The rate and predictors of progression among chronic kidney disease patients on follow-up, Addis Ababa, Ethiopia, 2020 – 2024

By

Getasew Kassaw Alemu (Dr)

Department of Internal Medicine, Nephrology Unit

Addis Ababa University (AAU), College of Health Sciences (CHS)

Addis Ababa, Ethiopia

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Thesis submitted in partial fulfillment of the requirement for the award of certificate of Nephrology Subspecialty

By

Getasew Kassaw Alemu (Dr)

Advisor: Dr. Addisu Melkie Ejigu: MD, Consultant Internist and Nephrologist

Department of Internal Medicine, Nephrology Unit

Addis Ababa University (AAU), College of Health Sciences (CHS)

Addis Ababa, Ethiopia

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DECLARATION

I hereby declare that the thesis project entitled “The rate and predictors of progression among chronic kidney disease patients on follow-up, Addis Ababa, Ethiopia, 2020 – 2024” for nephrology subspecialty certificate is my original work and has never been submitted for any prior academic award or qualification in this Institution.

Name of Investigator/Student: ______________________

Signature: _______________________

Date: ___________________

DEPARTMENT OF INTERNAL MEDICINE, NEPHROLOGY UNIT APPROVAL

	Signature	Date
Dr. Addisu Melkie	_______________	________________
Dr. Yewondwossen Tadesse	_______________	________________
Dr. Lisanne Seifu	_______________	________________
Dr. Nebiyu Getachew	_______________	________________

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ABBREVIATION/ACRONYMS

ACEI	Angiotensin converting enzyme inhibitor
ARB	Angiotensin Receptor blocker
CGN	Chronic glomerulonephritis
CKD	Chronic kidney disease
CLD	Chronic Liver Disease
CVD	Cardiovascular Disease
GFR	Glomerular filtration rate
ESRD	End stage renal disease
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV/AIDS	Human immunodeficiency virus/acquired immunodeficiency syndrome
GDB	Global disease burden (GDB)
GFR	Glomerular filtration rate
KDIGO	Kidney disease initiative global outcome
LMICs	Low, Middle Income Country
MRA	Mineralocorticoid receptor Antagonist
NSAID	Non-Steroidal Anti-inflammatory drug
RRT	Renal Replacement therapy
SGLT2I	Sodium Glucose Transporter 2 Inhibitor

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Abstract

Background: *Chronic kidney disease (CKD) is a progressive condition and a major global health issue that affects over 8 million people worldwide. However, information on the rate and predictors of CKD progression is limited. Therefore, this study aimed to assess the rate and predictors of CKD progression in chronic kidney disease patients who underwent follow-up in Addis Ababa, Ethiopia, from 2020 to 2024.*

Methods: *A retrospective cohort study was conducted among patients with chronic kidney disease in Tikur Anbesa Specialized Hospital and Saint Paul Millennium Medical College from June 1, 2020, to August 31, 2024. A systematic random sampling technique was used to collect 402 study participants using Kobo toolbox software. The data was exported to STATA version 17 for analysis. A linear mixed-effects model of statistical analysis was used considering the random and fixed effects of the longitudinal data, and the mean estimated glomerular filtration rate and overall mean difference were adjusted using Bonferroni corrections. Multivariable linear mixed effects regression was performed for variables with a p-value of < 0.20 on the bivariate analysis to identify independent predictors of chronic kidney disease and variables with a p-value less than 0.05 in the multivariable analysis were considered to have statistical significance.*

Results: *Among the 402 patients, 64.93% were males. The mean age of the participants was 55.9 ± 15.2 years, and 300 (74.63%) were in the age group of 40–74 years. The mean eGFR improved linearly by 2.7, 5.3, 7.63 and 6.44 from the baseline eGFR on years 1, 2, 3 and 4 respectively. The total chronic kidney disease events were 21.83% rapid progression with a total mean eGFR decline of -13.20 (SD = 8.97), 34.73% regression with mean eGFR 13.48 (SD = 7.65), 43.44% had a stable course with mean eGFR of 0.29 (SD =2.64) and 42.03% had achieved remission. Females, patients using ACEI or ARB, and metformin were predictors of a higher estimated glomerular filtration rate by 4.75 (CI: 1.43, 8.08), 5.17 (CI: 2.44, 7.89) and 4.58 (CI: 0.09, 9.07), respectively, compared to their counterparts. Baseline hemoglobin < 10.5g/dl, having diabetes mellitus, baseline proteinuria > +1 and primary education were predictors of declining estimated GFR by -11.02 (CI; -14.59, -7.45), -3.05 (CI; -5.75, -0.35), -3.47 (CI; -6.85, -0.09) and -5.28 (CI; -9.99, -0.57) respectively.*

***Conclusions**: Treatment or management strategies seem to be effective, leading to a notable improvement in kidney function over time in this patient cohort in this setting. This suggests that patients are moving toward recovery or at least significant stabilization of their condition. Close monitoring and addressing of these predictors, improvement of data registration systems by hospitals, and further research on the topic incorporating hospitals with no nephrologist care is recommended.*

Keywords*: chronic kidney disease, estimated GFR, Progression, Predictors, linear mixed effect model, Ethiopia*

1. CHAPTER 1: INTRODUCTION

1.1. STATEMENT OF PROBLEM

Chronic kidney disease (CKD) is one of the ever increasing major public health problems worldwide affecting one in ten individuals making the disease burden over 800 million people (>10% of the world's population) and majority of the disease burden is distributed in low and middle income countries (LMICs) (1, 2). With the limited data available in Africa, the estimated CKD burden is about 15.8% which is higher than the average global CKD burden (3). Understanding the concern of underestimation and underreporting, CKD is two and twenty times higher than the estimated number of patients with diabetes mellitus and HIV/AIDS respectively; this makes the problem worse in sub-Saharan Africa where communicable disease is still a huge burden (4).

It is a global public health threat with high mortality and morbidity. It caused the death of 1.43 million making it the 13^{th} causes of death once and it is estimated to cause 4.0 million deaths by 2040 which will make CKD to be the 5^{th} leading cause of death worldwide (5-8).

According to the 2024 Kidney Disease Improving Global Outcomes (KDIGO) CKD guideline, chronic kidney disease (CKD) is defined based on glomerular filtration rate (GFR) < $60ml/min/1.73m^2$ persisting for > 3 months or other structural criteria's, with implication to health and the definition had included the cause - GFR - albuminuria (CGA) classification system to address the spectrums and severity of the disease and possible causes of the CKD (9). Diabetes mellitus (DM), hypertension and chronic glomerulonephritis are the most common causes of CKD worldwide (10, 11).

Chronic kidney disease progression refers to the a decline in kidney function over time with equivalent progressive loss of nephron mass; however, there is a concept that CKD could remain stable and even regress or remit sometimes making the assumption that every CKD is always irreversible is wrong. CKD regression refers to sustained increase in GFR by $\geq$ 25% and improvement in GFR category or increase in GFR by $\geq$ 1ml/min/year while CKD remission refers to GFR $\geq$ $60ml/min/1.73m^2$ (12). Rapidly progressive CKD refers to a decline in GFR > $5ml/min/1.73m^2$/year (12). This had significant implication to delay CKD progression by addressing the predictors of CKD progression which had direct impact on health care cost, quality of life and overall kidney and health outcome (13-17).

