

ORIGINAL RESEARCH

Prevalence of Anemia and Its Associated Factors Among Chronic Kidney Disease Patients Attending Selected Public Hospitals of Addis Ababa, Ethiopia: Institutional-Based Cross-Sectional Study

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Background: Anemia is a global public health problem with high mortality and morbidity. It is becoming more prevalent in Ethiopia. Therefore, this study aimed to estimate the prevalence of anemia and its associated factors among chronic kidney disease patients at selected public hospitals of Addis Ababa, Ethiopia.

Methods: An institutional-based cross-sectional study was conducted on selected public hospitals in Addis Ababa for studies on anemia in CKD patients. Data was entered into EPI Info version 4.4.1 and exported to SPSS version 24 for analysis. Both bivariate and multivariate logistic regression analyses were used to identify independently associated factors of anemia in CKD patients. Multivariate analysis was used to control the possible effect of confounders.

Results: A total of 387 participants were included to estimate the prevalence of anemia among chronic kidney disease patients. The prevalence of anemia was 53.5% (95% CI). Being females were 2 times more likely to develop anemia as compared to their counterparts (AOR=2.04, 95%:1.18, 2.46) and hemodialysis history had two times higher odds for anemia (AOR=2.754, 95% CI: 1.218–6.229, P=0.015) compared to patients without hemodialysis history.

Conclusion: The overall prevalence of anemia across all stages of CKD is 53.5%. From the stage of CKD, stage 5 CKD has a higher (90.9%) anemia prevalence compared to others, and females showed a higher frequency of anemia when compared with males. Therefore, situation-based interventions and country context-specific preventive strategies should be developed to reduce the prevalence of anemia in this patient group.

Keywords: chronic kidney disease, anemia, prevalence, Ethiopia

Background

Chronic kidney disease (CKD) is a progressive, irreversible deterioration of renal function in which the body's ability to maintain metabolic, fluid electrolyte, and balance fail, which results in uremia or azotemia and can be classified into stages 1 to 5 based on the deterioration of glomerular filtration rate (GFR), with each increasing number indicating a more advanced stage of the disease.1

Anemia is a global public health problem of all developing and developed countries which affects not only human health but also both social and economic development and occurs at all age group of the population.² Anemia is defined as a state in which the quality and/or quantity of circulating red blood cells is below

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normal or the established cut-off point defined by the World Health Organization.³ According to the World Health Organization (WHO) diagnostic criteria, Patients are classified as anemic when hemoglobin (Hgb) is < 12 g/dl for females and <13g/dl for males.⁴

Anemia with CKD is defined as a situation in which the concentration of hemoglobin in the blood is below the mean Hg level, corrected for age and sex and the main cause of anemia in CKD is the inadequate production of endogenous erythropoietin either due to functional or absolute iron deficiencies.⁵ The prevalence of anemia was high in non-dialysis chronic kidney disease patients from stage 1 to the last stage. Certain factors that are associated with the development of anemia in patients with CKD include; diabetic nephropathy (DN), chronic kidney disease (CKD) stages, body mass index (BMI), smoking, leukocyte count, and serum albumin.⁶ The occurrence of anemia was higher for patients with both end-stage renal disease and CKD. It has also a greater prevalence among older persons, persons with diabetes, cardiovascular disease, and hypertension than persons without these conditions.⁵

Anemia is the commonest complication of CKD which accounts significant burden of cardiovascular diseases. CKD decreases the quality of life of patients. It suggested that CKD had a significant association with anemia and is considered as a possible cause when the glomerular filtration rate (GFR) is <60mL/min/1.37m2 and, it is more likely to be the cause if the GFR is <30mL/min/1.73m2. The use of iron therapies and erythropoiesis-stimulating agents (ESAs) has allowed improvement in patients with anemia of CKD.8

A study done in Korea showed that, as CKD stages increase the anemia has also direct relation with the stages. Current smokers showed a lower risk of anemia compared to the previous smoker and lower body mass index (BMI) had a higher risk of anemia but there is no significant association between gender and age with anemia.⁶ Therefore, this cross-sectional study aimed to estimate the prevalence of anemia in patients with CKD and its associated factors at selected public hospitals in Addis Ababa Ethiopia.

Methods

Study Design

A hospital-based cross-sectional study was conducted from November 15 to May 15/2020.

