

## *Retraction*

# **Retracted: Management Practice, and Adherence and Its Contributing Factors among Patients with Chronic Kidney Disease at Tikur Anbessa Specialized Hospital: A Hospital Based Cross-Sectional Study**

### **International Journal of Nephrology**

Received 10 January 2019; Accepted 10 January 2019; Published 5 February 2019

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*International Journal of Nephrology* has retracted the article titled “Management Practice, and Adherence and Its Contributing Factors among Patients with Chronic Kidney Disease at Tikur Anbessa Specialized Hospital: A Hospital Based Cross-Sectional Study” [1]. The article was previously published as Kefale B, Tadesse Y, Alebachew M, Engidawork E (2018) Management practice, and adherence and its contributing factors among patients with chronic kidney disease at Tikur Anbessa Specialized Hospital: A hospital-based cross-sectional study. *PLoS ONE* 13(7): e0200415. <https://doi.org/10.1371/journal.pone.0200415> [2].

### **References**

- [1] B. Kefale, Y. Tadesse, M. Alebachew, and E. Engidawork, “Management practice, and adherence and its contributing factors among patients with chronic kidney disease at tikur anbessa specialized hospital: a hospital based cross-sectional study,” *International Journal of Nephrology*, vol. 2018, Article ID 2903139, 15 pages, 2018.
- [2] B. Kefale, Y. Tadesse, M. Alebachew, and E. Engidawork, “Management practice, and adherence and its contributing factors among patients with chronic kidney disease at Tikur Anbessa Specialized Hospital: a hospital-based cross-sectional study,” *PLoS ONE*, vol. 13, no. 7, Article ID e0200415, 2018.

## Research Article

# Management Practice, and Adherence and Its Contributing Factors among Patients with Chronic Kidney Disease at Tikur Anbessa Specialized Hospital: A Hospital Based Cross-Sectional Study

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Received 28 January 2018; Revised 18 April 2018; Accepted 30 May 2018; Published 29 July 2018

Academic Editor: Franca Anglani

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The objective of this study was to assess the management practice, medication adherence, and factors affecting medication adherence in CKD patients at Tikur Anbessa Specialized Hospital (TASH). *Methods.* A cross-sectional study was conducted at the nephrology clinic of TASH. A total of 256 CKD (stages 1 and 2=50, stage 3=88, stage 4=55, and stage 5=63) patients were recruited through systematic random sampling. Data were collected from medical records and interviewing patients. The rate of adherence was determined using 8-item Morisky medication adherence scale. The data were analyzed using SPSS version 20.0 statistical software. Univariate and multivariate binary logistic regression were used to investigate the potential predictors of medication nonadherence. *Results.* About 57.3% of diabetes mellitus with hypertension were treated with combination of insulin and ACEI based regimens. Other cardiovascular comorbidities were predominantly treated with Acetyl Salicylic Acid in combination with  $\beta$ -blocker. Only 61.3% (stages 1 and 2=70%, stage 3=73.9%, stage 4=54.5%, and stage 5=43%) of the study population were adherent to their treatment regimens. Forgetfulness (79.8%) was the major reason for medication nonadherence. Patients who had an average and high monthly income were 4.14 (AOR=4.14, 95% CI: 1.45-11.84,  $p=0.008$ ) and 6.17 times (AOR=6.17, 95% CI: 1.02-37.46,  $p=0.048$ ) more likely to adhere as compared to those who had very low income. Patients who were prescribed with  $\geq 5$  drugs were 0.46 times (AOR= 0.54, 95% CI: 0.27-1.10,  $p=0.049$ ) less likely to adhere compared to their counterpart. Patients who were students, drivers, or teachers working in private school were about 7.46 times (AOR=7.46, 95% CI: 1.49-37.26,  $p=0.014$ ) more likely to adhere compared with patients who were farmers. *Conclusion.* Insulin and ACEIs based regimens were the most frequently used regimens in the treatment of diabetes mellitus and hypertension comorbidities. Very low income, increased number of prescribed medications, and being a farmer were the predictors of medication nonadherence.

## 1. Introduction

Chronic kidney disease (CKD) is defined as abnormal kidney structure or function persisting greater than 3 months [1]. It is a progressive, irreversible deterioration in renal function in which the body's ability to sustain metabolic and fluid and electrolyte balance fails, resulting in uremia or azotemia [2]. Increasing prevalence of declining renal function, diabetes,

hypertension, primary renal disorders, and obesity [3, 4] has contributed to CKD becoming one of the most common chronic diseases [5].

CKD has a complicated interrelationship with other diseases, most commonly diabetes and hypertension [6]. It is a global public health problem due to the rapid rise of common risk factors such that diabetes and hypertension will result in more profound burden that developing

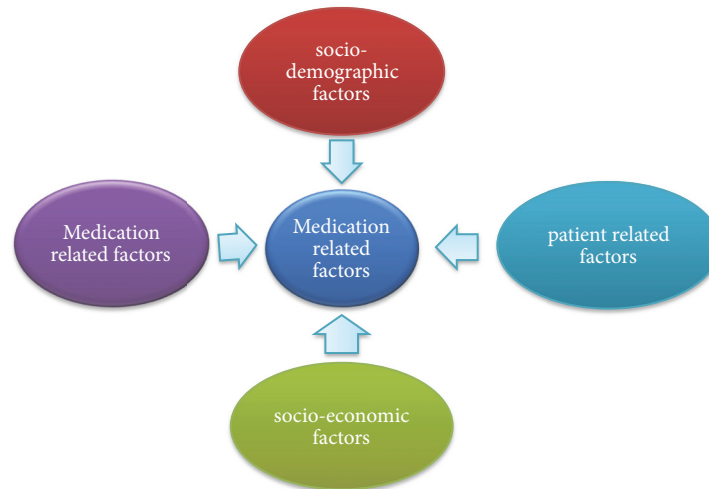


FIGURE 1: Structural framework for factors affecting medication adherence.

nations are not equipped to handle [7]. It is associated with serious consequences, including increased risk of mortality, accelerated CVD, and increased risk of acute kidney injury [1]. Mortality from CVD is estimated to be at least 8- to 10-fold higher in CKD patients as compared to non-CKD patients [7]. Recent studies have reported that CKD is an independent and major risk factor for cardiovascular disease (CVD) [1, 8]. Attention to cardiovascular risk factors remains the cornerstone of management to delay progression of CKD and prevent cardiovascular events. The direct management of CKD focuses on renin angiotensin aldosterone system, blood pressure, and glycemic control. Optimal management of common comorbid conditions and addressing cardiovascular risk factors are important to slow down its progression and reduce the risk of developing CVD for as long as possible [9].