Chronic kidney disease progresses to end stage renal disease (ESRD) unequally among different population groups and this is worst in the absence of proper treatment; the rate of CKD progression from one stage to the next is determined by many predictors and the high burden of CKD in the LMICs has direct implication to the presence of unaddressed issue in these known and unknown factors (18, 19). Chronic kidney disease is preventable and treatable disease costing million dollars per year (20). Understanding the clinical course and predictors of CKD progression had implementation implication though the individual patient's CKD course (remission, regression, stable or progressive) is variable and is an area of interest. Generally, early detection and proper management with regular medical follow-ups are crucial in slowing the progression of CKD and preserving kidney function.

The main aim of this research is to know rate and predictors of CKD progression among CKD patients who had follow-up in Tikur Anbesa Specialized Hospital (TASH) or Saint Paul Millennium Medial College (SPMMC) longitudinally.

1.2. LITERATURE REVIEW

1.2.1. CKD PROGRESSION

From a population based study in Alberta, Canada among 81,320 persons with mild, 35,929 persons with moderate and 12,237 persons with severe CKD showed that after entry to the cohort, the 5-year probability of regression was similar to that of progression or kidney failure in mild (14.3% vs. 14.6%), moderate (18.9% vs. 16.5%), and severe (19.3% vs.20.4%) CKD patients (21). A prospective cohort study involving 1,741 people with stage 3 CKD recruited from 32 primary care centers in United Kingdom had been followed for 5 years and after 5years 247 (14.2%) had died, 4 (0.2%) developed ESRD, 308 (17.7%) evidenced progression per KDIGO criteria, 593 (34.1%) remain stable and 336 (19.3%) met the definition of remission (22) According to the observational data from oxford renal cohort study involving 884 age > 60 years participants who had been followed for a period of 5 years showed a net GFR decline in all the participants and among the 686 participants with more than two eGFR tests with a median follow-up of 2.1 years showed that 164 (24%) had experienced rapid GFR decline, 185 (27%) experienced eGFR improvement, 82 of 394 (21%) meeting CKD stage 1– 4 at baseline experienced remission. (23). A multicenter prospective study in Italy among 1418 CKD patients with GFR ranging 60 to 15 ml/min/1.73 m2 having nephrology care at 47 clinics showed that 391 (27.6%) patients had CKD regression (24). A prospective longitudinal study among black patients with CKD attending at outpatient clinic of Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) in South Africa, between September 2019 to March 2022 involving 297/312 (95.2%) participants who completed the study, the prevalence of CKD progression was 49.5%, while that of CKD remission was 33% and CKD regression was 17.5% (25).

1.2.2. PREDICTORS OF CKD PROGRESSION

The data from chronic renal insufficiency cohort study showed that sociodemographic, behavioral, genetic, cardiovascular, metabolic, novel factors, treatments and nephrology care all can impact clinical course of CKD progression but with variable degree (26).

1.2.2.1. Sociodemographic predictors

The burden of kidney failure is higher among men while the prevalence of CKD is higher among women (27, 28). Age is determinant factor of CKD progression as noted in the Canadian study (21). Hispanics and blacks are two fold at higher risk to kidney failure than whites (29). Social parameters like educational attainment and social support from marriage could affect risk of CKD progression (30)

1.2.2.2. Behavioral and life style related predictors

Smoking cessation, limiting alcohol consumption, healthy diet and regular physical exercise as recommended by guidelines had evidenced to change the course of CKD progression (23, 31-34). Self-reported salt addition to meal had direct relationship with risk of CKD course (35).

1.2.2.3. Treatment related predictors

Drug stewardship in CKD patients to achieve effective and safe medication use is key message in the management of CKD patients (36). CKD regression or remission had been achieved with any of the angiotensin convertases enzyme inhibitors (ACEI) or angiotensin receptor blocker (ARB) or irbesartan (31, 37-39). Statins slowed risk of CKD progression both directly and indirectly from their cardiovascular benefit (40, 41). The use of sodium glucose co-transporter inhibitors (SGLT2) inhibitors had maintained kidney function better among the proteinuric CKD (42). Utilization of non-steroidal anti-inflammatory drugs (NSAIDs) had risk factor for rapid CKD progression though some evidences make the risk minimal (43, 44). Calcium channel and beta blockers could be renoprotective through their antihypertensive effect (45, 46)

1.2.2.4. Comorbidity related predictors

Multimorbidity is a bad predictor of CKD outcome (47). Low systolic blood pressure, better baseline GFR, absence of ADPKD and higher BMI are predictors of CKD regression as noted in the oxford renal cohort and the multicenter study in Italy (23, 24). Diabetes mellitus, hypertension, cardiovascular diseases (CVD) including heart failure were predictors of progression (28, 48, 49).

1.2.2.5 Clinical and laboratory related predictors

Proteinuria (48, 50), episodes of acute sickness leading to hospitalization(51), anemia (52), hyperphosphatemia (53) are predictors of CKD progression.

