	.022	4.659	1.247	17.402
	Absence of co morbid diagnosis	.003	13.215	2.462	70.929
CKD stages	GFR 30-59	.096	6.698	.712	63.029
	GFR 15-29	.011	22.255	2.065	239.840
	GFR<15	.000	10916.299	287.154	414988.113
Cause of CKD	DM	.003	38.352	3.509	419.240
	HTN	.064	5.413	.904	32.401
	Obstructive uropathy	.999	.000	.000	.
	Cause UNKNOWN	.001	50.768	5.507	468.050
Drugs	ACEi use	.400	1.756	.473	6.518
	CCB use	.001	.061	.012	.323
	diuretics use	.041	4.366	1.063	17.935

7. Discussion

Anemia management is an important aspect of care for CKD patients. Numerous benefits have been associated with good anemia control in CKD patients, including lower mortality and hospitalization risks, reduced occurrence of left ventricular hypertrophy, and improved mental function as well as substantial improvement in most indicators of health-related quality of life.

This study included 198 CKD patients who had followup at renal clinic in st paul hospital during the study period. Males dominate with 52% of patients in consistent with other studies from Nigeria, Spain, and Nepal. Patients are in age range of 18-92 years with mean age 49.5 yrs(± 16) slightly older than 43.5 ± 12 from Nigeria and younger than 67.8 ± 15.5 from Spain(14,15).

The most common cause of CKD in our study was hypertensive nephrosclerosis (32.3%), followed by unknown(23.7%) and diabetic nephropathy (15.2%) in contrast to chronic GN 37.6%, hypertension in 22.5%, DM in 15.1% and unknown 0.5% in similar study in Nigeria but with much similarity to vascular(includes hypertension) 25%, unknown 25.4% and diabetes 16.3% in Spanish study. In our setup most patients have advanced stage of CKD which increases the risk and severity of anemia substantially. The proportion of patients with stage 1-5 CKD is 7.1%, 6.1%, 29.8%, 22.2%, and 34.8% respectively in much similarity with other developing countries who have 20% in stage 1 and 2 and 45.1% in stages(14,15,20).

The overall prevalence of anemia our patients was 60.6% when WHO criteria is used to define anemia. For the sake of simplicity and comparison with other studies we took hgb<12gm/dl to define anemia in both male and female which gives overall prevalence 53.03%. The Nigerian study with the same cut point (hgb<12gm/dl) was higher than ours (77.5%)(15).

The stage of CKD has definite association with the anemia. The prevalence and severity of anemia increases with the stages of CKD. Anemia was seen in 0%, 33.3%, 23.7%, 54.5%, 91.3% of stage 1,2,3,4 and 5 patients respectively. This was also seen in different studies. In comparison in a study from Saudi Arabia, anemia was 42%, 34%, 48%, 71%, and

82% for stages 1-5 respectively. Similarly anemia was seen in 21.4%, 36.7%, 68.2%, 91.2%, and 98% of Nigerian CKD patients with stage 1-5 respectively(5,14). The severity of anemia also worsen with stages of CKD. The proportion of patients who have severe anemia increases with CKD stages as 0%, 16.7%, 0%, 9.1%, and 34.8% for stages 1 to 5 respectively. Most (80%) of severely anemic patients have stage 5 CKD.

The cause of CKD has significant effect to the prevalence of anemia. Specifically diabetic nephropathy and CKD with unknown cause are associated with higher prevalence of anemia as seen in Spanish study(15).

The other most important factors that could contribute for prevalence of anemia are drugs. In our study diuretics use was found to be a risk while CCB use was protective for anemia. In contrast ACEi use has no association with anemia. These findings contradict other studies which found diuretics and CCB use has no effect but ACEi use was a risk factor for anemia. The effect of diuretics on anemia may be misleading since many patients who are on diuretics are fluid overloaded which by itself may decrease the Hgb concentration(5,14,15).

The presence of family support and comorbid disease were protective for anemia. In contrast to other studies age, sex, BMI and ACEI use were not associated with anemia.(1, 12, 14,15,).

The peripheral morphology , iron study , serum vit b12 level and folate level was done in 10,24, 1 and 3 patients despite KIDIGO 2012 recommendation for all anemic patients(2). This was the same problem in most developing countries since availability and cost of laboratory tests is main issue. In the absence of that our patients RBC indices suggests high prevalence of iron deficiency. This needs further investigation since its easily correctable with significant reduction in morbidity and mortality.

Overall 51(48.6% of anemic) anemic patients are on either oral or intravenous iron therapy. Twenty four patients have iron study and 12 of them had absolute iron deficiency (50%) and 8 of them relative iron deficiency state. In comparison Among Spanish anaemic patients 36.3% had an absolute iron. Sixteen (15.2% of all anemic or 35.5% of those with

hgb<10gm/dl) of patients are getting ESA. All have moderate to severe anemia. Fourteen of them are also taking iron despite only 6 patients have iron study of which 4 have iron deficiency. This is very low when compared with study from Spain where 66% of patients have treatment for anemia. Among patients with Hgb<11gm/dl the use of ESA and iron was 52.6% and 46.6% respectively(15).