Globally, 10% of the population is affected by CKD, and millions die each year due to high economic cost treatment [1]. It affects 10–15% (western countries) [10], 17.2% (India) [11], and 14.82% (China) [12] of the adult population, many of whom require costly treatments. With increasing of aging population, elderly people are the highest risk group for CKD. Studies in US and China population showed prevalence of CKD (US & China) as follows: stage 1 (1.8% & 3.33%), stage 2 (3.2% & 2.49%), stage 3 (7.7% & 7.07%), and stages 4 and 5 (0.35 % & 0.97%) [12, 13].

Incidence of the disease increases at an annual rate of 8% and consumes up to 2% of the total global health expenditure [14]. The treatment of CKD in developing countries is expensive, unaffordable, and unavailable [15]. Suboptimal management of comorbid conditions and nonadherence to prescribed medication schedule have been the major problems in CKD patients and their occurrence can adversely impact the course of the disease [16, 17]. Poor adherence to medication regimens is common, contributing to substantial worsening of disease, death, and increased healthcare costs. According to World Health Organization, it is estimated that only 50% of people with chronic diseases take their medications consistently as prescribed because they consider them ineffective or experience untoward side effects [18]. The

pill burden in CKD patients is high, having to take on average around 8–10 tablets/day, due to comorbidities and dominant risk factors of CKD [19]. Hence, CKD patients belong to the group of subjects with one of the highest burdens of daily pill intake depending on severity of their disease [20]. This imposes high personal and economic burden on patients and their families [5, 17, 21].

Though nonadherence to treatment is an increasing problem for patients with CKD, it has not been extensively studied in patients with CKD [22]. Previous studies have reported that 24.8% [23], 26–28% [16], 46.1% [24], 22% [25], 18.4% [26], and 23.8% [27] of CKD patients were nonadherent in California, Brazil, the Netherlands, India, Germany, and southern Ethiopia, respectively.

The incidence of CKD in Ethiopia is rising because of increased risk factors [27]. Evidence-based research that evaluates management practice and medication adherence among patients with CKD in developing countries is scanty [28]. Thus, there should be a continuing need to routinely assess management practice and factors affecting adherence among patients with CKD in clinical practice [23, 29]. This is especially important in resource-limited countries like Ethiopia, as the preponderance of economic instability, low literacy level, and restricted access to healthcare facilities, pill burden, side effects of medication, inadequate follow-up, and comorbidities might have led to the increased incidence of medication nonadherence (Figure 1) [30, 31].

Evaluating the management practice, adherence, and identification of the factors leading to nonadherence to a prescribed treatment through a continued research can assist in planning interventions to overcome the barriers. Hence, this study was carried out to

- (i) give information on CKD management practice, and nonadherence and its contributing factors that may help in the healthcare system for whom it concerns;
- (ii) design an interventional method that can solve problems related to management practice and nonadherence;

- (iii) give recommendations on how to manage problems associated with inappropriate management and non-adherence in CKD patients;
- (iv) help as a baseline for further study on management and adherence of renal patients.

Hence, the present study was carried out to assess the management practice, medication adherence, and factors affecting adherence in CKD patients at TASH.

## 2. Methods and Materials

**2.1. Study Settings.** The study was conducted in the renal ambulatory clinics of Tikur Anbessa Specialized Hospital (TASH), which is located in Addis Ababa, Ethiopia. TASH is the largest general public hospital, where tertiary care is being provided in Ethiopia, with over 800 beds. TASH serves about 500,000 patients per year in its outpatient department, 40,000 in the inpatient and same number in the emergency department, and about >600 CKD patients. The renal clinic has nephrologists, nurses, and pharmacists. It provides treatment to different types of renal disease and its complications.

**2.2. Study Design and Period.** A cross-sectional study was conducted in two phases. The first was a patient interview phase, while the second was a retrospective patient chart review. The two phases were done for the same patient from May 1<sup>st</sup> – September 30<sup>th</sup> 2017 to assess management practice and adherence.

**2.3. Sample Size and Sampling Methods.** The sample size was calculated using single population proportion formula [32] as follows:

$$n = \frac{Z_{\alpha/2}^2 P(1-p)}{d^2} \quad (1)$$

where

$n$  is desired sample size for population >10,000;

$Z$  is standard normal distribution usually set as 1.96 (which corresponds to 95% confidence level);

$P$  means that we use positive prevalence estimated, to maximize sample size; negative prevalence =  $1 - 0.5 = 0.5$ ;

$d$  is the degree of accuracy desired (marginal error is 0.05); then the sample size is

$$n = \frac{1.96^2 0.5(1-0.5)}{(0.05)^2} = 384.16 \approx 384 \quad (2)$$

The expected number of source population in the study period ( $N$ ), based on the average number of patients coming to the clinic three days in a week with a total of 20 weeks, was 600 ( $20 \times 6 + 20 \times 12 + 20 \times 12$ ). The corrected sample size, using the following correction formula, was  $233.1 \sim 233$ :

$$\text{Corrected sample size} = \frac{n \times N}{n + N} \quad (3)$$

Then 10% contingency was added on 233:

$$233 \times 10\% = 23$$

$$233 + \text{contingency} = Nf = \underline{256}$$

(4)

A systematic random sampling method was used to recruit samples for the study in each day of the data collection process.

### 2.4. Inclusion and Exclusion Criteria

#### 2.4.1. Inclusion Criteria

- (i) All CKD ambulatory patients and on medications for more than 6 months
- (ii)  $\geq 18$  years of age

#### 2.4.2. Exclusion Criteria

- (i) Patients who refused to participate in the study
- (ii) Patients with cognitive impairment

### 2.5. Data Collection and Analysis

**2.5.1. Instruments.** Data were collected using structured questionnaire and data abstraction format to extract information from the patients and medical records, respectively. The questionnaire for the interview contained sociodemographic characteristics, 8-item Morisky medication adherence scale, and reasons for nonadherence to medications. In addition, data abstraction format was prepared to extract information such as management practices and clinical data.

**2.5.2. Data Collectors Recruitment and Training.** Three nurses were recruited as data collectors. Training was given to them regarding appropriate use of the data collection instruments focusing on uniform interpretation of questions, strict use of study criterion, explanation of study objectives and getting verbal consent from study participants, implementation of sampling technique, and confidentiality of the collected data.

**2.5.3. Data Quality Control.** The data collection instrument which consisted of the questionnaire and the data abstraction format was assessed by an expert physician in the field of nephrology for clarity and comprehensiveness of its contents. Pretesting was done on 5% of the study participants before the start of the actual study. All the necessary modifications and adjustments were done before implementing in the main study.