1.3. CONCEPTUAL FRAMEWORK

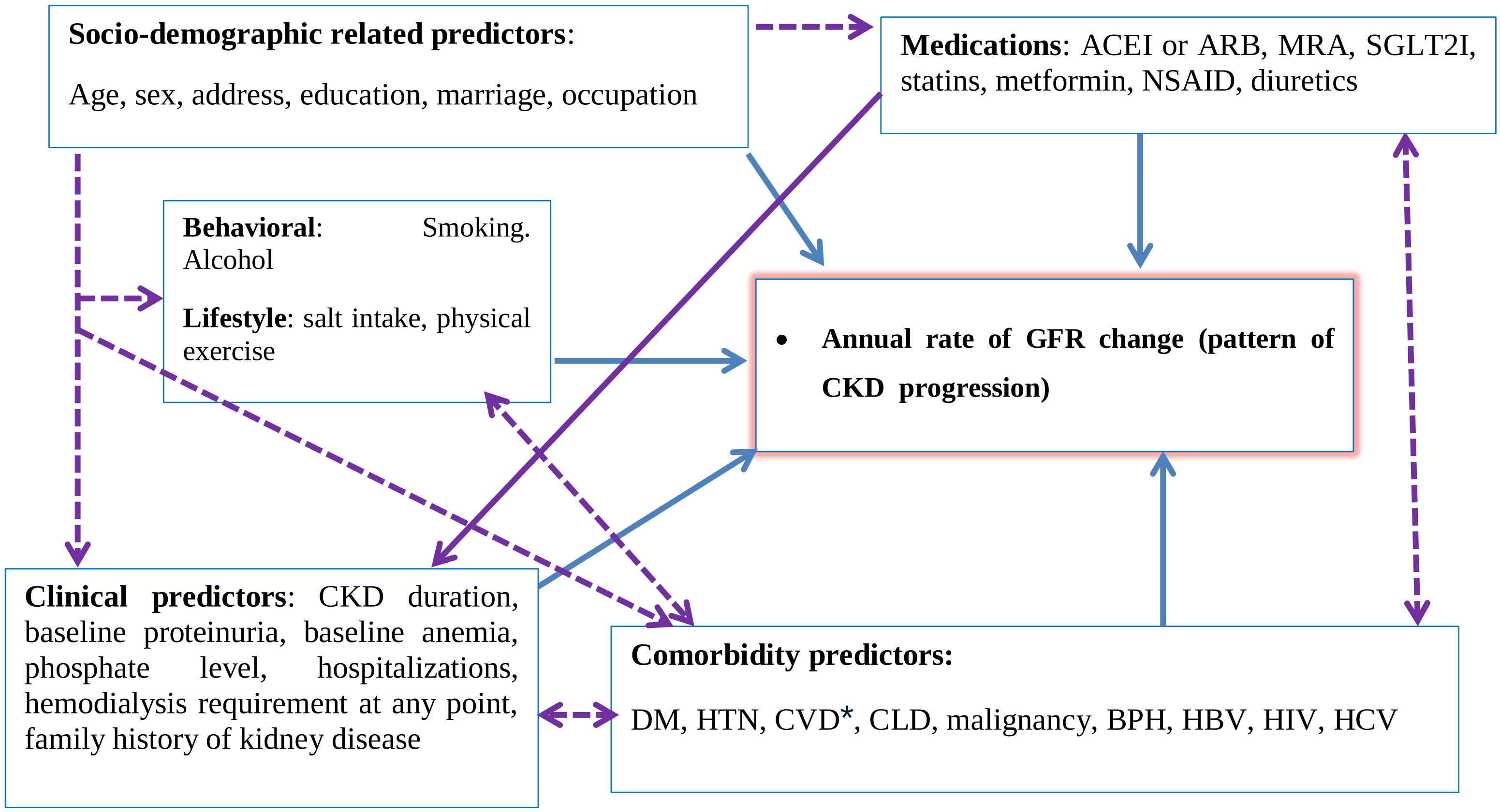

Figure 1: Conceptual framework: (21, 23, 24, 27, 37, 54-61).

Abbreviations: ACEI- angiotensin convertases enzyme inhibitor, ARB- angiotensin receptor blocker, BPH – benign prostatic hyperplasia, CKD – chronic kidney disease, CVD – cardiovascular disease, DM – diabetes mellitus, HBV – hepatitis B virus, HCV – hepatitis C virus, HIV – human immunodeficiency virus, HTN - hypertension, MRA – mineralocorticoid receptor antagonists,, NSAID – non-steroidal anti-inflammatory drugs, SGLT2I – sodium glucose cotransporter 2 inhibitor, * represents PDA – peripheral arterial disease, HF – heart failure, CVA – cerebrovascular accident.

1.4. JUSTIFICATION OF THE STUDY

Chronic kidney disease (CKD) is a major public health problem worldwide affecting more than 800 million people and of which more than 80% of the burden is limited to parts of the globe with low and middle income, where sub saran Africa is one of the highest spot areas. It is one of the costly disease demanding millions per year at individual and governmental level. The identification and treatment of predictors of rapid CKD progression could have direct implication in multidimensional way. This should be one of the future's cost effective directions in the management of CKD.

Additionally, understanding the concept that CKD patients could have different clinical course over time; some remain stable for longer period on the same stage while others could have regression, remission or others still progress rapidly to ESRD. The idea that CKD could improve is an important area for both clinicians and patients. Knowing the reason why and how many could fall in this clinical courses could give us one step solution to focus on the care we provide. Understanding this trajectory could be important with health policy implications and cost optimization at different levels.

This research is the first of its kind in Ethiopia and therefore it will give local data for healthcare providers and policy makers and the public at large will benefit from the study. Therefore, this study will give us evidences on annual rate of eGFR change, patterns of CKD progression and predictors of rapid CKD progression

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2. CHAPTER 2: OBJECTIVE

2.1. GENERAL OBJECTIVE

To assess the rate and predictors of progression among chronic kidney disease patients on follow-up at Tikur Anbesa Specialized Hospital (TASH) or Saint Paul millennium Medical College (SPMMC), Addis Ababa, Ethiopia, 2020- 2024.

2.2. SPECIFIC OBJECTIVE

To determine the rate of chronic kidney disease (CKD) progression of patients on follow-up at Tikur Anbesa Specialized Hospital (TASH) or Saint Paul millennium Medical College (SPMMC), Addis Ababa, Ethiopia, 2020- 2024.

To identify predictors of chronic kidney disease (CKD) progression of patients on follow-up at Tikur Anbesa Specialized Hospital (TASH) or Saint Paul millennium Medical College (SPMMC), Addis Ababa, Ethiopia, 2020- 2024.

3. CHAPTER 3: METHOD AND MATERIAL

3.1. STUDY SETTING

The study was conducted at Tikur Anbesa Specialized Hospital (TASH) and Saint Paul Millennium Medical College (SPMMC), Ethiopia. This are the two largest referral hospitals in the country with in-patient and outpatient (OPD) referral clinics. There are renal units under the department of internal medicine with active care both for inpatient and outpatient setting in these settings. Chronic kidney disease (CKD) patients have regular follow-up and the frequency may vary from one to four months depending on their medical condition. The patients have clinical evaluation, laboratory and pharmacy service during follow-up time. These hospitals are the best care centers for kidney disease patients and may not represent the Ethiopian setting kidney disease care.

3.2. STUDY DESIGN AND PERIOD

An institution-based retrospective cohort study was conducted from June 1st, 2020 to August 31th, 2024 and the data extraction period was from June 1st to August 30, 2024.

3.3. SOURCE AND STUDY POPULATION

3.3.1. SOURCE POPULATION

All adults (age ≥ 18) diagnosed with chronic kidney disease patients and followed at TASH or SPMMC.

3.3.2. STUDY POPULATION

All adults (age ≥ 18) diagnosed with chronic kidney disease patients and followed at TASH or SPMMC.

3.4. ELIGIBILITY CRITERIA

3.4.1. INCLUSION CRITERIA

All adults (age ≥18) chronic kidney disease patients and on follow-up at TASH or SPMMC in the year 2020 – 2024

The patient should have follow-up at least 1year

3.4.2. EXCLUSION CRITERIA

Chronic kidney disease patients who are already on maintenance hemodialysis or have done kidney transplantation

Chronic kidney disease patients with no proper creatinine measurement or documentation

3.5. SAMPLE SIZE DETERMINATION AND SAMPLING PROCEDURE

3.5.1. SAMPLE SIZE DETERMINATION

The sample size was calculated using a single population proportion formula. The prevalence of renal function impairment regression rate was 49.5% (25) from the study in Italy with 95%(CI):

$n = (Z_{\alpha/2})^2 \text{ x } P\ (1 - P)/\ d^2 = (1.96)^2 \text{ x } 0.495 \text{ x } (1\text{-}0.49.5)/\ (0.05)^2 = 0.96030396/0.0025 = 384$

Adding 5% non-response rate, the final sample size was 402 CKD patients. Where:

n = the desired sample size

P = proportion of patients with CKD among HIV AIDS

$Z\alpha /2$ = Critical value at 95% confidence level of certainty (1.96)

d = the margin of error between the sample and the population = 5%

The sample size calculation method had a limitation. The data was a cohort of longitudinal measurements, the minimum study duration being 1year with no limit on the maximum. The above sample size was calculated with the assumption and considering CKD regression outcome variable. The number of patients in the study (402) setting though may not be under representing the population.