Study Setting

The study was conducted in Addis Ababa. According to the data obtained from Addis Ababa City Administration Health Bureau, there are 11 public hospitals in Addis Ababa, which we are giving different services to the public. Three hospitals (St Paul Hospital, Tikur Anbessa Specialized Hospital, and Zewditu Memorial Hospital) were purposely selected to be the study areas among the public hospitals. These hospitals provide service to patients with the diverse socio-economic background. Besides, there is a high load of CKD patients in these three hospitals as compared to the other public hospitals in the city.

Eligibility Criteria

CKD patients (age >18 years old) who were attended Tikur Anbessa Specialized Hospital, St Paul Hospital, and Zewditu Memorial hospital outpatient department for follow up purpose at the time of data collection and who were willing to participate in the study were included.

Sample Size Determination and Sampling **Procedure**

The sample size was determined using a formula of estimating a single proportion for a cross-sectional study. Since the population size is less than 10, 000, the final sample size was estimated using the correction formula. The final sample size obtained including a 10% non-response rate was 387. Then, the number of participants in each selected hospital was determined using the population proportionate sampling (PPS). It is estimated using the formula: (E) = C*D, (C*BD in a health facility)/C, where, BD = proportion of CKD patients in the study in a given hospital, E = Final sample size obtained using correction formula (387), C is the total number of CKD patients in the selected hospitals.

Study Instrument

Interviewer structured questionnaire and checklist for chart review was used for data collection. The tool was adopted from a previous study at Gondar University Hospital, North West Ethiopia.9

Operational Definition

• CKD: CKD is defined as kidney damage or glomerular filtration rate (GFR) of less than 90 mL/min/1.73 m2 for three months or more, irrespective of cause or evidence of kidney damage. 10

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Stage of CKD: is classified as stage 1, 2, 3, 4, and 5 based on GFR category (Stage 1 CKD: eGFR 90 or Greater, Stage 2 CKD: eGFR between 60 and 89, Stage 3 CKD: eGFR between 30 and 59, Stage 4 CKD: eGFR between 15 and 29, Stage 5 CKD: eGFR Less than 15).

- Anemia: Anemia was defined as serum hemoglobin levels ≤12 g/dL in women and ≤ 13 g/dL in men age ≥18 years old, as recommended by the National Anemia Action Council and the World Health Organization.³
- Cigarette smoking: participants who have current and previous cigarette smoking history at the start of study.¹²
- Alcohol consumption: Excessive Alcohol Consumption in this study is defined as consumption of ≥6 drinks and ≥4 drinks on a single occasion in men and women respectively.¹³
- **BMI:** is a person's weight in kilograms (kg) divided by his or her height in meters squared. <18.5kg/m² for underweight, 18.5-24.9 for normal-weight, and ≥ 25.0 kg/m² for overweight.¹⁴
- **GFR:** can be estimated from calibrated serum creatinine and estimating equations, such as the Cockcroft-Gault formula (normalized for the body surface area [BSA]): (140 Age [years]) x weight (kg) x (0.86, if female) x 1.73/72 x serum creatinine (mg/dl) x BSA (m2). 15

Data Analysis

Data was entered into EPI Info version 4.4.1 and exported to SPSS version 24 for analysis. Descriptive statistics, such as median was used to compute continuous variables and counted with percentage for categorical variables. Both bivariate and multivariate logistic regression analyses were used to identify independently associated factors of anemia in CKD patients. The bivariate analysis was exported to multivariate analysis when P<0.2 to control the possible effect of confounders. Adjusted odds ratio (AOR) with 95% CI and P-value <0.05 were used to select variables associated with anemia in CKD patients.

Result

Socio-Demographic Characteristics of the Participants

In the present study, about 387 participants were included. Out of these more than half, 220 (56.8%) of

the participants were females. The median age of the participants was 55, while the minimum and maximum ages of the patient were 19 and 85 years respectively. About one third (32.6%) of participants were in the age group of 46–60 years old category. Two hundred twelve (54.8%) and two hundred eighty-five (73.6%) participants were urban dwellers and married respectively. More than 27% of the respondents were self-employed and 88 (22.7%) participants were civil servants. Around 25% of the respondents had a certificate of college achievement (Table 1).

