

**Department of Pharmacology and Clinical Pharmacy
School of Pharmacy
College of Health Sciences**



**Assessment of Medication Related Problems and Contributing Factors among
Ambulatory Patient with Chronic Kidney Disease at St. Paul's Hospital
Millennium Medical College, Addis Ababa, Ethiopia**

By: Eshetu Shiferaw

A Thesis Submitted to the Department of Pharmacology and Clinical Pharmacy,
School of Pharmacy, College of Health Sciences, Addis Ababa University in
Partial Fulfillment of the Requirements for the Master of Pharmacy Degree in
Pharmacy Practice

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Advisor: - Teshome Nedi (PhD)

Advisor: Leja Hamza (MD, Consultant Internist and Nephrologist)

Advisor: - Oumer Sada (Mphar)

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Abstract

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Eshetu Shiferaw

Addis Ababa University, 2020

Chronic kidney disease (CKD) is the reduction in the Glomerular Filtration Rate (GFR) and urinary abnormalities or a structural abnormality of renal tract which is explained by pathologic kidney abnormalities, persistent proteinuria, and other urine abnormalities on two occasions separated by ≥ 90 days. As kidney function declines, number and complexity of medication increase with the progression of the disease. Due to this Patients with this disease are at high risk for medication-related problems because of their condition and the multiple medications required for treatment of the causative disorders, and the complications associated with the disease. This study aimed at establishing the extent of medication related problems among patients with chronic kidney disease as well as exploring associations of different covariates with the problem identified. Hospital based cross-sectional study was conducted among ambulatory patients with chronic kidney disease at St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia from 1st of June to 30th of August 2019. Patient with chronic kidney disease stage 1, 2, 3, and 4 adult ambulatory patients were included in the study. A total of 325 medication related problems were identified from 204 (82.3%) study participants giving 1.6 MRPs per participants. One medication related problem was identified in 114 (55.9%) patients while two in 64 (31.4%). From the total of identified problems most common class of MRP identified were need additional drug therapy problems 114 (35.1%) followed by non-compliance 54 (16.6%). This study showed that only occupation (AOR=5.2, 95% CI: 1.292-21.288, P=0.020) and Angiotensin converting enzyme inhibitor (ACEI) use (AOR=6.6, 95% CI: 2.202-19.634, P=0.001) had association with the occurrence of medication related problems. In general, our study suggest that medication related problems experienced by each chronic kidney disease patients were high. In terms of types of MRPs, this study showed that need additional drug therapy was frequently identified types.

Key words: Chronic Kidney Disease, Medication Related Problems,

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Abbreviations and Acronyms

ADR	Adverse Drug Reaction
AOR	Adjusted Odds Ratio
CKD	Chronic Kidney Disease
CKDU	Chronic Kidney Disease Unknown
CRF	Chronic Renal Failure
CVD	Cardiovascular Disease
eGFR	Estimated Glomerular Filtration Rate
ENT	Ear, Nose and Throat
ESRD	End Stage Renal Disease
DRP	Drug Related Problems
GFR	Glomerular Filtration Rate
HTN	Hypertension
KDOQI	Kidney Disease Outcomes Quality Initiatives
MRP	Medication Related Problems
RAS	Renin Angiotensin System
UACR	Urine Albumin to Creatinine Ratio
UPC	Urine Protein to Creatinine
US	United States

1. Introduction

1.1 Background

Non-communicable diseases are the major concern in the 21st century world-wide (Centre,2005). Chronic kidney disease (CKD) is one of such non-communicable diseases of public health concern (Deegens,2012). It is defined as reduction in the Glomerular Filtration Rate (GFR) and urinary abnormalities or a structural abnormality of renal tract (Markus and Mary, 2017). It is also explained by any one of the following findings: pathologic kidney abnormalities, persistent proteinuria, other urine abnormalities, *e.g.*, renal hematuria, imaging abnormalities and $eGFR < 60$ mL/min/1.73 m² on two occasions separated by ≥ 90 days and that is not associated with a transient, reversible condition such as volume depletion (Kalantara-Zadeh, 2011).

This disease commonly affects the proximal tubules and the interstitium in turn giving rise to characteristic, recognizable histopathological and clinical features. In clinical evidence, the disease is manifested by tubular proteinuria, usually $\beta 2$ -microglobulinuria, and the absence of hypertension and edema. In addition the histological appearance of this disease reveals a tubule interstitial pathology that can commonly be observed in toxic nephropathies (Kore and Hm, 2018). Due to this effect incidence and prevalence of chronic kidney disease in both developed and developing had been regards as public health problems (Blagg and Harrington, 2008).

According to the 2010 Global burden of disease study chronic kidney disease was ranked 27th in the list of causes of total number of global deaths in 1990 (age-standardized annual death rate of 15.7 per 100 000), but rose to 18th in 2010 (annual death rate 16.3 per 100 000) (Lozano, Naghavi, Foreman, Lim, Shibuya, Aboyans, *et al.*, 2012). In developed country, the prevalence of end-stage kidney disease was estimated around 822-1,665 per million population (Collins, Honoraria, Amgen, Baxter, NxStageigma-TauTakeda and Robert Foley, 2010)(Mcdonald and Kylie, 2011). In Indonesia, kidney diseases accounted for top five diseases leading to hospitalization and death (Mcdonald and Kylie, 2011). While in Sub Saharan Africa, CKD is estimated to be 3-4 folds more than in developed country (Blagg and Harrington, 2008). Another study finding estimated prevalence of people who have experienced CKD is 11–13% and 13.9% worldwide and sub-Saharan Africa respectively (Vivekanand, Dm, Garcia-garcia, Iseki, Li,

Naicker, *et al.*, 2013). Chronic kidney disease is also a growing problem in Ethiopia (Fiseha, Kassim and Yemane, 2014).