3.5.2. SAMPLING TECHNIQUE AND PROCEDURE

The representative samples were selected using convenient (census) technique considering the total number of patients during the study period. Chronic kidney disease patients were accounting for about nearly 20% of the daily visits at TASH and 25% at SPMMC. The numbers of CKD patients on weekly outpatient clinic visit were about 30 – 45 per hospital.

3.6. STUDY VARIABLE

3.6.1. DEPENDENT VARIABLE

Annual rate of change in estimated glomerular filtration rate (GFR)

3.6.2. INDEPENDENT VARIABLES

Socio-demographic related predictors: Age, sex, address, occupation, education, and marriage

Behavioral and Life style related predictors: cigarette smoking, alcohol drinking, salt restriction, regular physical exercise

Comorbidity related predictors: diabetes mellitus, hypertension, benign prostatic hyperplasia, hydronephrosis, cardiovascular disease (cerebrovascular accident, heart failure, and peripheral arterial disease), chronic liver disease, solid cancer, leukemia/lymphoma, infection (Hepatitis B Virus, Human Immunodeficiency Virus, and Hepatitis C Virus)

Clinical related predictors: Duration of chronic kidney disease, family history of renal disease, hospitalization and pregnancy during the study period, dialysis requirement for short time at any point in time and possible cause of chronic kidney disease, baseline proteinuria, baseline hemoglobin and phosphate level.

Treatment-related predictors: ACEI or ARBs, SGLT2 inhibitor, statins, NSAIDS, diuretics

3.7. OPERATIONAL DEFINITION

Chronic kidney disease (CKD) was defined using the GFR based KDIGO definition (62); CKD progression was defined as follows (12, 63, 64):Regression when eGFR slope is improving by > 5ml/min/1.73m^2/year; Stable when eGFR is between -5 to 5 ml/min/1.73m^2/year; Remission when eGFR slope is > 60ml/min/1.73m^2/year; Rapid progression when eGFR declining > 5ml/min/1,73m^2/year; Proteinuria is defined as urine dipstick protein $\geq$ +1 which is equivalent to 24hour urine protein of 300mg/day (65), Hyperphosphatemia when serum phosphate level is $\geq$ 4.5 mg/dl from COSMOS study (66) and anemia is when serum hemoglobin level < 10.5mg/dl evidence from the CREATE treat (67), Comorbidities: It is defined as any medical conditions that coexist with CKD (68). Regular physical exercise means having a pattern of exercise.

3.8. DATA COLLECTION PROCEDURE AND QUALITY ASSURANCE

Data was collected using both participant interview and record documentation on the electronic data using kobo tool box software and the data abstraction tool was consisted of all the above variables. Pretesting was done on 5% randomly selected study subject members and the necessary revision on the data collection tool was made based on the test result. Patients were interviewed for the sociodemographic, behavioral and life style and some of the clinical variables. The electronic data record was main source of medications, comorbidity and other variables.

The principal investigator had given training on the basics of the data abstraction form and on how to use the form appropriately for two GPs. The collected data was checked for its consistency and completeness before any attempt to enter code and analyze it.

The outcome variable (predictors of rapid CKD progression), was calculated from serum creatinine. The serum creatinine value was taken from the electronic data record. During data collection considerable nearly yearly creatinine measurement was taken. Finally, estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation for all of the patients. Patients were not asked extra payment or appointment for this or other research related issues.

3.9. DATA MANAGEMENT AND ANALYSIS

Data was checked, sorted, categorized and coded manually on the excel sheet then transferred to STATA version 17 for further analysis. Both descriptive (frequency tables and mean with SD) and analytical analysis was performed. To identify predictors associated with the mean change in eGFR, a two-step analytical approach was employed, utilizing different p-value thresholds at each stage. In the initial bivariate analysis, each predictor was analyzed individually in relation to the mean eGFR. A lenient p-value threshold of 0.20 was applied at this stage to ensure that a broad range of potentially relevant predictors could be identified for further evaluation. This approach minimizes the risk of excluding variables that might have an important association with eGFR.

Subsequently, predictors with a p-value of less than 0.20 in the bivariate analysis were included in a multivariable mixed-effects model; a method employed for heterogeneous longitudinal data where a single patients' had multiple measurements collected over time with random and fixed effects. In this final model, all selected predictors were analyzed together to account for potential confounding factors and interactions. A more stringent p-value threshold of less than 0.05 was applied in this step to identify predictors that maintained a statistically significant association with change in mean eGFR after adjusting for other variables. This two-tiered strategy allowed for a comprehensive and rigorous analysis, ensuring the inclusion of potentially relevant predictors while reducing the likelihood of false-positive findings in the final results.

4. CHAPTER 4: ETHICAL CONSIDERATION

The study was conducted after obtaining ethical clearance from the Department of Internal Medicine Research and Ethics committee and IRB of the College of Health Sciences, Addis Ababa University with protocol number **135/24** and meeting number **48/23** and Saint Paul Millennium Medical College Ref. No. **Pm23/1371** Access to the collected information will be limited to the principal investigator and confidentiality will be maintained throughout the project.

5. CHAPTER 5: RESULTS AND DISCUSSION

5.1. Socio-demographic characteristics

A total of 402 CKD patients were involved in this study with a response rate of 99.8%. The mean age of the participants was 55.9 ± 15.2 years and the majority (74.63%) of the participant's age was 40 -74 years. More than half (64.93%) of the participants were males. Among all the participants 74.88% were from Addis Ababa, 76.12% were married, and 37.31% were employed in the government. The study participants are all black race, homogenous individuals, with relatively no significant cultural variation among them (**Table 1**).

Table 1: Sociodemographic characteristics of CKD patients on follow-up at Addis Ababa, Ethiopia, 2020 - 2024 (n=402)

Variable	Category	Number (n)	Percentage (%)
Age, years	18– 40	61	15.17
	41– 74	300	74.63
	≥75	41	10.20
	Mean (distribute was even)	55.9 ± 15.2 years	
Sex	Male	261	64.93
	Female	141	35.07
Residence	Addis Ababa	301	74.88
	Out of Addis Ababa	101	25.12
Marriage status	Divorced-widowed	48	11.94
	Married	306	76.12
	Single	48	11.94
Education level	Uneducated	44	10.95

	Primary Secondary Higher	92 162 104	22.89 40.30 25.87
Occupation	Daily Labor Farmer Employed Housewife Self-employed Student	60 61 150 50 74 7	14.93 15.17 37.31 12.44 18.41 1.74

5.2. Behavioral and lifestyle characteristics

The burden of cigarette smoking and alcohol drinking was reported among 30 (7.46%) and 122 (30.65%) of the participants respectively and most of the smokers and alcohol drinkers are from Addis Ababa. Only 12.94% had agreed that regular physical exercise was their routine while 24.63 % had claimed their job is physically demanding by itself undermining the need for regular physical exercise. The number of patients who had agreed that they adhered to salt intake restriction and reduction advice by the healthcare providers was only 54 (13.43%) (**Table 2**).