Table I Socio-Demographic Characteristics of Adult CKD Patients Attending Outpatient Department at Addis Ababa Public Hospital, Addis Ababa, Ethiopia, 2020 (N= 387)

We deble		F	D	
Variables		Frequency	Percentage	
	1	(n)	(%)	
Sex	Male	167	43.2	
	Female	220	56.8	
Age	19–30	29	7.5	
	31–45	109	28.2	
	46–60	126	32.6	
	61–75	107	27.6	
	> 75	16	4.1	
Residency	Urban	212	54.8	
	Rural	175	45.2	
Marital status	Married	285	73.6	
	Single	26	6.7	
	Divorced	12	3.1	
	Widowed	64	16.5	
Level of	Level of Unable to read and		20.9	
education	write			
	Able to read &	91	23.5	
	write			
	Primary school	67	17.3	
	High School	52	13.4	
	Collage and above	96	24.8	
Occupation	Civil Servant	88	22.7	
	Merchant	36	9.3	
	Farmer	94	24.3	
	Housewife	24	6.2	
	Self-employed	106	27.4	
	Daily labor	10	2.6	
	Student	5	1.3	
	Others	24	6.2	
Monthly	0–3200	173	44.7	
income	3201-10,900	193	49.9	
	>10,901	21	5.4	

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Table 2 Clinical Characteristics of Adult CKD Patients Attending Outpatient Department at Addis Ababa Public Hospitals, Addis Ababa, Ethiopia, 2020 (n=387)

Clinical Characte	Frequency	Percent %					
ВМІ	<18.5	93	24.0				
	18.5–24.9	256	66.1				
	25–29.9	32	8.3				
	≥ 30	6	1.6				
Duration of CKD	< I year I-2 years >2-3 years greater than 3 years	209 132 23 23	54.0 34.1 5.9 5.9				
HTN	Absent	233	60.2				
	Present	154	39.8				
Hemodialysis status	No	323	83.5				
	Yes	64	16.5				
Had DM	No	165	42.6				
	Yes	222	57.4				
HIV status	Negative	278	71.8				
	Positive	20	5.2				
	Unknown	89	23				

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; HTN, hypertension; DM, diabetics mellitus; HIV, human immunodeficiency virus.

Clinical Characteristics of Respondents

One hundred fifty-four (39.8%) and two hundred twenty-two (57.4%) of respondents were hypertensive and diabetes mellitus patients respectively. Of all participants, more than half (54.0%) of the respondents had CKD of less than one-year duration. About two-thirds (66.1%) of the participants had normal weight with a BMI label of between 18.5–24.9 (Table 2).

History of hemodialysis was present in 64 (16.5%) of the respondents. As few as 20 (5.2%) of the respondents were HIV positives confirmed by the laboratory (Table 2).

Nearly 70% of the participants were diagnosed having stage 3 and stage 4 CKD while only 2.8% of them were at an early stage (stage 1) of CKD. [Figure 1].

Behavioral Characteristics of Respondents

Three hundred thirty-two (85.8%) of the respondents were not smoking currently. But 72 (18.6%) of the respondents were smokers before and stopped smoking currently. Sixty-four (16.5%) of the participants still take alcohol (Table 3).

CKD stage Catagory

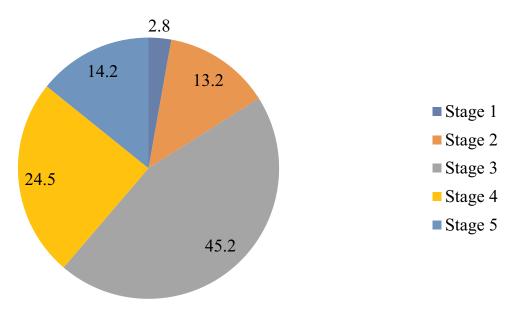


Figure I CKD stages of adult CKD patients attending outpatient department at Addis Ababa Public Hospital, Addis Ababa, Ethiopia, 2020 (n= 387).

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Table 3 Behavioral Characteristics of Adult CKD Patients Attending Outpatient Department at Addis Ababa Public Hospital, Addis Ababa, Ethiopia, 2020 (n=387)

Behavioral Characteristics	Frequency Percent %		
Smoking currently	No	332	85.8
	Yes	55	14.2
Current Use of Alcohol	No	323	83.5
	Yes	64	16.5
Smoking Previously	No	315	81.4
	Yes	72	18.6
Previously Use of Alcohol	No	177	45.7
	Yes	210	54.3

Prevalence of Anemia

Study participants' charts were reviewed to assess the prevalence of anemia, and the clinical characteristics of the respondents. Accordingly, from a total of 387 CKD patients who were on follow-up at Zewditu Memorial, St. Paul, and Tikur Anbessa specialized hospitals, a total of 207 (53.5%) CKD patients were found anemic. Hence, the current study confirms an overall 53.5% prevalence of anemia in CKD patients.