High degree of anemia may be related to the peculiarity to the environment including parasitic infestation, malnutrition, deficiencies of iron, folate, vitamin B12 etc. These causes could not be excluded completely in this study.

8. Strength and limitation of the study.

Strength

- It is the first study on anemia in ND-CKD patients in Ethiopia.
- It identified gaps in work up and management of anemia in CKD.

Limitations

- cross-sectional study , difficult to assess management pattern and patient response
- Laboratory results are incomplete
- Single hospital based study
- Important co founders like volume status of the patient and dialysis requirement are not included.

9. Conclusion and recommendation

The prevalence of anemia in our CKD patients is 60.6%. More than half (51.4%) of our patients are not getting any treatment for their anemia. The baseline laboratory workups recommended by KDIGO for every anemic patient are lacking. Despite that many patients seem to have iron deficiency which is relatively easy to diagnose and treat.

Finally I would like to recommend

To policy makers

- The study showed that majority of our CKD patients are in the younger age group unlike other countries and it is better if CKD prevention programs become widely available.
- Hypertension and diabetes mellitus are responsible for majority of CKD in our patients. Early diagnosis and proper management could have prevented or delayed onset of CKD in these patients.

To the hospital

- Basic laboratory tests recommended for anemic patients with CKD should be available in the hospital.

To Researchers

- Further studies are mandatory with better laboratory work up of anemic patients with CKD.

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11. Consent form

11.1 Consent form English

Patient’s information document

Dear participants;

My name is _____, I am a member of data collectors for a research which is conducted by Dr. Anteneh getachew on the study intended to assess the prevalence of Anemia and associated factors in patients with chronic kidney disease not on dialysis but on follow up at SPHMMC. You are invited to participate on this project..

Procedure

If you are willing to participate on this study, you will be interviewed by the data collector. Your card will be used to complete important laboratory values. You don't need to tell your name to the data collector and all your response and the results obtained will be kept confidentially by using coding system. You don't have to write or sign, verbal consent is enough.

Risk/discomfort

By participating in this research project, you may feel that it has some discomfort especially on wasting time about 20 minutes. We hope you will participate in the study for the sake of the benefit of the research result. There is no risk in participating in this research project.

Benefits and incentives

If you participate in this research project, there may not be direct benefit to you but your participation will likely help us to meet the research objective which is intended to improve the management of Anemia in CKD patients not on dialysis.

You will not be provided any incentives or payment to take part in this project.

Confidentiality and privacy

The information collected from this research project will be kept confidential. Information will be stored in a file without your name, only code number is used. It will not be revealed to anyone except the principal investigator and it will be kept locked with key.

Right to refuse or withdraw:

You have full right to refuse from participating in this research. You can choose not to respond to some or all question if you do not want to give your response. You have also full right to withdraw from this study at any time you wish without losing any of your right.

Person to contact

This research project will be reviewed and approved by the IRB Saint Paul's Hospital Millennium Medical College.

If you have any question you can contact any of the following individuals and you may ask any time you want.

Contact address of principal investigator: -

Name: Dr. anteneh getachew

Tell: 0929175601

Email: antget2366@gmail.com

11.2 Amharic version of the research consent form

የጥናቱ ተሳታፊዎች የመረጃ ቅጽ

በቅድሚያ በዚህ ጥናት እንዲሳተፉ ስንል በአክብሮት ጥያቄያችንን እያቀረብን ጥናቱ የሚካሄደው በኩላሊት ታካሚዎች ደም ማነስ ዙሪያ ነው።
የጥናቱ ዓላማ፡ በኩላሊት ታካሚዎች ደም ማነስ ሁኔታ ማጥናት ነው።

ሊደርስ የሚችል አደጋ፡- በዚህ ጥናት ውስጥ አደጋ የሚያደርስ ድርጊት የለም።

የሚገኝበት ጥቅም፡- ይህ ጥናት ለበሽተኞች ልዩና ቀጥተኛ የሚባል ጥቅም የለውም። ይሁን እንጂ ወደፊት የጥናቱ ውጤት በኩላሊት ታካሚዎች ደም ማነስ ሕክምና አሰጣጥ እንዲሻሻል ከፍተኛ አስተዋጽኦ ያደርጋል።

ሚስጥራዊነት፡- የማንኛውም የጥናቱ ተሳታፊ መረጃ በሚስጥራዊነት ይያዛል። የእያንዳንዱን ግለሰብ መረጃ ከዋናው ተመራማሪና ከአማካሪዎቹ በስተቀር ማንም ሊያገኝ አይችልም።

ፈቃደኝነትን ስለማቋረጥ

በዚህ ጥናት ውስጥ የመሳተፍ መብትዎ ሙሉ በሙሉ በፈቃደኝነት ላይ የተመሰረተ ነው። በጥናቱ ለመሳተፍ ፈቃደኛ መሆን ወይም ራስዎን ማግለል ይችላሉ። እንዲሁም በጥናቱ ባለመሳተፍዎ ምክንያት በአሁን ወይም የወደፊት የህክምና እርዳታ ላይ ተፅእኖ አይኖርም፡