Table 2: Behavioral and lifestyle characteristics of CKD patients on follow-up at Addis Ababa, Ethiopia, 2020 - 2024 (n=402)

Variable	Category	Number (n)	Percentage (%)
Cigarette smoking	No Yes	372 30	92.54 7.46
	Compared with address	Addis Ababa Out of Addis Ababa	22 (73.3%) 8 (26.7%)

Alcohol drinking	No Yes	280 122	69.65 30.65
	Compared with address	Addis Ababa Out of Addis Ababa	96 (78.7%) 26 (21.3%)
Regular physical exercise	No Yes	350 52	87.06 12.94
Physically active job	No Yes	303 99	75.37 24.63
Self-reported salt restriction	No Yes	348 54	86.57 13.43

5.3. Medical comorbidity-related characteristics

One or more comorbidity was reported among all the CKD patients (100%). The most common comorbidity identified was hypertension (85.07%) followed by diabetes mellitus (46.02%). The presence of hypertension among CKD patients could create a chicken-egg dilemma where it could be the cause or consequence of CKD. Different forms of cardiovascular disease (CVD) were diagnosed among 120 (29.85%) of the CKD participants. The most common infectious comorbidity was HIV (8.21%). Benign prostatic hyperplasia (BPH) was seen among 36 (8.99%) of the participants and there were 26 (6.47%) patients with obstructive uropathy diagnosis (**Table 3**).

Table 3: Medical comorbidity related characteristics of CKD patients on follow-up at Addis Ababa, Ethiopia, 2020 - 2024 (n=402**)**

Variable	Number	Percentage
Patients with comorbidity	402	100
Hypertension	342	85.07

Diabetes mellitus	185	46.02
Cardiovascular disease*	120	29.77
Benign prostatic hyperplasia	36	8.99
Obstructive Uropathy	26	6.47
HIV infection	33	8.21
Hepatitis B virus (HBV) infection	9	2.24
Malignancy **	15	3.74
Others	11	2.74

Abbreviations and Symbols: * Represents PDA – peripheral arterial disease, IHD, - Ischemic heart disease, DCM – dilated cardiomyopathy, VHD – Valvular heart disease, HF – heart failure, CVA – cerebrovascular accident; HIV - human immunodeficiency virus (HIV) list; ** represents that 4 patients (1%) with leukemia and 11 patients (2.74%) with solid cancer; others represents 2 chronic liver disease, 4 rheumatoid arthritis, 4 systemic lupus erythematosus patients and 1 hepatitis c virus patients

5.4. Clinical and laboratory-related predictors

Almost half of the participants (51%) had a history of hospitalization (> 24 hours) during the study period making them vulnerable to different kidney injury risk factors. During their kidney disease course, 9.95% of the CKD patients had required hemodialysis for a short period which was stopped subsequently. The mean duration of CKD was 2.8 + 3.1 years (SD= 3.06). One-third (33.58%) and half (50%) of the enrolled patients had dipstick proteinuria during initial enrollment and at the end year of the study. Among the participants, 68 (16.92%) and 255 (63.43%) had baseline anemia and recent hyperphosphatemia respectively (**Table 4**).

Table 4: Clinical and laboratory characteristics of CKD patients on follow-up at Addis Ababa, Ethiopia, 2020 - 2024 (n=402)

Variable	Number (n)	Percentage (%)
Hospitalization during study period ($\geq$ 24hours)	205	51
Family history of kidney disease	49	12.19

Hemodialysis requirement at any time for short period and stopped subsequently		40	9.95
CKD duration (mean) in years		2.8 ± 3.1	
Baseline proteinuria	Trace or negative ≥+ 1	135 267	33.58 66.42
Recent proteinuria	Trace or negative ≥+ 1	201 201	50 50
Baseline hemoglobin (g/dl) Mean = 12.95 (12.70 – 13.20)	≥ 10.5 <10.5l	334 68	83.08 16.92
Recent phosphorus (mg/dl) Median = 3.88 (Q1=3.36, Q2= 4.64)	<4.5 ≥4.5	147 255	36.57 63.43

5.5. Possible CKD causes

The possible causes of CKD were documented from physicians' diagnoses and not from biopsy evidence. 376/402 (93.53) of the CKD patients had a possibly considered cause for the CKD while 26 (6.47%) of the participants had no comorbidity or risk factor identified to explain why they have CKD. The most commonly identified causes of CKD were diabetes mellitus and hypertension followed by obstructive causes. Significant numbers of patients (24.38%) have multiple comorbidities including diabetes mellitus and hypertension (**Figure 1**).

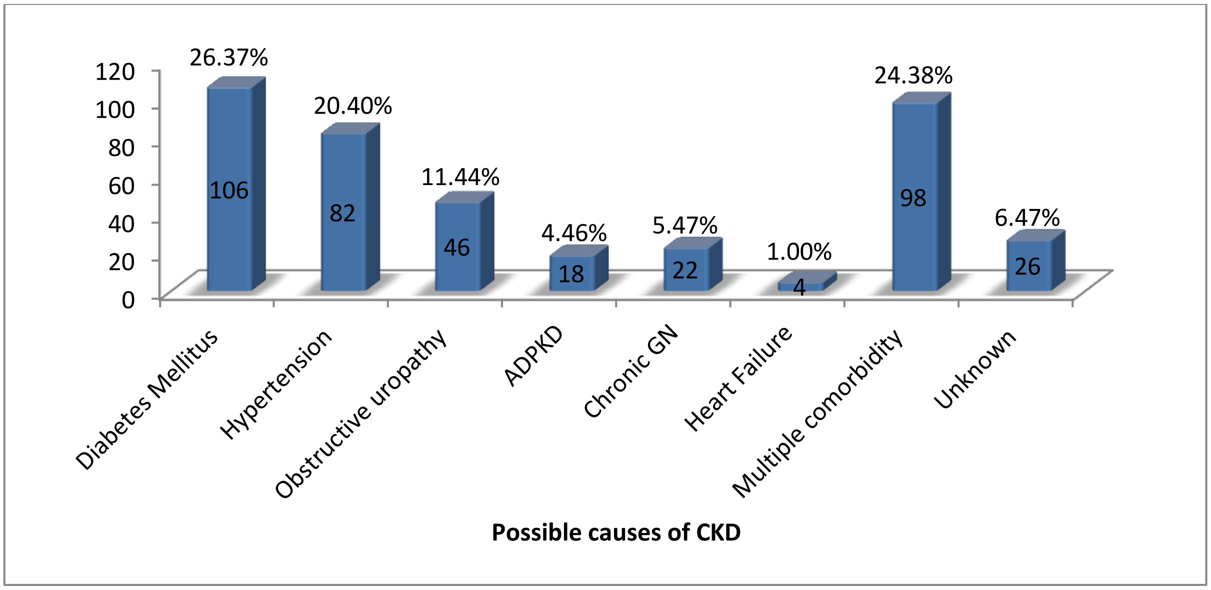

Figure 2: Possible causes of CKD patients on follow-up at Addis Ababa, Ethiopia, 2020- 2024 (n=402).