**2.5.4. Data Analysis and Interpretation.** Data were sorted, cleaned, coded, and entered into SPSS version-20.0 statistical software for management and analysis. Descriptive statistics including frequency, mean, and standard deviation were used to summarize patients' baseline sociodemographic data and evaluate distribution of responses. Bivariate analysis was conducted to see the existence of association between adherence and independent variables. All variables with  $p < 0.2$  in the



bivariate analysis were included in the multivariate binary logistic regression, which was performed to determine the potential predictors of nonadherence. Adjusted Odds Ratio (AOR) with its p value and confidence interval (95%) was reported in each logistic regression analysis. P value < 0.05 was considered as statistically significant.

**2.6. Ethical Consideration.** Ethical clearance and approval of the study protocols were obtained from the Ethical Review Board of School of Pharmacy, Addis Ababa University. In addition, permission was sought from the respective heads of Department of Internal Medicine and renal clinic to conduct the study in the clinic. Prior to data collection, individuals 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 to minimize social desirability bias and enhance anonymity.

### 3. Results

**3.1. Sociodemographic Characteristics.** Males comprised 58% of the sex category. Majority of the participants were in the age group of less than 61 years, which accounted for 54.3%. Mean age of the study population was 52.5 (SD=16.8) years (range 18 to 90 years). Married participants accounted for 69.9% and being retired (25.4%) and government employee (23.4%) accounted for the highest percentage of occupation. Education-wise, 34.4% and 27.7% attended primary and higher education, respectively. Majority of the participants were non-health professionals (97.3%). A significant proportion of the study participants (29.7%) had low level of monthly family income. Stage 3 and 5 CKD patients accounted for the highest percentage of the study participants (Table 1).

**3.2. Disease Related Characteristics.** Overall, patients had been diagnosed with CKD for an average of 4.7 (SD=3.5) years, ranging from under five years (158, 61.7 %) through 5-10 years (75, 29.3%) to above ten years (23, 9%) (Figure 2).

Regarding clinical and laboratory parameters,  $\geq 3$  comorbidities (31.7%) and complications (6.9%) were commonly found in stage 5 CKD patients. Fasting blood sugar, serum creatinine, and blood urea nitrogen increased, while hemoglobin decreased across the stages (Table 2).

About two-thirds (64.4%) of the study participants did not have long term complications. Cardiovascular disease and anemia accounted for the highest percentage among patients that had at least one long term CKD complications. Almost all (96.5%) patients had at least one comorbid condition, hypertension being the major type of comorbidity (91.1%) (Table 3).

**3.3. Nonpharmacological Management Approaches.** The present study revealed that diet restriction, exercise, and no-smoking were the most commonly used nonpharmacological approaches. Agreed dietary plan was found to be present in most (68.8%) of the patients (Table 4).

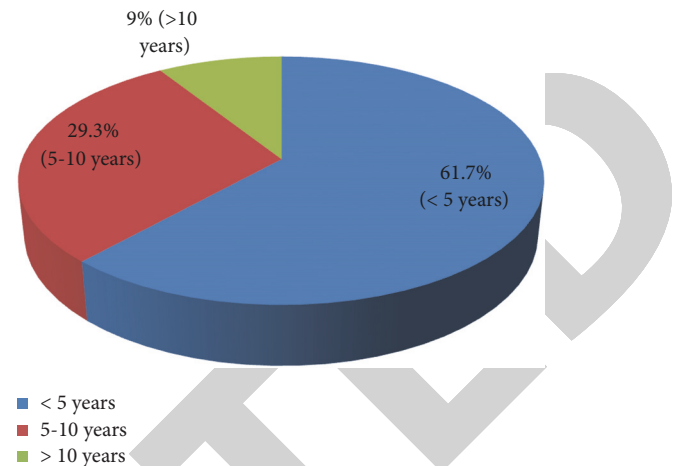


FIGURE 2: Duration of chronic kidney disease among patients attending the renal clinic of Tikur Anbessa Specialized Hospital.

**3.4. Profile of Prescribed Medications.** Table 5 presents medication profile of patients based on CKD stages. It revealed that enalapril (133, 52%) was the most commonly prescribed drug followed by furosemide (128, 50%) and amlodipine (124, 48.4%). Insulin and ASA (Acetyl Salicylic Acid) were found to be the major type of antidiabetic and cardiovascular medications which were prescribed for 69 (27%) and 70 (27.3%) patients, respectively. The average number of prescribed drugs per patient was 3.9 (SD=2.2) with a range of 0-12 drugs (Table 5).

**3.5. Management Practice for Comorbidities and Complications.** Respondents were placed on different medications for treatment of CKD comorbidities or complications. Hypertension was managed by combination of drugs, non-ACEI based (55%) being the most commonly used combination followed by ACEI based (45%). Insulin and metformin were the most commonly prescribed drugs in the management of diabetes mellitus alone. In diabetes mellitus and hypertension comorbidities, insulin and ACEI based combinations (57.3%) and ACEI based combinations (19.8%) were the two most commonly used combinations (Table 6).

**3.6. Types of Regimens Used in the Management of Complications of Chronic Kidney Disease.** ACEIs alone (18%) or in combination (52%) were the most commonly prescribed agent for treating CVD related complications. About three-fourth of anemia and osteodystrophy were treated with iron preparation and calcium-based formulations, respectively. Likewise, 92.3% of fluid buildup, 40% of hyperkalemia, and 88.9% of peripheral neuropathy were treated with furosemide, calcium gluconate, and amitriptylin, respectively (Figure 3).

**3.7. Rate of Adherence and Reasons for Nonadherence.** Assessment of patients' responses to the 8-item Morisky medication adherence scale showed that 157 (61.3%), 51 (19.9%), and 48 (18.8%) patients exhibited high, medium, and poor adherence to the prescribed regimens, respectively (Figure 4).

TABLE 1: Sociodemographic characteristic of chronic kidney disease patients attending the renal clinic of Tikur Anbessa Specialized Hospital.