Further, CKD was associated with alteration in the pharmacokinetics properties of a range of drugs especially renal-excreted drugs. This alteration may include changes in drug bioavailability, protein binding level, drug distribution and elimination. Unfortunately, this pharmacokinetics change will make patients vulnerable to medication related problems and other co-morbidities (Ramadaniati, Anggriani, Wowor and Rianti, 2016).

Mostly CKD patients present with several co-morbidities such as diabetes mellitus, hypertension, coronary artery disease and anemia (Care, Sys, Ahlawat, Sanjay and Tiwari, 2016). Thus, for this group of patients, medication therapy management services are mandatory for optimum therapeutic outcome and improved quality of life. A core principle of medication therapy management is medication therapy review (Njeri, William, Ogallo, Gitonga, Sylvia, Opanga, *et al.*, 2018).

As kidney functions begin to declines; additional medications to prevent and manage CKD complications are unavoidable, including treatment for mineral and bone disorders, anemia, hyperlipidemia and cardiovascular complications. So it is not amazing that by the time patients reach stage 5 CKD on dialysis; they need an average of 10–12 medications. But polypharmacy in this condition does not necessarily reflect inadequate medical management or abuse of medications. However, the large number of medications and the presence of renally altered drug disposition put such patient population at high risk for having medication-related problems (Mason, 2011). In general the above factors increase the patients' risk of having medication related problems (MRPs)(Quintana-bárcena, Lord, Lizotte, Berbiche and Lyne Lalonde, 2018).

The number and complexity of drugs increase with the advanced stage of CKD which in turn cause the patient to be noncompliant and develop adverse drug reactions. But currently, the implementation of specific renal pharmaceutical care will help for identification, prevention and resolution of medication related problems (MRPs) (Belaiche, Romanet, Allenet, Calop and Zaoui, 2012).

Medication related problem (MRP) is as “an event occurring, as a result, the medication therapy that actually or potentially interferes with desired health outcomes” (Robert, Linda and Peter, 2004). It has been evident that the prevalence of MRPs may result in high burden morbidity and decrease patients’ quality of life in different clinical settings (AM and AA, 2012).

All stages of the medication usage process starting from prescribing to dispensing stage will be the source of MRP. Inadequate follow-ups and reassessment of treatment outcomes may also contribute to occurrence of MRPs. Now a day to tackle and monitor such therapeutic problems, pharmaceutical care process was integrated to the health care delivery system. Basically, pharmaceutical care is a team work activity in collaboration with other health care professionals and offered directly to the patient for improved quality use of medicines and achieves the desired treatment outcomes. Ultimately, pharmaceutical care process identifies and resolves actual or potential MRPs (Adepu and Adusumilli, 2014).

According to Robert J. Cipolle, there are seven basic categories of MRPs. The first two categories of drug therapy problems (unnecessary drug therapy and need additional drug therapy) are associated with the indication. The third and fourth categories of drug therapy problems (ineffective drug therapy and too low dose) are associated with effectiveness. While the fifth and sixth categories of drug therapy problems (adverse drug reaction and too high dose) are associated with safety. And the seventh category deals with patient compliance. Robert J. Cipolle mentioned this order is significant in that it describes the rational decision making process of the pharmacotherapy.

1.2. Statement of the Problem

The impact of CKD not only lies in the burden related with the disease but also in the burden associated with the proper use of medications in this disease. Because patients with CKD require complex drug regimens to prevent and retard CKD progression and treat associated co morbidities, they are at a higher risk of developing MRPs than other patient population (Alshamrani, Almalki, Qureshi and Yusuf, 2018)(Mason, 2011).

Since the occurrence of MRPs increase in CKD patients as their clinical condition become worsens, with more associated cardiovascular risk factors and more treatments to stabilize their clinical condition, health professionals should be aware regarding such problems and ensure the adoption and implementation of a preventive strategy (Belaiche, Romanet, Allenet, Calop and Zaoui, 2012). One of the preventive strategy is early identification of those MRPs. But still there is no base line data about this problems in this hospital.

Currently, MRPs are of a major concern in health care delivery system because of increased burden in cost, morbidity and mortality. It was also known to be associated with lower quality of life (Cardone, Bacchus, Assimon, Pai and Manley, 2010). One study conducted in India indicates that the cost of drug related morbidity and mortality exceeded \$177.4 billion in 2000 of total costs, followed by long-term-care admissions, which accounted for 18% (\$32.8 billion) (Adepu and Adusumilli, 2016).

Another study showed that MRPs are also the dominant reasons for admission. A retrospective cross-sectional study in Singapore showed that 71.9% of MRPs resulted in admission (Koh and BM, 2003), while from a prospective multicenter study among 13,000 unplanned admissions, 714 (5.6%) were medication related (Leendertse, Egberts, Stoker and Van Den Bemt, 2008). One study in New York showed that MRPs were associated with mortality, morbidity, and lower quality of life (Cardone, Bacchus, Assimon, Pai and Manley, 2010).

Unlike in high income countries, there is a shortage of literature that reveals prevalence of MRPs in CKD in low- and middle-income countries such as those in Sub- Saharan Africa. Furthermore, little is known about the exact prevalence and specific predictors of MRPs in patients with CKD residing in Ethiopia. Because of differences in genetics make up, socio-demographic

characteristics as well as differences in healthcare practices, study results on this area in other side of the world may not show the true state of MRPs among CKD patients in Ethiopia. So additional studies are therefore essential to investigate the prevalence of MRPs in patients with CKD residing in this region. And this study would establish the extent and types of MRPs among patients with CKD, as well as identify various related risk factors contributing to MRPs among those population group.

Primarily, this study result would give insight about MRP. Because creating awareness about MRPs, are core principal elements of developing strategy for preventing and resolving of such problems and may contribute to diminishing medication-related morbidity and mortality incidence.

From this research different predictors of potential medication related problems were identified. Since early identification of predictors, types and patterns of MRPs may enhance the prevention of MRPs. This in turn can help improve the health care system for CKD patients, improve quality of life, decrease preventable hospitalizations, and decrease costs to the healthcare system.