Note: Multiple includes the coexistence of different causes together; for example: diabetes mellitus, hypertension, heart failure

5.6. Medication used during the follow-up

Almost half (47.62%) of the enrolled patients were on ACEI or ARB while only 84 (20.9%) of the patients were taking SGLT2 inhibitors and this is possibly due to the introduction of SGLT2I in the market being recent as compared to ACEI or ARBs. Non-steroidal anti-inflammatory drugs (NSAID) as anti-pain was used by 113 (28.11%). 45/185 (24.32%) of the diabetes mellitus patients were using metformin. Diuretics were used by more than half of the participants (**Table 5**).

Table 5: Medication used during the follow-up period among CKD patients at Addis Ababa, Ethiopia, 2020- 2024 (n=402)

Drugs	Number of users (N)	Percent of users (%)
ACEI or ARB	191	47.51
SGLT2i	84	20.9
Metformin	45	11.19
Atorvastatin	214	53.23

NSAIDS	113	28.11
Diuretics	188	46.65
Dihydropyridine CCB	254	63.18
Beta blocker	151	37.56
Others drugs*	63	15.63

Abbreviation and symbols: ACEI – Angiotensin convertases enzyme, ARB – angiotensin receptor blocker, CCB – Calcium channel blocker, SGLT2 – sodium glucose co transporter 2 inhibitor, NSAIDs – Non-steroidal anti-inflammatory drugs; Symbol: * represents gabapentin or pregabalin /ART drug/spironolactone/any chemotherapy in 4.73%/2.74%/6.72%/1.49% of the total subjects.

5.7. Annual rate of change in eGFR

As indicated on the plot (**Figure 2**), the individual profile plots suggested that there were heterogeneity within- and between-study subjects' eGFR measurements over time. The individual trajectory of eGFR for patients shows that patients had considerably different eGFR at baseline and over time as well. Each individual had different intercepts and slopes over time; this suggests the use of a mixed-effects model that includes both random intercepts and slopes is statistically advisable. The second plot (**Figure 3**) shows the mean structure of eGFR measurements suggesting a linear change positively in the mean eGFR measurement over time. The 2nd and 3rd-year eGFRs were better than the remaining eGFRs possibly showing the effects of the treatment have shown good progress for patients and there seems a slight decline in the 4th eGFR, which may be related to the natural course of the disease or treatment adherence issues.

Yearly CKD patients' distribution with eGFR Category

The number of participants was 402 in the first year due to the mandatory 1year follow-up. However, after that, it decreased possibly due to missing creatinine determination or undocumented measurement in most of the cases but some patients had no follow-up anymore may be from death or a change in the follow-up center. Here, the main reason could be related to a poor registry in creatinine as most of the patients had regular follow-ups 2-4 times per year (**Table 6**)

Table 6: Yearly CKD patients distribution with eGFR Category at Addis Ababa, Ethiopia, 2020-2024 (n=402)

eGFR	Year					Total
	2020	2021	2022	2023	2024	
< 15	81	56	17	14	10	178
15 – 29	104	88	39	16	16	263
30 – 44	113	145	67	47	20	392
45 – 59	89	103	53	44	41	330
≥ 60	15	10	11	7	2	45
Total	402	402	187	128	89	1,208

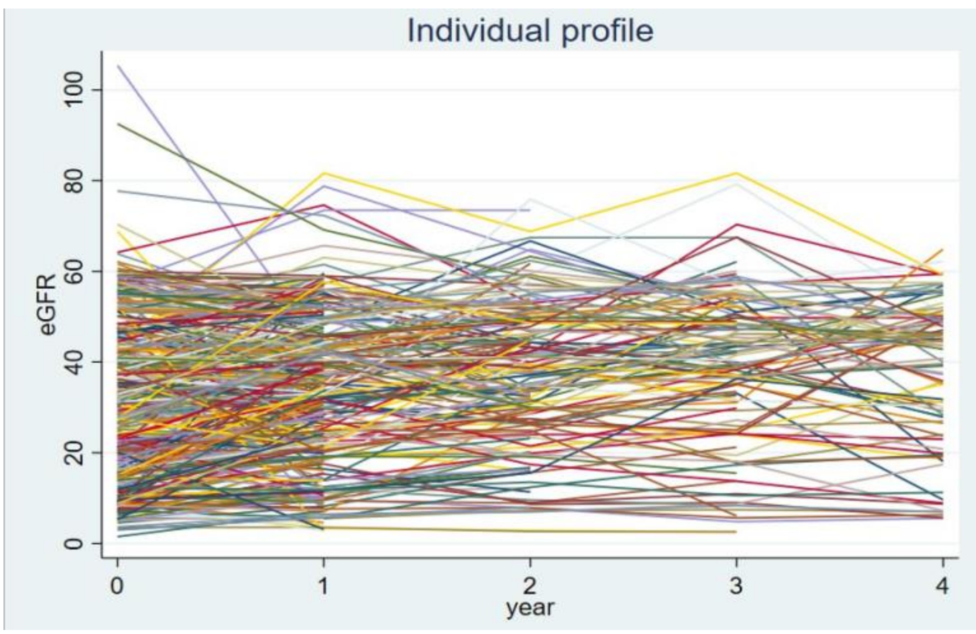

Figure 3: Individual eGFR profile pattern among chronic kidney disease patients, Addis Ababa, Ethiopia, 2020 – 2024 (N=402)

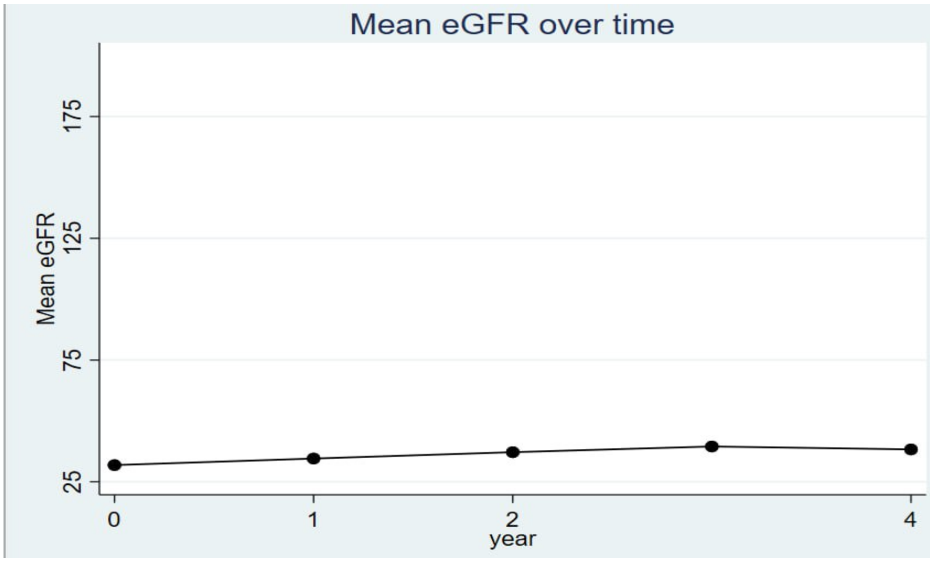

Figure 4: Mean eGFR change over time among CKD patients, Addis Ababa, Ethiopia, 2020 – 2024 (N=402)