Variables	Stage of CKD				Total (n= 256)
	1 & 2 (n=50)	3 (n = 88)	4 (n = 55)	5 (n = 63)	
<b>Sex</b>					
Male	25 (50)	60 (68.2)	31 (56.4)	33 (52.4)	149 (58)
Female	25 (50)	28 (31.2)	24 (43.6)	30 (47.6)	107 (42)
<b>Age (years)</b>					
≤60	38 (76)	41 (46.6)	28(50.9)	32(50.8)	139 (54.3)
>60	12(24)	47 (53.4)	27(49.1)	31(49.2)	117 (45.7)
<b>Marital status</b>					
Single†	14(28)	23(26.1)	20(36.4)	20(31.7)	77 (30.1)
Married	36(72)	65(73.9)	35(63.6)	43(68.3)	179 (69.9)
<b>Occupation</b>					
Farmer	6(12)	8(9.1)	4(7.3)	6(9.5)	24 (9.4)
Gov't employee	18(36)	19(25.6)	11(20)	12(19.1)	60 (23.4)
Merchant/trade	7(14)	5(5.7)	5(9.1)	6(9.5)	23 (9)
Daily laborer	2(4)	6(6.8)	4(7.3)	7(11.1)	19 (7.4)
House wife	7(14)	11(12.5)	8(14.5)	11(17.5)	37 (14.5)
Retired	6(12)	27(30.7)	18(32.7)	14(22.2)	65 (25.4)
Others*	4(8)	12(13.6)	5(9.1)	7(11.1)	28 (10.9)
<b>Profession</b>					
Health professional	3(6)	1(1.1)	2(3.6)	1(1.6)	7 (2.7)
Non-health professional	47(94)	87(98.9)	53(96.4)	62(98.4)	249 (97.3)
<b>Educational status</b>					
Cannot read and write	5(10)	11(12.5)	7(12.7)	7(11.1)	30 (11.7)
Primary	13(26)	31(35.23)	20(36.4)	24(38.1)	88 (34.4)
Secondary	10(20)	23(26.1)	19(34.5)	15(23.8)	67 (26.2)
Higher Education	22(44)	23(26.1)	9(16.4)	17(27)	71 (27.7)
<b>Monthly family income (ETB)**</b>					
Very low (≤860)	4(8)	10(11.4)	11(20)	15(23.8)	40 (15.6)
Low (861-1500)	13(26)	21(23.9)	17(30.9)	21(33.3)	72 (28.1)
Average (1501-3000)	10(20)	33(37.5)	18(32.7)	15(23.8)	76 (29.7)
Above average (3001-5000)	17(34)	20(22.7)	6(10.9)	8(12.7)	51 (19.9)
High (≥5001)	6(12)	4(4.5)	3(5.5)	4(6.4)	17 (6.7)

†Single, divorced, and widowed; \*students, driver, garage (mechanic), guard, or teacher working in private school; \*\* based on the Ethiopian Civil Service monthly salary scale for civil servants.

Up on evaluation of the reasons for CKD medication nonadherence, it was identified that forgetfulness (79.8%) was the main reason for their nonadherence. Furthermore, side effects of the medications and high cost of medications accounted for 49.5% and 38.4% of medication nonadherence, respectively. Feeling well without treatment and physicians mode of approach were, however, the least common reasons for nonadherence (Figure 5).

**3.8. Factors Associated with Medication Adherence.** Based on the results of univariate binary logistic regression analysis, variables such as sex, age, occupation, educational status, family income, CKD stage, number of medications, and comorbidities were included in the multivariate logistic regression analysis. After controlling different demographic, economical, and other factors through the use of multivariate logistic regression analysis, this study showed that

only family income, total number of prescribed drugs, and occupation had significant association with CKD medication adherence. Accordingly, patients who had an average and high family monthly income were about four (AOR=4.14, 95% CI: 1.45-11.84, p=0.008) and six (AOR=6.17, 95% CI: 1.02-37.46, p=0.048) times, respectively, more likely to adhere as compared to those who had very low income. During a multivariate logistic regression analysis, it was also found that patients with other groups (students, driver, and teacher working in private school) of occupation had a significant association with their adherence condition and were about seven (AOR=7.46, 95% CI: 1.49-37.26, p=0.014) times more likely to adhere compared with patients who were farmers. On the other hand, patients who were prescribed with five and above drugs were 0.46 (AOR= 0.54, 95% CI: 0.27-1.10, p=0.049) times less likely to adhere compared to those prescribed with less than five drugs (Table 7).

TABLE 2: Clinical and laboratory parameters according to the stage of chronic kidney disease patients attending the renal clinic of Tikur Anbessa Specialized Hospital.

Clinical/laboratory parameters	Stage of CKD				
	1 & 2 (n = 50)	3 (n = 88)	4 (n = 55)	5 (n = 63)	Total (n=256)
Number of comorbidities					
≤ 2	43 (91.5)	77 (90.6)	46 (83.6)	41 (68.3)	207 (83.8)
3 or more	4 (8.5)	8 (9.4)	9 (16.4)	19 (31.7)	40 (15.6)
Number of complications					
≤ 2	9 (100)	29 (100)	23 (95.8)	27 (93.1)	88 (96.7)
3 or more	0	0	1 (4.2)	2 (6.9)	3 (3.3)
FBS	125 ± 46	140 ± 46	149 ± 69	155 ± 57	141 ± 56
Scr	1.6 ± 0.8	2.0 ± 0.8	3.5 ± 1.6	7.6 ± 3.1	3.6 ± 3
BUN	41 ± 20	56 ± 34	93 ± 46	136 ± 66	80 ± 57
Hgb	16.0 ± 18.9	13.6 ± 14.1	10.5 ± 2.6	10.3 ± 2.8	12.6 ± 12.0
MAP	104.9 ± 12.2	101.7 ± 9.6	104.3 ± 14.3	103.6 ± 14.3	103.4 ± 12.4
GFR	74.7 ± 15.4	43.3 ± 8.4	23 ± 4.8	10.4 ± 2.9	37 ± 24.2

FBS = fast blood sugar, Scr = serum creatinine, BUN = blood urea nitrogen, Hgb = hemoglobin, MAP = mean arterial pressure, and GFR = glomerular filtration rate.