The study thus aimed at establishing the extent and types of MRPs experienced by patients with CKD in St. Paul's Hospital Millennium Medical College as well as exploring associations of different covariates with MRP identified. And ultimately the findings would assist pharmacists to identify patients with CKD at risk of MRPs and institute appropriate intervention strategies.

1.3.Literature Review

Chronic kidney disease is a world-wide public health problem result in adverse outcomes of kidney failure, cardiovascular disease (CVD), and premature death (Wali, 2010). Every year, more than 60% of all deaths worldwide are because of chronic disease. And about 10% of the world's population has some degree of CKD (Damien, Lanham, Parthasarathy and Shah, 2016). Research conducted in Addis Ababa, Ethiopia at public hospital reveals that 66 (15.6%) of participants have normal/stage 1, 49 (11.6%) of participants have stage 2, 82(19.4%) of the participants have stage 3, 62 (14.7%) stage 4 and 163 (38.6%) stage 5 CKD respectively (Kore and Hm, 2018).

Medication-related problems are frequent in renally compromised patients. One study conducted in Indian hospital revealed that three hundred and twenty-seven MRPs were identified with 308 renally compromised patients (Castelino, Sathvik, Parthasarathi, Gurudev Mbbs, Shetty Mbbs and Narahari, 2011). A prospective study on hemodialysis patients in Toronto identified indication without drug therapy as the most common (51%) MRP in the study population (Ong, Fernandes, Cesta and Bajcar, 2006).

Another study conducted in India tried to show that a total of 90 drug-related problems were observed in chronic kidney disease patient's prescriptions. Noncompliance (22), untreated indications (18) and drug interactions (14) were the most commonly found drug-related problems (Adepu and Adusumilli, 2016).

One study in some tertiary hospitals in Nigeria has revealed a very high proportion (70.03%) of CKD patients with DRPs. This high proportion of DRPs might be due to relatively older population involved in the study, as well as severe CKD patients with multiple co-morbidities included in the study (Adibe, Igboeli and Ukwe, 2017).

Hospital based cross sectional study conducted in Jimma on admitted chronic kidney disease patients identified that around 78% of study participant had medication related problems (Garedow, Bobasa, Wolide, Dibaba, Fufa, Tufa, *et al.*, 2019)

In a pooled analysis of seven studies reporting medication- related problems in ambulatory dialysis patients, 395 patients took an average of 11.8 medications to treat a mean of 6.2 co-

morbid conditions. Of the nearly 1600 medication-related problems identified, the predominate MRP was unnecessary drug therapy (14.9%) (Ong, Fernandes, Cesta and Bajcar, 2006).

Another study revealed that odds of having an improper drug selection among CKD stage 4 was 6.09 (95% CI 1.60–31.49, $p = 0.015$) times the odds of having an improper drug selection among CKD stage 3 patients (Njeri, William, Ogallo, Gitonga, Sylvia, Opanga, *et al.*, 2018). One cross-sectional study conducted in Saudi Arabia in hemodialysis outpatient unit indicate that medication use without indication, was the highest identified MRPs at 36% (Alshamrani, Almalki, Qureshi and Yusuf, 2018).

In one study in Iraq many MRP have been identified in hemodialysis center; one of the identified MRP was untreated condition which is 9.2% (Dlear, Bushra and Kawa, 2015). Among The 3 most frequent MRP categories identified in the study conducted in Florida, potentially untreated indication was found in 62 (43.7%) of patients (Tillotson, Douglas and Patti, 2006). Another study detected around 22 of untreated condition from the total of 125 need related problems (Guerro-prado, Olmo-revuelto and Catalá-pindado, 2018). One study showed that 68% of the patients who are maintained on hemodialysis presented with hyperphosphatemia, from those only 53 of them receive treatment (Dlear, Bushra and Kawa, 2015). The commonest medication related problems identified in Kenya was indication without drugs(18.1%) (Njeri and Fulfilment, 2018a). An indication that was not currently being treated (13.5%) were the most common MRP identified in another study which was held in USA (Manley, Drayer and Muther, 2003).

One study in Spain identified around 10 ineffective therapy from the total of 151 medication related problems from complex chronic kidney patients (Guerro-prado, Olmo-revuelto and Catalá-pindado, 2018). Another study also tried to show that the prevalence of ineffective therapy in patients who undergone hemodialysis was 14.4% (Castelino, Sathvik, Parthasarathi, Gurudev Mbbs, Shetty Mbbs and Narahari, 2011). In Suleiman hemodialysis center 27.7% of ineffective therapy were identified (Dlear, Bushra and Kawa, 2015).

Many MRP have been identified in the hemodialysis center which is found in Iraq; including under dose 29% (Dlear, Bushra and Kawa, 2015). Another study in Nigeria tried to identify that the prevalence of dosing problems were around 20.09%, among which dose too low and short duration took the major value (Adibe, Igboeli and Ukwe, 2017). Different class of medication

related problems were identified in other study conducted in Kenya, from those sub therapeutic dose which is 31.7% were common (Njeri, William, Ogallo, Gitonga, Sylvia, Opanga, *et al.*, 2018). In another finding sub therapeutic dosing, was the second identified MRPs 23% (65/280) (Alshamrani, Almalki, Qureshi and Yusuf, 2018). One of the major drug related problems identified in Saudi Arabia at hemodialysis patients were sub-optimal effect of drug treatment (28.7%) (Ramadaniati, Anggriani, Wowor and Rianti, 2016).

Most commonly, the pharmacist identified MRP were adverse drug reactions (20.7%) in USA (Manley, Drayer and Muther, 2003). Another study results in USA demonstrated a high rate of potential ADEs (55.3 per 100 admissions) in the sampled hospitalized patients with elevated serum creatinine concentrations (Fink and Chertow, 2009). In Kenya one study showed that adverse drug reactions accounted for 24 (8.9%) of the MRPs, (Njeri, William, Ogallo, Gitonga, Sylvia, Opanga, *et al.*, 2018). Among those 62 (12.1%) experienced a probable or definite ADR during hospital stay.