5.8. Mean eGFR changes among CKD patients

5.8.1. Comparison of eGFR by year (Bonferroni correction):

The overall mean difference across the given study periods in years shows the pairwise comparisons of estimated glomerular filtration rate (eGFR) by year, adjusted using Bonferroni corrections. If the glomerular filtration rate (GFR) increases, reflected by positive mean differences that are significant, it indicates an improvement in kidney function, which would be a positive outcome. Year-to-Year Comparisons: Year 1 vs. Year 2: the Mean Difference is = +2.60503 (p = 0.748), and in Year 2 vs. Year 3: the Mean Difference is = +2.33244 (p = 1.000) which showed no significant change statistically. Year 3 vs. Year 4: The mean Difference is = -1.19592 (p = 1.000) which shows a slight decline but not significant. From this analysis, it appears that patients are improving based on the positive and significant changes in eGFR between Year 0 and subsequent years (especially Years 2, 3, and 4). The improvement is most pronounced in Year 3 (+7.63431), and while there is a slight decline in Year 4 compared to Year 3, the eGFR remains significantly better than at baseline. In conclusion, the treatment or management strategies seem to be effective, leading to a notable improvement in kidney function over time for this patient cohort. This suggests that the patients are moving toward recovery or at least significant stabilization of their condition (**Table 7**).

Table 7: Mean eGFR changes among CKD patients on follow-up at Addis Ababa, Ethiopia, 2020- 2024 (n=402)

Year	Mean eGFR Δ	Mean eGFR Δ	Mean eGFR Δ	Mean eGFR Δ
1	2.70 (p=0.207)			
2	5.30 (p=0.003) *	2.61 (p=0.75)		
3	7.63 (p=0.0001) *	4.94 (p=0.033) *	2.33 (p=1.00)	
4	6.44 (p=0.009) *	3.74 (p=0.532)	1.14 (p= 1.00)	-1.20 (p=1.00)

* Represents statistical significance and Δ - represents mean eGFR difference.

5.8.2. Patterns of chronic kidney disease (CKD) progression

A total of 806 CKD patients' events were analyzed across the study period. The distribution shows that 21.83% (n = 176) of patients experienced rapid progression, 34.73% (n = 280) showed regression, 43.44% (n = 350) had stable and 42.03% (n=339) remission in kidney function. The total mean eGFR decline is -13.20; with a standard deviation of 8.97 and a total frequency of 176 patients with rapid CKD progression and the total mean eGFR change is 0.29, with a standard deviation of 2.64 and a total frequency of 350 patients with stable CKD. The total mean eGFR increase is 13.48, with a standard deviation of 7.65 and a total frequency of 280 patients with CKD regression (**Table 8**).

Table 8: Patterns of CKD progression at Addis Ababa, Ethiopia, 2020- 2024 (n=402)

Year	Progression status	Mean eGFR (+/- SD)	Observation (n)	Observation (%)
1	Rapid progression	-14.7 (11.1)	83	220.65
	Regression	14.5 (8.1)	156	38.8
	Stable	0.24 (2.5)	63	40.6
	Total		402	100
2	Rapid progression	-11.7 (5.3)	39	20.7
	Regression	12.5 (7.5)	62	33.2

	Stable	0.7 (2.7)	68	46.0
	Total		187	100
3	Rapid progression	-10.3 (4.1)	24	18.7
	Regression	11.8 (5.9)	40	31.3
	Stable	0.01 (2.7)	64	50.0
	Total		128	100
4	Rapid progression	-13.4 (8.4)	30	33.7
	Regression	26 (7.4)	22	4.7
	Stable	-0.02 (2.8)	37	41.6
	Total		89	100
	Remission (Total events)		339	42.0

5.8.3. Predictors of annual change in estimated GFR

Those CKD patients with female sex, using ACEI or ARBs, using metformin have higher eGFR while those with baseline hemoglobin < 10.5 g/dl, with only primary education as compared to higher education, baseline proteinuria > +1 and those with diabetes mellitus have lower eGFR as compared to their counterpart comparator (**Table 9**).

Random Effects:

Sd(year) = 4.86 represents the standard deviation of the random effect of year and it suggests that there is substantial variation in the eGFR values over time across individuals. This variation is statistically significant (the confidence interval does not include zero). Sd (_cons) = 12.99 represents the standard deviation of the random intercept for individual initial eGFRs (i.e., individual-specific variation in the baseline level of eGFR) and it is statistically significant, indicating that the eGFR varies between individuals even after accounting for the fixed effects. Corr(year, _cons) = -0.48 represents the correlation between the random intercept and random slope (i.e., between the baseline level of eGFR and the change over time). The negative correlation suggests that individuals who start with higher baseline eGFR may experience smaller increases (or larger decreases) in eGFR over time (**Table 9**).

Table 9: Predictors of annual change in eGFR of CKD patients in Addis Ababa, Ethiopia, 2020 – 2024 (N = 402)

Variable	Category	Coefficient (95% CI)	P value
Age	> 75	-0.62 (-3.67, 2.43)	0.689
Sex	Female	4.75 (1.43, 8.08)	0.005*
Alcohol	Drinking	-1.52 (-4.40, 1.36)	0.302
Occupation	Farmer	-1.09 (-5.82, 3.64)	0.651
	Employed	2.22 (-1.96, 6.41)	0.297
	Housewife	-0.28 (-5.56, 5.01)	0 .919
	Self-employed	-1.31 (-5.97, 3.36)	0.583
	Student	3.63 (-6.87, 14.12)	0.498
Address	Living out of Addis Ababa	- 1.64 (-4.70, 1.41)	0.292
Salt use	Salt taking	-2.96 (-6.72, 0.81)	0.124
Baseline hemoglobin	< 10.5	-11.02 (-14.59, -7.45)	0.0001*
Education	Primary education	-5.28 (-9.99, -0.57)	0.028*
	Secondary education	-3.54 (-8.21, 1.14)	0.138
	Higher education	-4.59 (-9.64, 0.45)	0.074
Baseline proteinuria	≥ +1	-3.05 (-5.75, -0.35)	0.027*
Comorbidity	Hypertension	-2.51 (-6.36, 1.34)	0.201
	Diabetes mellitus	-3.47 (-6.85, -0.09)	0.044*
Medications	ACEI - ARBs	5.17 (2.44, 7.89)	0.0001*
	SGLT2I	2.62 (-0.88, 6.13)	0.142
	Atorvastatin	-1.27 (-4.56, 2.02)	0.448
	NSAIDS	1.30 (-2.01, 4.61)	0.441
	Metformin	4.58 (0.09, 9.07)	0.046*
	Hydrochlorothiazide	3.22 (-0.36, 6.80)	0.078
Random effects			

Parameter	Estimate	95% Conf. Interval
sd(year)	4.86	[4.03, 5.88]
sd(_cons)	12.99	[11.84, 14.26]
corr(year, _cons)	-0.48	[-0.60, -0.33]
sd(Residual)	7.88	[7.38, 8.42]

Symbol: * represents statistically significant values

6. CHAPTER 6: DISCUSSION

The annual change in estimated glomerular filtration rate (eGFR) shows statistically non-significant linear improving in the first three years and shows a slight decline in the last year of the study period contradicting the general notion that eGFR typically declines by about 1ml/min/1.73m2/year after the age of 40 years though this number could vary with many life variables (69). The age of the participants in this study was from 40-74 in 75% and the expectation is that their eGFR would have being declining accordingly. This study highlighted the total value that CKD patients' eGFR could improve with treatment as seen in the first 3years and there is a slight decline in the eGFR in the last year of the study period possibly due to poor adherence to treatment or ascribed to the natural course of the CKD as it is naturally progressive disease.