The prevalence of anemia concerning age was 33.3 for those aged 46–60 years. Married CKD patients had a higher prevalence (76.3%) of anemia as compared to unmarried. The prevalence of anemia was 28% in respondents who attended at least college. (Table 4). Furthermore, the prevalence of anemia is increasing as the stage of CKD is increasing. Two (18.8%) among 11 stage one CKD patients, 14 (27.5) out of 52 stage 2 CKD patients, 72 (41.1) among 175 stage 3 CKD patients, 69 (72.6%) among 95 stage 4 CKD patients, and 50 (90.9%) out of 55 stage 5 CKD patients were anemic (Figure 1). Among the respondents who were hypertensive and diabetics, 68.8% and 59.5% were found anemic respectively (Figure 2).

Higher anemia prevalence was noted in stage 3 and stage 4 CKD patients. More than 12% of the respondents who smoke currently and 13% of the respondents who used to smoke cigarettes have developed anemia. Nearly 50% of the respondents who had a history of alcohol consumption and 14.5% of the respondents who are currently taking an alcohol developed anemia (Table 4).

Factors Associated with Anemia Among CKD Patients

To identify factors associated with anemia among CKD patients, a logistic regression model was fitted. On binary

logistic regression analysis, sex, CKD stages, previous history of alcoholic and smoking, presence of proteinuria, HTN, DM, BMI, hemodialysis, and duration of CKD were associated with anemia. Finally, after obtaining statistically significant variables at p<0.05 in binary logistic regression analysis, multiple logistic regression analysis was carried out to see the independent predictors of anemia among CKD patients. The multivariable logistic regression was carried out by taking anemia as a covariate in addition to those variables where the significant association was obtained in binary logistic regression. After adjusting potential cofounders, being female, presence of proteinuria, comorbidity with HTN and DM, CKD stages, and hemodialysis remained statistically significant for the occurrence of anemia among CKD patients (Table 5).

Discussion

This study aimed to synthesize evidence on the magnitude of anemia and its associated factors in patients with CKD at selected hospitals of Addis Ababa, Ethiopia. According to this study, the overall prevalence of anemia in patients with CKD was 53.5% which is higher than reported data by a study conducted in Korea (44.9%), Tanzania (33%), United States (15%), UK (6.76%), and Dessie, Ethiopia (39.5%).^{6,7,18,19} However, it is lower than the reports made by other researchers that showed, 77.5%, 67%, and 64.5% in Nigeria, Kenya and University of Gondor Ethiopia respectively.^{23,24} The low prevalence in our study is because of differences in the definition of anemia, study population, and survey period. The variation of the prevalence may be due to differences in the methodology, variation of quality of care and quality of reporting, policy, and strategic difference.

The prevalence of anemia was varied by the stages of CKD. This study demonstrated that 18.2%, 27.5%, 41.1%, 72.6% and 90.9% of stag1, 2, 3, 4 and stage 5 patients were anemic respectively. A comparable trend was also observed from the recent Korean cohort with a prevalence of 10% at stage 1 to 96.5% at stage 5.18 NHANES survey in the United States with a prevalence of anemia from 8.4% at stage 1 to 53.4% at stage 5.19 It is also similar to studies conducted in the University of Gonder Ethiopia study with a prevalence of 20% at stage 1 to 93.8% at stage 5 CKD.20 It indicates that an increasing prevalence of anemia was associated with the CKD stage.

This study has clinical implications in that the high magnitude of anemia in patients with CKD should guide Alemu et al Dovepress

Table 4 Distribution of Anemia by Demographic, Clinical, and Behavioral Characteristics Among Adult CKD Patients Attending the Outpatient Department