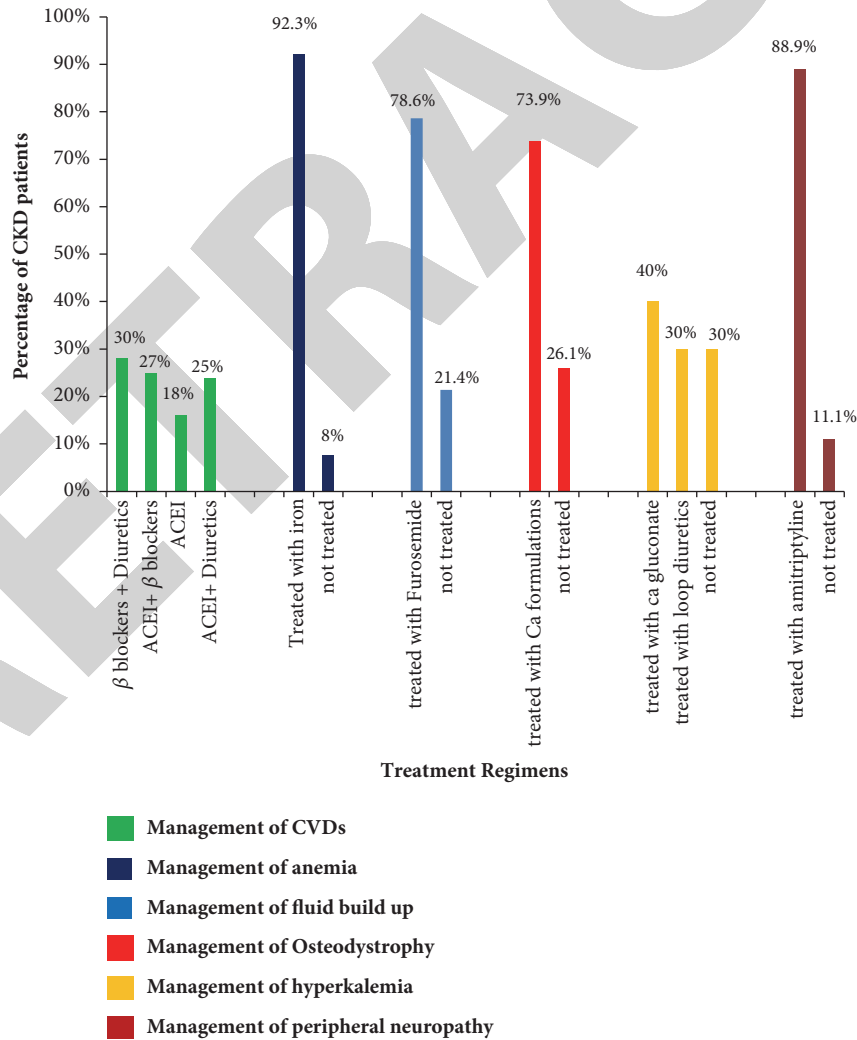


FIGURE 3: Management practice of complications among chronic kidney disease patients attending the renal clinic of Tikur Anbessa Specialized Hospital. ACEI: angiotensin converting enzyme inhibitor.

TABLE 3: Presence of comorbidities and complications among chronic kidney disease patients attending the renal clinic of Tikur Anbessa Specialized Hospital.

Variables	Frequency	Percent
<b>Comorbidities</b>		
Absent	9	3.5
Present	247	96.5
<b>Specific Comorbidities (n=247)</b>		
Hypertension	225	91.1
Diabetes mellitus	114	46.2
Ischemic Heart Disease	33	13.4
Dyslipidemia	31	12.6
Stroke	10	4.1
Others*	22	13
<b>Complications</b>		
Absent	165	64.4
Present	91	35.6
<b>Specific complications (n=91)</b>		
Cardiovascular disease	29	31.9
Anemia	28	30.8
Osteodystrophy	23	25.2
Fluid build up	14	15.3
Hyperkalemia	10	11
Peripheral neuropathy	9	9.9

\*Gouty arthritis, asthma, Parkinson, nephritic syndrome, and pyelonephritis.

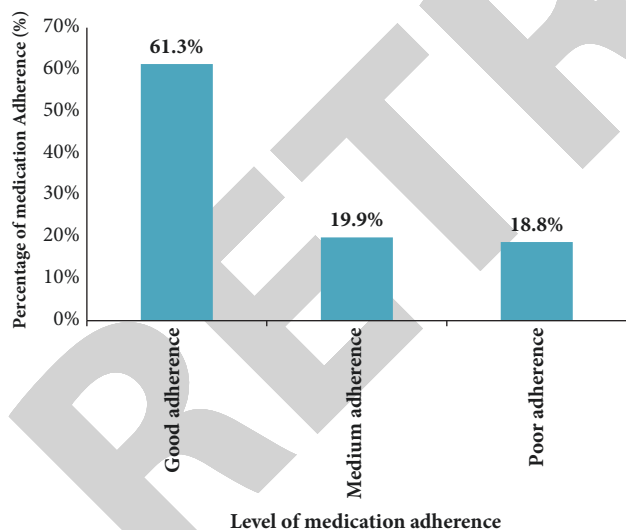


FIGURE 4: Rate of adherence to medications among chronic kidney disease patients in renal clinic of Tikur Anbessa Specialized Hospital.

#### 4. Discussion

In the present study, different medications were used in the management of comorbidities and complications of CKD. Enalapril and hydrochlorothiazide were prescribed in 50.8% and 32.7% of CKD stage 4 and 5 patients, although little robust evidence exists on the use of ACEIs in advanced

CKD. ACEIs/ARBs increase potassium and decrease GFR [33, 34] and withdrawal of ACEIs/ARBs increase eGFR and hence delay the onset of renal replacement therapy [35]. Hydrochlorothiazide was used inappropriately in advanced CKD patients, since thiazide diuretics are deemed ineffective [36]. Based on comorbidity status, non-ACEI based combinations were the most commonly used treatment regimens in the management of hypertension alone. Contrastingly, various clinical guidelines done by Stevens and Levin [37] and Bilo *et al.* [38] stated that ARBs or ACEIs are considered as the first-line agents in both diabetic and nondiabetic patients with CKD. ARBs or ACEIs are used not only to decrease BP but also slow down the progression of CKD by reducing proteinuria [39, 40]. The probable reason for this variation in TASH may be due to the absence of local standard treatment guideline for the management of CKD patients and lack of awareness of physicians practicing in the renal clinic. Besides, it might be due to difficulty in communication between physicians, shortage of multidisciplinary care team, and heavy workload on nephrologists. Coordinated multidisciplinary care team could improve management and outcomes of patients with CKD and essential for the appropriate management of CKD due to associated comorbidities and complex regimens. Indeed, a systematic review showed that lack of awareness of evidence-based guidelines for CKD results in large variability in the treatment of CKD comorbidities and complications [41]. A deficiency in the nephrology workforce especially nephrologists for the provision of appropriate management is a critical problem in developing countries [15]. Hence, targeted training for physicians to raise awareness about the management of CKD and development of clinical guidelines should be emphasized.

Regarding the management of diabetes mellitus and hypertension, the present study revealed that combinations of insulin and ACEI based combinations were the most commonly used treatment regimens. This is in agreement with studies done by Levin *et al.* [42], Tomson and Baily [43], and Bilo *et al.* [38], which stated that ACEIs based combinations were the first-line regimens in the management of diabetes mellitus and hypertension comorbidities in CKD patients. Previous studies demonstrated that if ACEIs were not effective in controlling BP, then CCB might be added but not used alone since CCBs may lead to albuminuria and greater hyperfiltration [42].