Medication-Related Problem identified in outpatient hemodialysis unit at Saudi Arabia was overdosing, 15% (41/280) (Alshamrani, Almalki, Qureshi and Yusuf, 2018). Compared to patients with CKD stage 3, patients with CKD stage 4 were 4.7 times more likely to experience over dosage (Njeri, William, Ogallo, Gitonga, Sylvia, Opanga, *et al.*, 2018). In other study over dosage was identified with the value of 14.4% (Manley, Drayer and Muther, 2003). One of the identified medication related problems in other study conducted in Kenya was over dosage (7.4%) (Njeri and Fulfilment, 2018a). Similarly, other study in New York revealed that from total of 161 MRPs, over dosage accounts (n =27) (Cardone, Bacchus, Assimon, Pai and Manley, 2010).

Research conducted in Iraq identified (9.2%) non-adherence hemodialysis kidney disease patients (Dlear, Bushra and Kawa, 2015). The most frequently identified MRPs in one study done in Kenya was medication non-adherence (16%) (Njeri, William, Ogallo, Gitonga, Sylvia, Opanga, *et al.*, 2018).

Pharmacokinetic and pharmacodynamics properties of many medications are greatly affected by kidney disease. Therefore, when prescribing medications in patients with kidney disease,

multiple factors must be taken into account: drug absorption, distribution, metabolism, and excretion of active or toxic metabolites may all be affected by kidney disease (Brater, 2009). As kidney function declines, the type and amount of medications a patient consumes increases, thereby putting them at a higher risk for MRPs (Cardone, Bacchus, Assimon, Pai and Manley, 2010).

In addition, the progression of CKD may lead to the increased number of medications taken by patients to manage the complications and the co morbidities, and subsequently increase the prevalence of DRPs (Anne, Lioyd, Brian and Robin, 2009). Prevention of progression of renal disease is important in reducing incidence of medication related problems (Ong, Fernandes, Cesta and Bajcar, 2006).

Compared to patients with CKD stage 3, patients with CKD stage 4 were 5.9 times more likely to have an improper drug selection and 4.7 times more likely to experience over dosage. Other significant predictors of MRPs were number of medications per prescription and number of co-morbidities per patient (Njeri, William, Ogallo, Gitonga, Sylvia, Opanga, *et al.*, 2018).

One study conducted in Kansas City, United States of America explained that occurrence of MRPs has been associated with several factors. These include a high number of co-morbidities, a high number of prescribed medications, old age, advanced stage of CKD, and frequent dosage changes (Manley, Drayer and Muther, 2003).

2. Objective

2.1. General Objective

To assess medication related problems and contributing factors among ambulatory patient with chronic kidney disease at St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia

2.2. Specific Objectives

- ✓ To determine the overall prevalence of medication related problems among ambulatory patient with chronic kidney disease
- ✓ To identify different types of medication related problems according to Cippole's classifications
- ✓ To investigate risk factors associated with MRPs in ambulatory patients with CKD

3. Methodology

3.1. Study Area

The study was conducted at St. Paul's Hospital Millennium Medical College, which is located in Addis Ababa Ethiopia. The hospital was established in 1968, while the medical school opened in 2007 (Geletu, Teferra and Sisay, 2018). Currently, it is one of the tertiary public Hospitals in Ethiopia with more than 400 beds which provide service for different categories of ambulatory and admitted patients coming from different corners of the country. It has different clinics which provide an out-patient service where patients with specific chronic disease are referred for follow-up and routine health services for the city community as well as for different population come from regional states of Ethiopia. Renal clinic is one of the specialty clinic that provide service to the patient at this hospital.

3.2. Study Design and Period

Hospital based cross-sectional study was conducted among ambulatory patient with chronic kidney disease who came to St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia from 1st of June to 30th of August 2019.

3.3. Study Population

The study population was consisted of ambulatory adult patients diagnosed with CKD and undergoing treatment and had follow up at St. Paul's Hospital Millennium Medical College during the study period from 1st of June to 30th of August 2019.

3.4. Eligibility Criteria

3.4.1. Inclusion Criteria

Ambulatory adult patient with chronic kidney disease (stage 1, 2, 3, 4), and those who underwent treatment at St. Paul's Hospital Millennium Medical College during the study period as well as those who gave voluntary informed consent. The stage of kidney disease was categorized using eGFR calculated based on the serum creatinine levels using the MDRD formula.

3.4.2. Exclusion Criteria

Patients who were at post renal transplant, hemodialysis patient and patients with cognitive impairment were excluded from the study participant.

3.5. Sample Size Determination and Sampling Techniques

The number of patients to be involved in the study was determined by using the single population proportion formula:

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

Where

n= Minimal sample size required.

P = Estimated prevalence of MRPs in CKD.

$Z_{\alpha/2}^2$ = Standard normal deviate at 95% confidence interval corresponding to 1.96

d = Absolute error between the estimated and true population prevalence of CKD of 5%.

The calculated sample size using this formula is 384. The expected number of source population in the study period (N), based on the average number of patients coming to the renal sites during the study period gave us 540.

Corrected sample size = $n \times N / n + N \sim 225$. 10% contingency was considered, thus final sample size used in this study was **248**.

3.5.1. Sampling Techniques

A systematic random sampling technique was used to recruit samples for the study in each day of the data collection process. The actual sampling fraction (k^{th}) was calculated through dividing

the total number of source population attending the renal clinic during the study period (540) by the corrected sample size (248). The first patient was selected randomly then every other patient was selected from patient registration list and interviewed after physician visit and his/her medical record was reviewed in the same day after the interview until the total sample size was reached.