Variables	Category	Anemia	Anemia				Total	
		Yes		No	No		7	
		n	%	n	%	n	%	
Sex	Male	69	33.3	98	54.4	167	43.2	
	Female	138	66.7	82	45.6	220	56.8	
Age	19–30	11	5.3	18	10.0	29	7.5	
	31–45	66	31.9	43	23.9	109	28.2	
	46–60	69	33.3	57	31.7	126	32.6	
	61–75	51	24.6	56	31.1	107	27.6	
	>75	10	4.8	6	3.3	16	4.1	
Marital Status	Married	158	76.3	127	70.6	285	73.6	
	Single	9	4.3	17	9.4	26	6.7	
	Divorced	8	3.9	4	2.2	12	3.1	
	Widowed	32	15.5	32	17.8	64	16.5	
Educational status	Unable to read& write	47	22.7	34	18.9	81	20.9	
	Abel to read &write	43	20.8	48	26.7	91	23.5	
	Primary school	30	14.5	37	20.6	67	17.3	
	High school	29	14	23	12.8	52	13.4	
	Collage &above	58	28	38	21.1	96	24.8	
CKD stages	Stage I	2	0.51	9	2.3	П	2.8	
	Stage 2	14	3.6	37	9.5	51	13.2	
	Stage 3	72	18.6	103	26.6	175	45.2	
	Stage 4	69	17.8	26	6.7	95	24.5	
	Stages 5	50	12.9	5	1.3	52 13. 96 24. 11 2.8 51 13. 175 45. 95 24. 55 14. 209 54 132 34.	14.2	
Duration of CKD	≤ I year	86	41.5	123	31.7	209	54	
Marital Status Educational status CKD stages Duration of CKD Smoking before Smoking currently Alcoholic before	2 years	86	41.5	46	11.8	132	34.1	
	3 years	16	7.7	7	3.9	23	5.9	
	> 3 years	19	9.2	4	2.2	23	5.9	
Smoking before	No	180	87	135	77	315	81.4	
	Yes	27	13	45	25	72	18.6	
Smoking currently	No	182	87.9	150	83.3	332	85.8	
	Yes	25	12.1	30	16.7	55	14.2	
Alcoholic before	No	105	50.7	72	40	177	45.7	
	Yes	102	49.3	108	60	210	54.3	
Alcoholic currently	No	177	85.5	146	81.1	323	83.5	
•	Yes	30	14.5	34	18.9	64	16.5	
n: frequency								

healthcare professionals to minimize the risk of anemia by guiding the patient who could be detected in health checkups, give information about possible risk factors during routine patient care, and provide knowledge about the potential risk of anemia. Besides, identifying associated risk factors may help health care professionals treat anemia patients with CKD during their clinical care. The current study indicated that patients with the presence of diabetes mellitus were 2 times more likely to develop anemia as compared to patients with non-diabetes (AOR = 2.156; 95% CI: 1.231, 3.776), and patient with HTN had 3 times more likely to develop anemia as compared to patients with non-hypertensive (AOR = 2.776; 95% CI: 1.597, 4.827). A similar study

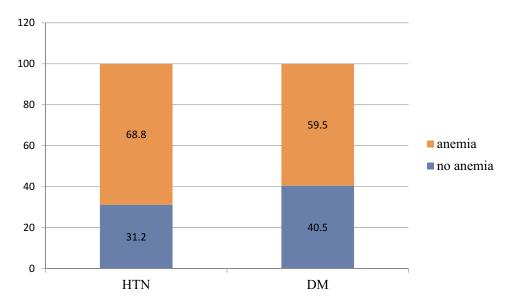


Figure 2 Distribution of anemia in HTN and DM patient among adult CKD patients attending outpatient department at Addis Ababa Public Hospital, Addis Ababa, Ethiopia, 2020 (n=387).

was conducted in Kenya.¹⁸ The result indicates that the prevalence of anemia among hypertensive and DM CKD respondents is higher than those who are not. This

finding suggests that any CKD patient who presents with HTN and DM should be more closely monitored for anemia.

Table 5 Bivariate and Multivariate Analysis for the Occurrence of Anemia Among CKD Patients (N= 387)