Insulin was the most widely used treatment agent in the management of diabetes alone comorbidity with CKD at TASH accounting for 44.4%. The finding of this study is comparable with similar studies by Albers *et al.* [44] and Dasari *et al.* [45], which indicated that renal patients with diabetes suitably managed with insulin. Though metformin is inexpensive and effective for type 2 diabetes mellitus, there is much concern about the safety of metformin in advanced CKD, particularly the risk of lactic acidosis [45, 46]. Hence, the frequent use of insulin as first-line agent may probably be linked to this notion.

In the present study, statins were predominantly used for the treatment of dyslipidemia and reduction of the relative risk of cardiovascular events in CKD patients. Likewise, studies [45] and practice guidelines [47] have shown that



TABLE 4: Nonpharmacological management approaches used among chronic kidney disease patients attending the renal clinic of Tikur Anbessa Specialized Hospital.

Variables	Frequency	Percent
<b>Dietary Approach</b>		
Presence of agreed dietary plan with physician		
Yes	175	68.4
No	81	31.6
Salt restriction (n = 175)		
Yes	167	95.4
No	8	4.6
Cut off sweet carbohydrate meals (n=114)	114	100
<b>Exercise</b>		
Presence of agreed exercise plan with physicians		
Yes	130	50.8
No	126	49.2
Exercising according to plan (n=130)		
Yes	120	92.3
No	10	7.7
Days per week doing moderate intense exercise		
< 3 Days	7	5.4
≥3 Days	123	94.6
Duration of moderate intense exercise per week in minutes		
< 140 Minutes	64	49.2
≥140 Minutes	66	50.8
<b>Cigarette</b>		
Ever smoked		
Yes	28	10.9
No	228	89.1
Smoking now (n = 28)		
Yes	4	14.3
No	24	85.7

statins are routinely used in the treatment of dyslipidemia and reduction of cardiovascular risk. This frequent usage might be due to the superior pharmacological effects of statins to reduce cardiovascular complications as compared to other lipid lowering agents. In addition, statins may have a role in preventing progression of kidney disease and reducing albuminuria [48]. Thus, statins are the standard treatment of choice in the prevention of cardiovascular risks in patients with and without CKD [49]. Furthermore, ASA and  $\beta$ -blocker combinations were predominantly used treatment regimens in ischemic heart disease. This finding is in agreement with a study [45] and practice guideline [47] that reported  $\beta$ -blockers should be initiated for the relief of symptoms and ASA in the primary prevention of cardiovascular events.

Regarding the management of CKD complications, ACEI based combinations were the most commonly used treatment regimens in cardiovascular complications. This finding is in line with a systematic review that reported ACEIs or ARBs appeared to be the most commonly used regimens to treat heart failure in renal patients [50]. The present study also revealed that iron preparations were predominantly used in the treatment of anemia in CKD patients. Contrastingly,

various studies reported that the use of erythropoietin stimulating agents with iron preparations was routinely used in the treatment of anemia in renal patients [51]. Hence, the lesser usage of erythropoietin stimulating agent could probably be due to the financial constraints and limited availability of this agent at TASH. Although Malluche *et al.* [52] and Miller [53] demonstrated that the use of calcium-based phosphate binders has been associated with the development of low bone turnover, bone loss, and worsening of vascular calcifications, calcium containing phosphate binders were the most commonly used agents in the management of osteodystrophy at TASH. This could probably be due to the inaccessibility of new nonaluminum, noncalcium (sevelamer hydrochloride and lanthanum carbonate) phosphate binders in this setting, which have lower risk of vascular calcification [54].

Adherence to CKD medications was observed in 61.3% of the study participants. This finding is similar with previous studies conducted in Netherland [24], India [55], and Spain [56] and different from other studies conducted in Saudi Arabia [20], India [25], German [26], southern Ethiopia [27], Italy [57], United States [58], and Australia [59]. This variation could be attributed to differences in the definition of

TABLE 5: Profile of prescribed medications for chronic kidney disease patients attending the renal clinic of Tikur Anbessa Specialized Hospital.

Variables	Stage of CKD				Total (n=256)
	1 & 2 (n = 50)	3 (n = 88)	4 (n = 55)	5 (n = 63)	
<b>ACEI</b>					
Enalapril	41 (82)	47 (53.4)	32(58.2)	28(44.4)	148 (57.8)
<b>CCB</b>					
Amlodipine	21(42)	41(46.6)	25(45.5)	37(58.7)	124 (48.4)
Nifedipine	8(16)	13(14.8)	17(30.9)	13(20.6)	51 (19.9)
<b>Diuretics</b>					
Furosemide	14(28)	38(43.2)	30(54.5)	46(73)	128 (50)
Hydrochlorothiazide	10(20)	23(26.1)	14(24.5)	22(34.9)	69 (27)
Spirolactone	4(8)	12(13.6)	4(7.3)	10(15.9)	30 (11.7)
<b><math>\beta</math>-blocker</b>					
Atenolol	6(12)	13(14.8)	10(18.2)	20(31.7)	49 (19.1)
Metoprolol	4(8)	5(5.7)	3(5.5)	1(1.6)	13 (5.1)
Carvedilol	0(0)	4(4.5)	1(1.8)	2(3.2)	7 (2.74)
<b>ARB</b>					
Losartan	1(2)	2(2.3)	2(3.6)	0(0)	5(2)
<b>Antidiabetic Medications</b>					
Insulin	14(28)	14(15.9)	20(36.4)	21(33.3)	69 (27)
Metformin	9(18)	8(9.1)	4(7.3)	5(7.9)	26 (10.2)
Glibenclamide	1(2)	5(5.7)	2(3.6)	0(0)	8 (3.1)
<b>Other medications</b>					
ASA	8(16)	23(26.1)	20(36.4)	19(30.2)	70 (27.3)
Statins	9(18)	18(20.5)	8(14.5)	15(23.8)	50 (19.5)
Calcium supplement	1(2)	3(3.4)	6(10.9)	15(23.8)	25 (9.8)
Iron	0(0)	4(4.5)	9(16.4)	15(23.8)	28 (10.9)
Antibiotics	1(2)	5(5.7)	5(9.1)	5(7.9)	16 (6.3)
Others*	15(30)	23(26.1)	13(23.6)	17(27)	68 (26.6)
<b>Number of medications</b>	3.2 $\pm$ 1.6	3.5 $\pm$ 1.7	4.3 $\pm$ 2	4.9 $\pm$ 2.9	3.9 $\pm$ 2.2

\* Phenobarbitone, warfarin, prednisolone, antiretroviral therapy, carbamazepine, and chlorpromazine; ACEI = angiotensin converting enzyme inhibitor; CCB = calcium channel blocker; ARB = angiotensin receptor blocker; ASA = Acetyl Salicylic Acid.

nonadherence between studies. In addition, methodologies may differ between studies, contributing to variation in the data. For example, direct monitoring methods include drug concentration assays, use of pill markers, and direct observation of pill taking; indirect methods include patient self-reports, structured interview, compliance ratings by nurses, prescription refills, and pill counts [60].