አድራሻ ማወቅ ካስፈለግዎ፡-

የዋናው ተመራማሪ አድራሻ ፡ ዶ/ር አንተነህ ጌታቸው

ስልክ ቁጥር፡- 0929175601

ለጥናቱ ቃለመጠይቅ ለማድረግ የግለሰቦች ፈቃደኝነት መጠየቂያ ቅጽ

በቅድሚያ በዚህ ጥናት እንዲሳተፉ ስንል በአክብሮት ጥያቄያችንን እያቀረብን ጥናቱ የሚካሄደው በ ኩላሊት ታካሚዎች ደም ማነስ ዙሪያ ነው።

ስምዎበዚህመጠይቅውስጥየማይጠቀስመሆኑናበቃለመጠይቁየሚሰጡትንመረጃሁሉበሚስጥርተይዞ
ለጥናትአገልግሎትብቻየሚውልመሆኑንላረጋግጥልዎአወዳለሁ።

እርስዎበዚህጥናትላይየመሳተፍያለመሳተፍወይንምበማንኛውምወቅትቃለመጠይቁንየማቋረጥሙሉ
መብትአለዎትነገርግንእርስዎበጥናቱተሳትፈውየሚሰጡትንመረጃጥናቱንውጤታማለማድረግናበአ
ግባቡለመሰጠትከፍተኛጠቀሜታአለው።

በጥናቱለመሳተፍቃደኛነዎት?

1. አዎ

2. አይደለሁም።

መልሱአዎንከሆነአመሰግናለሁቃለመጠይቁንያካሒዱ።

መልሱአይደለሁምከሆነአመሰግናለውወደሌላተጠያቂይለፉ፤

ግለሰብቃለመጠይቁለማሳተፍምንምአይነትማስገደጃወይምጫናመደረግየለበትም።

ቃለመጠይቁየተካሄደበትቀን ----- ወር ----- 2011 ዓ.ም

12. Annex. Questionnaire (English version)

Instruction: please Mark “√” in the provided space for the choice questions and for the questions that need direct answer, write the answer in the space provided.

Part I: socio demographic characteristics of respondents

1) Age ____

2) Sex: Male ☐ Female ☐

3) BMI= $\frac{wt}{ht^2}$ (weight in Kilograms, and Height is meter)

- a) <18.5
- b) 18.5-25
- c) 25-30
- d) >30
- e) Can't asses

4) Education level

- a) Illiterate _____
- b) Elementary Education _____
- c) High school education _____
- d) College and above _____

5) Religion

- a) Orthodox _____
- b) Muslim _____
- c) Protestant _____
- d) Other _____

6) Address

- a) Addis Ababa _____
- b) If Out of Addis Ababa, approximate distance from Addis Ababa in kilometer

7) Monthly income

- a) <1000 birr _____
- b) 1000-5000 birr _____
- c) 5,000-10,000birr _____
- d) >10,000birr _____

8) Source of income

- a) The patient him/her self
- b) Family support
- c) Other (specify)

9) History of smoking

- a) Yes
- b) No

10) If yes to question no 9 ,how many pack years

- a) <5
- b) 5-10
- c) >10
- d) Can't specify

Part II—CKD and anemia clinical characteristics

11) How long is the diagnosis of CKD

- a) <6 month
- b) 6month – 1 year
- c) 1 year-5 years
- d) >5 years

12) Are you known to have diabetes prior to diagnosis of CKD?

- a) Yes
- b) No

13) If yes to the above Question, number of years since the diagnosis of diabetes? _____

14) Are you hypertensive before CKD

- a) Yes
- b) No

15) If hypertensive, how many years are you known to have hypertension_____

16. Other co morbid diagnosis _____

17. Does the patient have any of easy fatigability, light headedness, tinnitus, or pallor attributable to anemia?

- a) Yes
- b) No

18. Does the patient has any history of blood transfusion?

- a) yes
- b) No

NB. Fill the following information from patient card

19. What is his/her last creatinine? _____

20. Possible cause of CKD (from the card)

- a. DM
- b. HTN
- c. Glomerular diseases
- d. Obstructive uropathy
- e. Unknown
- f. Other (specify)_____

21. CBC results in the last 3 months.

- a) Hemoglobin_____
- b) MCV_____
- c) MCH_____
- d) MCHC_____
- e) RDW_____
- f) WBC_____
- g) PLT_____

22. Did the patient had Peripheral morphology

- c) Yes
- d) No

23. If yes to question 22, what was the finding?_____

24. Does the patient have iron study at any point?

- a) Yes
- b) No

25. If yes to question no 24, please write the results

- a) Serum iron _____
- b) Serum ferritin _____
- c) TIBC _____
- d) TSAT _____

26. Serum B12 _____

27. Serum folate _____

28. stool occult blood test result

- a) positive
- b) negative
- c) patient have overt GI bleeding
- d) not done

29. Is the patient taking any of the following (tick on the space)

	Yes	No
a) Iron therapy		
b) ESA		
c) folate		
d) cobalamine		
e) other please specify		

Thank you for your time!!!