Variable		Anemia		COR (95% CI)	P-value	AOR (95% CI)	P-value
		Absent	Present				
Sex	Male	98(58.7%)	69(41.3%)	I	<0.001	I	
	Female	82(37.3%)	138(62.7%)	2.390(1.583–36.08)		2.047 (1.182–2.468)	0.01*
CKD stages	Stage- I	9(81.8%)	2(18.2%)	I		I	
	Stage-2	37(72.5%)	14(27.5%)	0.378(0.202-0.700)	0.002	1.928 (0.311-11.942)	0.480
	Stage-3	103(58.9%)	72(41.1%)	0.699(0.515-0.945)	0.020	3.355(0.591-19.033)	0.172
	Stage-4	26(27.4%)	69(72.6%)	2.654(1.690-4.166)	<0.01	8.124(1.381–47.798)	0.021*
	Stage-5	5(9.1%)	50(90.9%)	10.00(3.988–25.075)	<0.01	34.165(4.66–250.502)	0.001*
Duration of CKD	≤l year	123(58.9%)	86(41.1%)	I	1	I	
	2 years	46(34.8%)	86(65.2%)	1.870(1.307-2.674)	0.001	1.463(0.826-2.591)	0.197
	3 years	7(30.4%)	16(69.6%)	2.286(0.940-5.556)	0.068	3.048(0.982–9.457)	0.054*
	> 3years	4(17.4%)	19(82.6%)	4.750(1.616–13.962)	0.005	3.501(0.993-12.347)	0.051*
Presence of proteinuria	No	142(63.1%)	83(36.9%)	I		I	
	Yes	38(23.5%)	124(76.5%)	3.263(2.296–4.693)	<0.01	2.320(1.323-4.067)	0.003*
HTN	No	132(56.7%)	101(43.3%)	I		I	
	Yes	48(31.2%)	106(68.8%)	2.208(1.570–3.106)	<0.01	2.776(1.597-4.827)	0.000*
DM	No	90(54.5%)	75(45.5%)	1		1	
	Yes	90(40.5%)	132(59.5%)	1.467(1.122–1.917)	0.005	2.156(1.231–3.776)	0.007*
Hemodialysis statues	No	169(52.3%)	154(47.7%)	I		I	
	Yes	11(17.2%)	53(82.8%)	4.818(2.517–9.224)	<0.01	2.754 (1.218–6.229)	0.015*

Note: *P value \leq 0.05.

Abbreviations: COR, crude odds ratio; CI, confidence interval; AOC, adjusted odds ratio; CKD, chronic kidney disease; HTN, hypertension; DM, diabetic mellitus; I, constant.

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In this study, patients with hemodialysis history had two times higher odds for anemia (AOR=2.754, 95% CI: 1.218–6.229, P=0.015) compared to patients without hemodialysis history which is similar to the study in the university of Gonder Ethiopia.²⁰ This is because hemodialysis requiring patients with advanced renal disease, in which the presence of anemia was prevalent.

The present study demonstrated that females were 2 times more likely to develop anemia as compared to their counterparts (AOR=2.04, 95% CI:1.18, 2.46). This finding is supported by previous studies conducted in the World Journal of Nephrology, Nepal, and Nigeria. 17,21,22 This would suggest those female patients had lower HGB concentrations than male patients, which likely explains why females had a greater risk of developing anemia. However, sex was not significantly associated with anemia as reported in Korea study. 6

The current study revealed that those patients who had urine protein were 2 times more likely to develop anemia as compared with patients who do not have proteinuria (AOR=2.320, 95% CI: 1.323, 4.067). This finding is in agreement with Korea.²³ The evidence further supports that low serum albumin due to protein malnutrition and/or inflammation.

Conclusion and Recommendation

Prevalence of anemia was increased when stages of chronic kidney disease increased and worsened with a progressive decline in kidney function. HTN, DM, presence of proteinuria, CKD stages, and having hemodialysis history were independently associated with anemia in CKD patients. There is a need to improve multiple aspects of CKD management, including early diagnosis and treatment of anemia. Periodic screening and intervention for anemia in CKD patients should be practiced to prevent its complication.

Abbreviations

BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; CKD, chronic kidney diseases; DM, diabetic mellitus; EGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HCT, hematocrit; HGB, hemoglobin; HIV, huma immune virus; KDOQI, Kidney Disease Outcomes Quality Initiative; RBC, red blood cell; UK, United Kingdom; USA, The United States of America; WHO, World Health Organization.

Data Sharing Statement

The data analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

To confirm the Declaration of Helsinki (1964) and the Population Screening Act, Addis Ababa University Institutional Review Board approved the study. Participation was voluntary, and information was collected anonymously after obtaining written consent from each respondent. Confidentiality of data was ensured throughout the study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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This study was conducted in collaboration with Addis Ababa University. Every step of the project was followed by Addis Ababa University, College of Health Sciences, School of Nursing and Midwifery. The university has no role in designing, analyzing, and writing the study.

Disclosure

The authors declare that they have no competing interests.

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