3.6. Study Variables

3.6.1. Independent Variables

- ✓ Patient age
- ✓ Sex
- ✓ Economic status
- ✓ Social drug use
- ✓ Level of education
- ✓ Presence of co morbidities
- ✓ Number of co morbidities
- ✓ Presence of complication
- ✓ Stage of CKD
- ✓ Type and number of drugs

3.6.2. Dependent Variable

- ✓ Medication related problems

3.7.Data Collection

3.7.1. Data Collectors

The data collection period was between 1st of June to 30th of August 2019. The data collection was conducted by three nurses, one clinical pharmacist and principal investigator. One day training was given to all data collectors prior to data collection on how to interview patients and use the abstraction format to gather information. Data collectors completed an interviewer administered questionnaire which aimed at collecting socio demographic details and medication history data from the patient. Then the investigator reviewed the patient medical records and treatment chart belongs to each study participant.

3.7.2. Data Collection Techniques

In general data collecting process have two basic steps. The first was patient interview: once informed consent was obtained the investigator interviewed the patient by using structured questionnaire. The starting section of the questionnaire was used to obtain the baseline Sociodemographic details such as age, sex, marital status, level of education, occupation, level of income and patient status on cigarette smoking and alcohol intake. It was also provide past medical history, medication history and MRPs reported by the patient and other aspects of patient related risk factors associated with MRPs.

The second step was medication chart review: this was done using the second section of the questionnaire. This was conducted such that medical history, physical examination notes and results of laboratory and diagnostic tests, working diagnosis and treatment was reviewed. In addition presence of co morbidities, number of co morbidities, and presence of complication, stage of CKD and type as well as number of drugs were reviewed in this section.

3.8.Data Processing and Analysis

Identification and classification of MRPs using appropriate guidelines was assessed by 2 clinical pharmacists through review and analyses of all medication orders, administration sheets, laboratory and diagnostic test results and working diagnosis. The identification of MRPs and principles of medication use in the CKD were based on evidence-based clinical guidelines and standards of practice like: KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis,

Evaluation, Prevention, and Treatment of Chronic Kidney Disease, National Kidney Foundation, Guidelines on Clinical and Programmatic Management of Major Non Communicable Diseases 2016 and Standard Treatment Guideline for General Hospital 2014. For every participant, we defined a MRP as a single binary variable indicating the presence or absence of the identified MRP. Drug–drug interactions were checked using IBM Micromedex and Medscape online clinical information software.

After data was checked for completeness, it was edited, cleaned, and analyzed. The collected data was entered into Epi Info 7 software version 7.1.4 (Centers for Disease Control and Prevention, Atlanta, GA) and analyzed using IBM SPSS statistics for Windows version 25 (IBM Corp. Descriptive statistics was used. Categorical variables were summarized using frequencies and percent proportions.

Bivariate logistic regression was used to analyze the associations between presence of MRPs and the covariates identified. This analysis was achieved in two steps. First, uni-variate logistic models of each variable and presence of MRPs was constructed and their odds ratios, the 95% confidence intervals of the odds ratio, and the associated p-values computed.

Second, multivariable logistic regression models were constructed to investigate the associations between those variables and presence of MRPs while adjusting for possible confounding by other covariates. Then result with p value <0.05 was considered as significant.

3.9.Data Quality Control and Assurance

The data abstraction format was assessed by an expert physician in the field of nephrology for clarity. Pre-test study was done among 13 patients before two days of data collection period to check for the uniformity and understandability of the questionnaire. The data collectors were trained for one days on how to collect the data. During data collection, regular supervision and follow up was made. Principal Investigator was cross-checked for completeness and consistency of data every day. All materials used for data collection was arranged sequentially.

3.10. Ethical Consideration

Ethical clearance was obtained from the Ethical Review Committee of School of Pharmacy and Ethical Review Board of St. Paul's Hospital Millennium Medical College. Then after official letter was written by Ethical Review Board of St. Paul's Hospital Millennium Medical College, to the outpatient renal clinics. The aim of the study was fully explained to the patients after they have been seen by the physician. This was done by the study personnel who use a screening and eligibility form (annex) to recruit eligible patients. An explanation on the procedure, harm, benefits and confidentiality of the study was given to those eligible before administering a consent explanation form (Annex). Verbal consent from the patients was obtained and confidentiality of the information was assured by using code numbers than personal identification names.

3.11. Operational Definition

Medication related problems: is any undesirable event experienced by a patient which involves, or is suspected to involve, and that interferes with achieving the desired goals of therapy.

Social drug use: use of alcohol cigarette smoking and chewing khat for one or more than one year

Identified drug-drug interaction was defined as follow:

- a) Major drug–drug interactions: the interaction may be life-threatening and require medical intervention to minimize or prevent it
- b) Moderate drug–drug interactions: the interaction may result in exacerbation of the patient's condition and require an alteration in therapy.
- c) Minor drug–drug interactions: the interaction would have limited clinical effect.

4. Results

4.2. Sociodemographic Characteristics of the Study Participants

In this study, a total of 248 patients were included. Majority 132(53.2%) of them were males. Mean age of the study participants was 53.01 ± 15.2 years. More than half (59.3%) of the patients were in the age group of 18-59. Majority of the participants were married (54.4%) and 4.0% of them were divorced. Regarding their educational status, 37.1% has completed secondary education. Among the study participants, 44.8% were employed and 40.3% were unemployed. Regarding social drug use behavior, 5.6% use alcohol, and 4.4% chew khat and (Table 1).