Among the total observations occurred in this analysis of this longitudinal CKD data with the random effect, 21.83% (N = 176) had rapid progression, 43.44% (N = 350) had stable, 34.73% (N = 280) had regression and 42.03% (N= 339) had remission. The finding had shown consistent finding and concept that CKD patients could achieve stable course or regression and remission as it is noted in the Canadian (21), United Kingdom (22), Oxford (23), Italy (24) and South Africa (25). The finding in this study, (34.7% regression, 42.03% remission and 43.44% stable) is a glimmer of hope for CKD patients who otherwise were considered to have irreversible and progressive course (70). In this study, CKD patients with rapid progression were 21.83% compared to studies in UK (17.7%), Oxford (24%) and South Africa (49.5%). The difference in the percentage observed is likely to be multifactorial as studies here are done across different levels of genetic risk, socioeconomic and care level. In this study, the highest proportion of patients with stable kidney function possibly suggests that interventions for CKD are generally effective, but the significant decline in eGFR among the rapid progressive group may indicate a subset of patients requiring targeted therapies, closer clinical monitoring and management. The group of patients with regression of CKD (34.7%) is encouraging and reflects potential reversibility with effective treatments.

This study shows that females have, on average, 4.75 statistically higher eGFR compared to males. This is consistent with general understanding that females are commonly affected by chronic kidney disease but the risk of rapid declining in eGFR is more common among men (27, 28). Men have rapidly progressive CKD as compared to women for many hypothetical reasons including hormonal, dietary, hemodynamic, renal mass and behavioral related factors (71).

Patients taking angiotensin convertases enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) have eGFR value 5.17 higher than those who don't take any of these medications. This finding is consistently demonstrated in in RCTs involving proteinuric CKD patients (72) and Ramipril Efficacy In Nephropathy (REIN) trial (58). These medications have been incorporated in the guidelines to delay the progression of CKD (62). The result in this study head shown that it renin-angiotensin system inhibitors does beyond delaying CKD progression through their main anti-hypertensive and anti-proteinuric effect but their additional anti-inflammatory and anti-fibrotic effect may also paly significant role (73). Though their renoprotective effect had evolved overtime (74, 75). These medications have shown paramount effect in improving eGFR as noted in this study, it may be important to consider steps back to use them in certain situations (76, 77).

Patients with diabetes mellitus on metformin have eGFR values 4.58 higher than those who didn't take metformin. This result is consistent with the recent study that showed metformin use was associated with reduced risk of kidney disease composite outcome including ESRD and death (78) possibly from its anti-inflammatory and anti-oxidant effects (79, 80) in addition to its potency for glycemic control effect (81). Glycemic control (normoglycemia) maintained over 5years following pancreas transplantation had demonstrated evidence of improvement in the histologic changes of the diabetic kidney disease (DKD) (37).

Participants with low baseline hemoglobin have eGFR values 11.02 lower than those with normal hemoglobin. Anemia is complication of moderate to severe chronic kidney disease (82) and it has been clearly shown to cause CKD progression leading to tubular hypoxia and oxidative stress (52, 83). Early correction of anemia had been postulated to have benefit (84).

Patients’ with only primary education have eGFR values 5.28 lower as compared to CKD patients with higher education. This is possible explained with the role of education on the healthcare. Participants having CKD with less advantage to higher education could have poor healthy living style (85, 86) and poor adherence to the CKD managements provided by the health care provider. The level of patients’ education affects their understanding about their health and the treatment related educations directly and those with better understanding have better care, quality of life, knowledge and self-management unlike those with poor understanding (30, 87, 88).

In the current study, presence of baseline urine dipstick proteinuria $\geq$ +1 have eGFR values 3.05 lower than those without proteinuria. The presence of proteinuria is surrogate marker and predictor of kidney injury (50, 89, 90). The finding in this study, though measurement is different, is consistent to the finding in the CKD-ROUTE study, where patients with normal-range proteinuria had lower risk of CKD progression than proteinuria ones (91). The finding in Italy better regression with low proteinuria (24)

This research had revealed that the presence of diabetes as a comorbidity have eGFR values 3.47 lower than those with no diabetes mellitus. This result is consistent, being diabetic as predictor of CKD progression to ESRD and dialysis, with evidences in China (89), poor glycemic control as marker of ESRD (92). Though the scientific world making diabetes as one predictor of CKD progression, other evidences, however, show that it plays little role in the progression of CKD (28).

7. CHAPTER 7: STRENGTH AND LIMITATION OF THE STUDY

Strength

This study is base for to do further cohort researches prospectively. This study also encourages for having CKD registry at national level to have a very clear understanding about the care. As the first study in the area with this title, it showed us that CKD patients care is better with better care. This study also had addressed some of the predictor variables so that the treating physician can consider in the care. The patients with rapid CKD progression needs close monitoring and appropriate interventions.

Limitation

The main limitation of this study is that the hospitals selected in this study are the best care center for kidney disease patients and the finding may not represent CKD patients in the whole country (selection bias). The care in this two hospitals, unlike to the other part of the country, for kidney disease patients is by nephrologists. The creatinine needs standardized laboratory measurement than taking the results from different reports. The other limitation of this study is the retrospective study design and sample calculation changes. Additionally incorporation of other variables (quantified proteinuria, glycemic and hypertension control, body mass index (BMI), serum bicarbonate, serum albumin, dietary profile other than salt intake, serum uric acid, genetic risk profile and exposure to different toxins and medications lists) is important. This were not included because most are not done very routinely in the care and some of them like BP and glycemic control lakes consistency in the value making it difficult to choose one.

8. CHAPTER 8: CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

The treatment or management strategies seem to be effective, leading to a notable improvement in kidney function over time for this patient cohort in this setting. This suggests that the patients are moving toward recovery or at least significant stabilization of their condition. Female sex, use of ACEi-ARB, use of metformin were associated with improvement in the mean estimated GFR change while low baseline hemoglobin, baseline proteinuria, being diabetic and educationally disadvantaged were predictors of rapid mean estimated GFR decline.

RECOMMENDATIONS

To Federal Democratic Republic of Ethiopia Ministry of Health

To facilitate further research about CKD patients' progression status in collaboration with the respective institution's to, taking more hospitals in to consideration. Additionally, role of education in the care of the patients and its impact on the outcome needs advocating.

To Addis Ababa University and Saint Paul millennium Medical College

The hospitals, especially SPMMC, better to develop complete data registry strategy to identify and manage outcome and predictor variables. The care provided may be a good reference to other centers.

To Healthcare Providers

Progression of CKD could be changed with better care and management and those with declining GFR need close monitoring, identifying the why and addressing it accordingly.

To Future Researchers

In order to have a better evidence, researchers better to conduct a prospective multicenter cohort study incorporating hospitals with no nephrologist using and addressing the limitations is recommended.

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