Prevalence of adherence in the present study was below the recommended level in the literature to attain optimum outcomes [61]. In the light of poor management of CKD comorbidities and alleged failure of therapeutic regimen, healthcare providers are urged to measure CKD patients' treatment adherence. Efforts are needed to increase the medication adherence of these patients so that they could realize the full benefits of prescribed therapies. When accurate and clear information on the importance of medication adherence is provided, patients are encouraged towards self-care and adherence to drug therapy. Healthcare professionals should be more vigilant towards identifying these concerns to address adherence issues. Nonadherence to drug therapy is detrimental and costly in renal patients [62], as these patients have increased burden of coexisting illness and are

prescribed with multiple complex regimens to treat various comorbidities [63–65]. Different studies demonstrated that medication nonadherence has been associated with presence of comorbidity [66], increased risk of hospitalization, medication and hospitalization-related costs, and death [67].

In this study, multivariate logistic regression analysis showed that total number of prescribed drugs, occupation, and family income were found to be significantly associated with CKD medication adherence. As the number of prescribed drugs increased from <5 medications to  $\geq$ 5 medications, the odds of being adherent were about 0.46 times less and this implies that patients with  $\geq$ 5 medications were found to be less likely to adhere to their medications. Numerous literatures support this finding, as pill burden negatively affects patient adherence to treatment. A study done in USA and Italy demonstrated that patients with high pill burden were more likely to be nonadherent [57, 58]. Similar studies also reported that the number of prescribed medications had a significant inverse association with CKD medication adherence [25, 62, 68]. Moreover, occupation had significant association with CKD medication adherence. Patients who were students, drivers, and teachers working

TABLE 6: Types of regimens used in the management of chronic kidney disease comorbidities patients attending the renal clinic of Tikur Anbessa Specialized Hospital.

Comorbidities	Frequency	Percent (%)
<b>Hypertension (n=129)</b>		
ACEI based regimens	58	45
Non-ACEI based regimens	71	55
<b>DM + HTN (n=96)</b>		
Insulin + ACEI based regimens	55	57.3
ACEI based regimens	19	19.8
Metformin + ACEI based regimens	13	13.5
Insulin + Non-ACEI based regimens	5	5.2
Metformin + Non-ACEI based regimens	4	4.2
<b>DM (n=18)</b>		
Insulin	8	44.4
Metformin	6	33.3
Glibenclamide	3	16.7
Insulin + Glibenclamide	1	5.6
<b>IHD (n=33)</b>		
ASA + $\beta$ -Blocker	33	100
<b>Dyslipidemia (n=31)</b>		
Statins	31	100
<b>Stroke (n=10)</b>		
ASA	10	100
<b>Others* (n=12)</b>		
ASA + others <sup>‡</sup>	7	58.3
Statins + others <sup>‡</sup>	5	41.7

DM = diabetes mellitus; HTN = hypertension; IHD = ischemic heart disease; ACEI = angiotensin converting enzyme inhibitor or an angiotensin receptor blocker; ASA = Acetyl Salicylic Acid; \*asthma, HIV/AIDS, gout, and nephritic syndrome; <sup>‡</sup>phenobarbitone, antibiotics, prednisolone, antiretroviral therapy, and carbamazepine.

in private school were more likely to engage in adherence compared to those who were farmers. This could probably be due to the fact that farmers might be less aware of their disease and the importance of medication adherence when compared with students, driver, and teacher working in private school and thus more likely to be more nonadherent.

On the other hand, monthly family income was significantly associated with medication adherence as the family income increased, and patients were found to be more likely to adhere to their medications. This finding is in line with previous study, which reported that socioeconomic status had a significant association with medication adherence [69]. A qualitative study done in Australia to explore factors associated with medication adherence in ESRD patients indicated that financial constraints had contributed to medication nonadherence [59]. Income status has been implicated in nonadherence in several studies of renal patients. In addition, low socioeconomic status has been significantly associated for medication nonadherence among CKD patients [16]. Most CKD patients in developing countries have no access to health insurance and this makes care for CKD unaffordable and consequently affects their adherence rates to the prescribed treatment regimen. According to World Kidney Day [70], the majority of patients commencing dialysis in low income countries die or stop treatment within three months

of initiating dialysis due to cost constraints. Limited economic resources of patients in developing countries result in reduced frequency of dialysis and eventually discontinuation of therapy [71].

In this study, patients with poor adherence reported several reasons for not adhering to their medications. The most common reasons were found to be forgetfulness, experiencing side effects, cost, and complex regimen. Most of the patients missed their CKD medications due to forgetfulness which is similar with other studies [25, 59]. A qualitative study by Lindberg and Lindberg [72] revealed that forgetfulness and complex regimen due to polypharmacy were identified as the main obstacle for medication adherence.

Adherence to therapies is a primary determinant of treatment success. Failure to adherence is a serious problem, which affects not only the patient but also the healthcare system. Medication nonadherence in patients leads to substantial worsening of disease, death, and increased healthcare costs. Varieties of factors are likely to affect adherence. This could be classified as patient centered, therapy related, social and economic, disease, and healthcare system factors, with interactions among them. Identifying specific barriers for each patient and adopting suitable techniques to overcome them will be necessary to improve medication adherence. Healthcare professionals such as physicians, pharmacists, and