Table 1: Sociodemographic characteristic of chronic kidney disease patients having follow up at renal clinic of St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, June-August, 2019,

Variables	Category	Numbers	Percent (%)
Gender	Male	132	53.2
	Female	116	46.8
Age	18-59	147	59.3
	≥ 60	101	40.7
Marital status	Single	63	25.4
	Separated	29	11.7
	Married	135	54.4
	Divorced	10	4.0
	Widowed	11	4.4
Educational level	Can't read & write	32	12.9
	Primary	80	32.3
	Secondary	92	37.1
	College and above	44	17.7
Occupation	Unemployed	100	40.3
	Employed	111	44.8
	Retired	37	14.9
Social drug use	Alcohol use	16	5.6
	Cigarette smoking	6	2.4
	Khat chewing	11	4.4

4.3. Clinical Characteristics of Study Participants

More than half (53.6%) of the study participants were in stage 4 while 36.7% were in stage 3. Approximately 86.7% of the patients had one or more co-morbidities. Among these 54% had single co-morbidities. The most common documented co-morbidities in study participants were hypertension (37.5%) and diabetic mellitus (17.7%). Greater than 60% of the study participants had one or more complications. The most common types of complication were anemia (56.9%) and hyperphosphatemia (46.9%). A total of 922 medications were used. The mean number of drugs per day was 3.72 ± 1.4 per patient. Approximately, 40% of the patients received ≤ 3 drug per day (Table 2).

Table 2: Clinical characteristics of chronic kidney disease patients having follow up at renal clinic of St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, June -August, 2019

Variables	Category	Number	Frequency (%)
Stage of CKD	Stage 1	5	2.0
	Stage 2	19	7.7
	Stage 3	91	36.7
	Stage 4	133	53.6
Co morbidities	Present	215	86.7
	Absent	33	13.3
Specific co morbidities	HTN	81	37.5
	DM	38	17.7
	CVD	14	6.5
	DM nephropathy	24	10.9
	HTN nephropathy	33	14.9
	Glomerulonephritis	4	1.6
	Hepatitis	13	6
	Uropathy	3	1.2
	HTN nephrosclerosis	12	5.6
	TB	3	1.2
	HIV	4	1.6
Complication	Present	160	64.5
	Absent	88	35.5
Specific complication	Anemia	91	56.9
	Osteodystrophy	28	17.5
	Hyperkalemia	3	1.9
	Hyperphosphatemia	75	46.9
	Neuropathy	21	13.1
No of medication per patients	≤3	86	42.2
	≥4	118	57.8

* Others: Community acquired pneumonia, urinary tract infection, gout, peptic ulcer disease, asthma, Parkinson

The most common prescribed class of drugs among the study participants, in decreasing order, were diuretics (70.2%), CCB (50%) and ACEI (37.1%). From the least iron supplement and erythropoietin were prescribed with 3.25%, 4.9% respectively (figure 1).

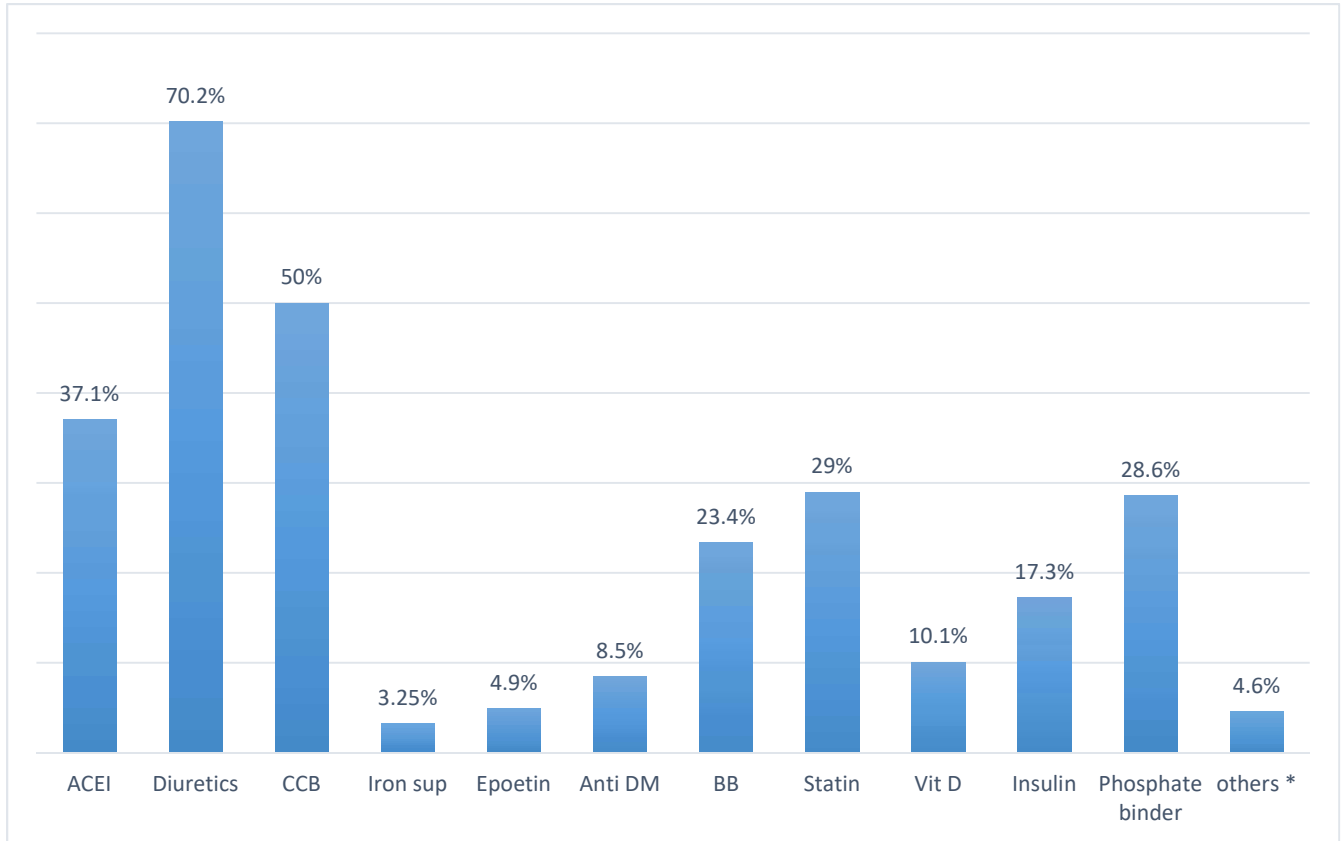


Figure 1: Frequently prescribed drug class in chronic kidney disease patients having follow up at renal clinic of St. Paul’s Hospital Millennium Medical College, Addis Ababa, Ethiopia, June - August, 2019,

* *Others: aspirin, anticoagulant, antibiotics, antiparkinson, proton pump inhibitors, histamine 2 antagonist, short acting beta agonist, allopurinol, anti-retroviral drugs, tricyclic anti-depressant, anti-tuberculosis, steroids*

-ACEI: angiotensin converting enzyme inhibitors (enalapril, Lisinopril, captopril), diuretics (furosemide, hydrochlorothiazide), CCB: calcium channel blockers (nifedipine, amlodipine), iron supplement (ferrous sulfate, ferrous gluconate, ferrous sucrose), Anti-DM: anti-diabetics (metformin, glibenclamide), BB: beta blockers (atenolol, metoprolol, carvedilol), statins (atorvastatin, simvastatin), phosphate binders (calcium carbonate)

Commonly prescribed top five class of drug in stage 4 patients were diuretics (79.7%), CCB (61.7%), iron supplement (45.1%), phosphate binders (42.9%), and BB (32.3%). In stage 3 patients widely prescribed class of drugs were ACEI (63.7%), diuretics (59.3%), and CCB

(36.3%). Similarly, most common prescribed class of drugs in stage 2 patients was ACEI (73.7%), diuretics (57.9%), CCB (47.4%), and statins (15.8%) (Table 3).

Table 3: Distribution of medication used by the study participant across chronic kidney disease stages among those patients having follow up at renal clinic of St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, June -August, 2019,

Variables	Stage of CKD								
	Stage 1		Stage 2		Stage 3		Stage 4		
	N	%	N	%	N	%	N	%	
ACEI	YES	5	100	14	73.7	58	63.7	15	11.3
	NO	-	-	5	26.3	33	36.3	118	88.7
Diuretics	YES	3	60	11	57.9	54	59.3	106	79.7
	NO	2	40	8	42.1	37	40.7	27	20.3
CCB	YES	-	-	9	47.4	33	36.3	82	61.7
	NO	5	100	10	52.6	58	63.7	51	38.3
Iron sup	YES	1	20	1	5.3	18	19.8	60	45.1
	NO	4	80	18	94.7	73	80.2	73	54.9
Epoetin	YES	-	-	-	-	-	-	12	9.02
	NO	5	100	19	100	91	100	121	90.98
Anti DM	YES	1	20	2	10.5	10	10.99	8	6.01
	NO	4	80	17	89.5	81	89.01	125	93.99
BB	YES	-	-	2	10.5	14	15.4	43	32.3
	NO	5	100	17	89.5	77	84.6	90	67.7
Statin	YES	1	20	3	15.8	31	34.1	37	27.8
	NO	4	80	16	84.2	60	65.9	96	72.2
Vit D	YES	-	-	-	-	5	5.5	20	15
	NO	5	100	19	100	86	94.5	113	85
Insulin	YES	-	-	1	5.3	10	10.99	32	24.1
	NO	5	100	18	94.7	81	89.01	101	75.9
Phosphate binder	YES	-	-	2	10.5	12	13.2	57	42.9
	NO	5	100	17	89.5	79	86.8	76	57.1
others	YES	-	-	2	10.5	46	50.5	70	52.6
	NO	5	100	17	89.5	45	49.5	63	47.4

4.4. Prevalence and Types of Medication Related Problems

A total of 325 MRPs were identified from 204 (82.3%) study participants giving 1.6 MRPs per participant. One MRP was identified in 114 (55.7 %) patients and two MRPs in 64 (31.4%). Common class of MRPs identified were need additional drug therapy problems 114 (35.1%), non-compliance 54 (16.6%) and ineffective drug therapy 37 (11%) (Figure 2).