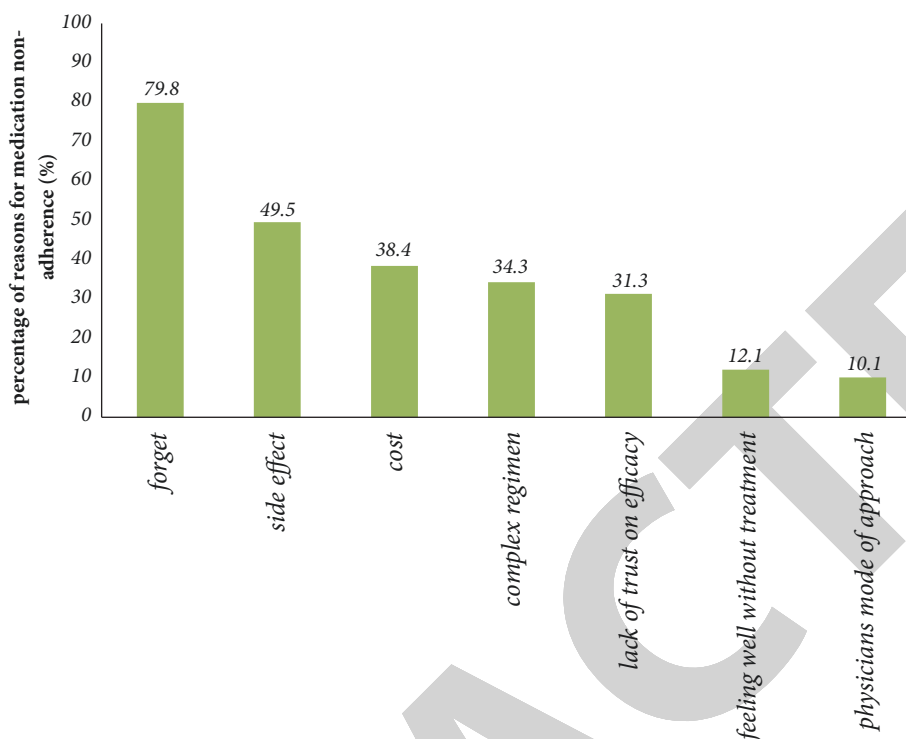


FIGURE 5: Reasons for medication nonadherence among chronic kidney disease patients attending the renal clinic of Tikur Anbessa Specialized Hospital.

nurses have significant role in their daily practice to improve patient medication adherence [73]. Even though a number of sociodemographic (age, sex, and educational status) and clinical factors (number of comorbidities and complications, severity of the disease, and laboratory parameters) were found to be significantly associated with nonadherence in various studies [73], in this study they were not statistically significant associated. The probable reason for this variation could be due to the sample size and methodological difference. Hence, prospective studies with multiple methods of adherence assessment may be required to identify different factors which affect medication adherence.

## 5. Conclusions

In summary, the present study showed that 55% of hypertensive patients were treated with non-ACEI based regimens, which are inappropriate. Insulin and ACEIs based regimens were the most frequently used regimen in the management of diabetes mellitus and hypertension with diabetes comorbidities. Calcium containing phosphate binders were used inappropriately in the management of osteodystrophy CKD complications. In addition, medication adherence in CKD patients at TASH was found to be suboptimal (61.3%). Forgetfulness was the most important reason preventing optimal adherence to prescribed medications. Socioeconomic status and pill burden had an important role in determining adherence rate to medications. Very low family income, increased number of prescribed drugs, and being a farmer were significant predictor of medication nonadherence.

## Abbreviations

ACEI:	Angiotensin converting enzyme inhibitor
AOR:	Adjusted odds ratio
ARB:	Angiotensin receptor blocker
CCB:	Calcium channel blocker
CI:	Confidence interval
CKD:	Chronic kidney disease
COR:	Crude odds ratio
CVD:	Cardiovascular disease
GFR:	Glomerular filtration rate
MMAS-8:	8-item Morisky medication adherence scale
RAAS:	Renin Angiotensin Aldosterone System
SPSS:	Statistical Package for Social Sciences
TASH:	Tikur Anbessa Specialized Hospital
USA:	United States of America.

## Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethical Approval

Approval and permission were sought from Ethical Review Board of School of Pharmacy and Department of Internal Medicine of Addis Ababa University.

TABLE 7: Univariate and multivariate binary logistic regression analysis of predictors of medication nonadherence.

Variables	Adherence		COR, 95 % CI	AOR, 95% CI
	Low to moderate adherence	High adherence		
<b>Sex</b>				
Female	51	56	1.00	1.00
Male	48	101	1.92(1.15, 3.20)*	1.56(0.76, 3.2)
<b>Age in years</b>				
≤60	43	96	1.00	1.00
> 60	56	61	0.49(0.29, 0.81) *	0.64 (0.29, 1.42)
<b>Occupation</b>				
Farmer	13	11	1.00	1.00
Gov't Employee	20	40	2.36(0.90, 6.21)	1.14(0.30, 4.34)
Merchant/Trade	6	17	3.35(0.98, 11.45)	2.99(0.67, 13.36)
Daily Laborer	7	12	2.03(0.59, 6.93)	2.03(0.43, 9.52)
House wife	21	16	0.90(0.32, 2.53)	1.41(0.34, 5.88)
Retired	27	38	1.66(0.65, 4.27)	2.52(0.63, 10.13)
Others*	5	23	5.44(1.55, 19.11)*	7.46(1.49, 37.26)*
<b>Educational status</b>				
Cannot read & write	16	14	1.00	1.00
Primary	43	45	1.2(0.52, 2.74)	0.49(0.14, 1.68)
Secondary	24	43	2.05 (0.85, 4.91)	0.69(0.18, 2.69)
Higher Education	16	55	3.93(1.59, 9.74)*	1.14 (0.24, 5.38)
<b>Family income category</b>				
Very Low	25	15	1.00	1.00
Low	39	33	1.41(0.64, 3.1)	1.37(0.49, 3.85)
Average	19	57	5.0(2.19, 11.4)**	4.14(1.45, 11.84)*
Above Average	13	38	4.88(1.99, 11.96)**	3.39(0.91, 12.66)
High	3	14	7.78(1.92, 31.59)*	6.17(1.02, 37.46)*
<b>CKD stage</b>				
1 & 2	15	35	1.00	1.00
3	23	65	1.21(0.56, 2.61)	1.42(0.58, 3.47)
4	25	30	0.51 (0.23, 1.15)	0.68(0.27, 1.71)
5	36	27	0.32 (0.15, 0.70)*	0.45(0.18, 1.13)
<b>Number of medications</b>				
<5	57	120	1.00	1.00
≥ 5	42	37	0.42 (0.24, 0.72)*	0.54 (0.27, 1.10)*
<b>Number of comorbidities</b>				
0-2	75	141	1.00	1.00
≥ 3	24	16	0.36(0.18, 0.71)*	0.85(0.35, 2.11)

COR = crude odd ratio; AOR = adjusted odd ratio; \*statistically significant at  $P \leq 0.05$  and \*\*statistically significant at  $p \leq 0.001$ ; \*students, driver, garage (mechanic), guard, or teacher working in private school.

## Conflicts of Interest

The authors declare that there are no conflicts of interest to disclose.

## Authors' Contributions

Belayneh Kefale conducted the actual study and the statistical analysis. Belayneh Kefale, Yewondwossen Tadesse, Minyahil Alebachew, Ephrem Engidawork were involved in developing the idea, designing of the study, and the write up of the manuscript. All authors approved the submitted version of the manuscript.

## Acknowledgments

The authors would like to acknowledge Addis Ababa University for financial support towards this project.

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