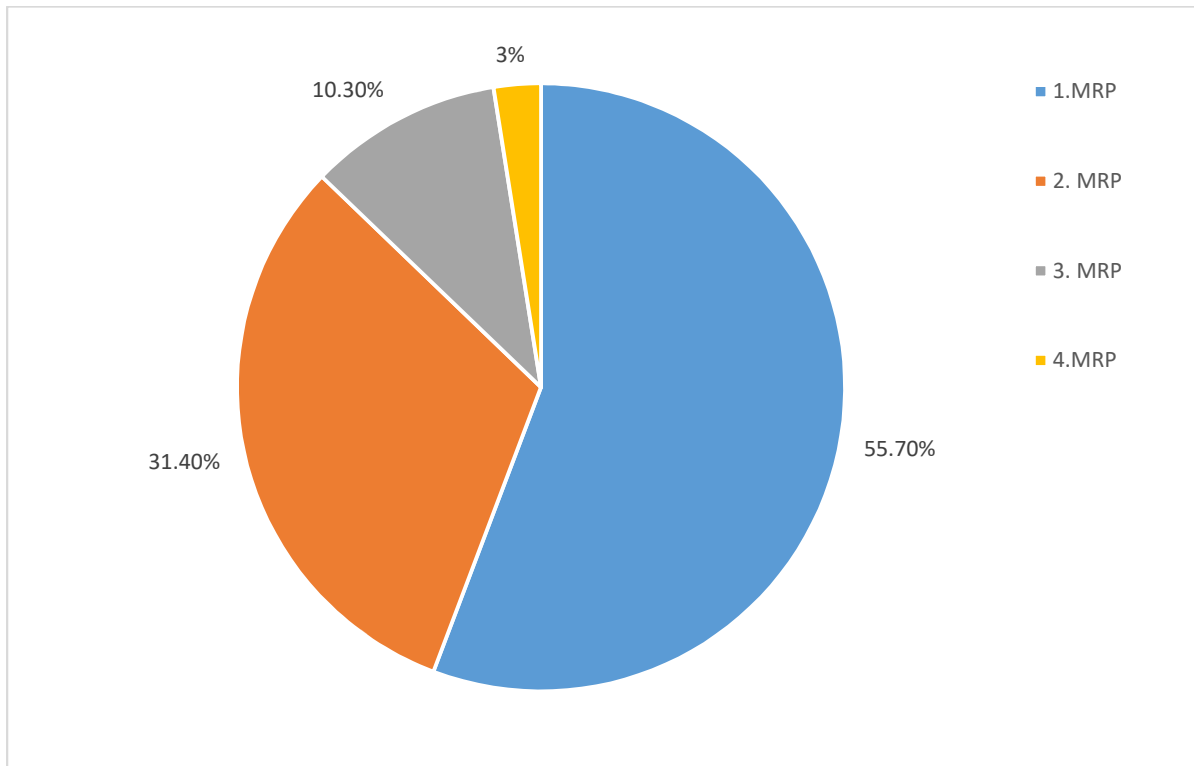


Figure 2: Number of medication related problems per patients among chronic kidney disease patients having follow up at renal clinic of St's Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, June -August, 2019,

4.5. Types of and Causes of MRP Identified in Study Subject

From 46 unnecessary drug therapy problems, 16(34.8%) of them were due to patient used medicine as recreation and 18 (39.1%) of them were due to medicines used for treating side effect of the other drugs. The most common identified cause of need additional drug therapy were need of preventive drug therapy 80 (70.2%), and presence of untreated condition 27 (23.7%). Regarding about ineffective drug therapy, 65% of them were due to using the least effective drug to treating the condition. On the other hand drug interaction 33 (71.7%) and less

frequent administration 8 (17.4%) were mostly identified cause of dosage too low. Commonly identified causes of ADR were drug interaction 10 (43.5%) and usage of unsafe drugs 7 (30.4%). Prescribed drugs with high dose 4 (80%) was common cause of dosage too high therapy. The two most common reported cause of non-compliance were unaffordability of drugs 26(48.1%) and lack of patient understanding about drug instruction 10 (18.5%) (Table 4).

Table 4: Types of and causes of MRP identified from chronic kidney disease patients having follow up at renal clinic of St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, June -August, 2019,

MRP category	Cause of MRP	Number	Percent (%)
Unnecessary drug therapy (n=46)	Medicine for recreation	18	39.1
	Medicine for treating side effect	16	34.8
	Drugs without indication	8	13.4
	Duplicate therapy	4	8.5
Need additional drug therapy (n=114)	Preventive drug therapy needed	80	70.1
	Untreated condition	27	23.7
	Synergistic therapy	7	6.1
Ineffective drug therapy (n=37)	Not the most effective drugs	24	64.9
	Drug interaction	13	35.1
Dosage too low (n=46)	Drug interaction	33	71.7
	Less frequent administration	8	17.4
	Low dose	6	13
	Short duration	1	2.2
ADR (n=23)	Cause undesirable effect	5	21.7
	Unsafe drugs	7	30.4
	Drug interaction	10	43.5
	Incorrect administration	1	4.3
Dosage too high (n=5)	High dose	4	80
	More frequent	1	20
Non-compliance (n=54)	Can't afford	26	48.1
	Not understand instruction	10	18.5
	Patient prefer not to take	5	9.3

Forget to take	8	14.8
Can't swallow	2	3.7
Not available	3	5.6

A total 56 drug-drug interaction were identified. From this 11 (19.7%) of them were major DDI, while 14 (25%) of them were moderate, and 26 (46.5%) were minor DDI. Majority of major DDI were by Aspirin + Metformin (10.7%). Whereas Iron sulfate + Omeprazole accounts for 9% of moderate DDI (Table 5).

Table 5: Frequency of major drug interaction in chronic kidney disease patients having follow up at renal clinic of St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, June - August, 2019,

Drug involved in DI	Frequency	Severity	Possible effect
Aspirin + Metformin	6(10.7%)	Major	Risk of hypoglycemia
Aspirin + Furosemide	4(7.1%)	Major	Reduced effectiveness
Allopurinol + Enalapril	1(1.9%)	Major	Risk of hypersensitivity
Iron sulfate + Omeprazole	5(8.9%)	Moderate	Risk of low bioavailability
Iron gluconate + Omeprazole	2(3.6)	Moderate	Risk of low bioavailability
Aspirin + Calcium carbonate	4(7.1%)	Moderate	Reduced effectiveness
Aspirin + Metoprolol	3(5.4%)	Moderate	Risk of hypotension
Iron sulfate + Calcium carbonate	16(28.6%)	Minor	Risk of low bioavailability
Calcium carbonate + iron gluconate	10(17.9%)	Minor	Risk of low bioavailability

4.6. Predictors of Medication Related Problems

The variables that showed an association in uni-variate analysis were occupation, stage of CKD, presence of co morbidities, presence of complications, number of medicine used per patients, ACEIs use, CCB use, iron supplement use, BB use, and phosphate binder use.

Based on the result of uni-variate binary logistic regression analysis, the above variable was included in the multivariate logistic regression analysis. Finally, this study showed that only occupation (AOR=5.2, 95% CI: 1.292-21.288, P=0.020) and ACEIs use (AOR=6.6, 95% CI: 2.202-19.634, P=0.001) showed association with the occurrence of MRP. In multivariate logistic regression analysis, it was found that, those individual who were unemployed were about five times more likely to have MRP compared with who were employed. On the other hand, patients who were not using ACEIs were seven times more likely to have MRP compared to those using ACEIs (Table 6).

Table 6: Univariate and Multivariate analysis of factors associated with MRP among chronic kidney disease patients having follow up at renal clinic of St's Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, June -August, 2019,

Variables	Category	MRP		Crude odd ratio (COR)	Adjusted odds ratio (AOR)	P-value
		Yes	No			
Occupation	Unemployed	86(42.2%)	14(31.8%)	1.8(0.498-6.828)	5.2(1.292-21.288)	0.020*
	Employed	84(41.2%)	27(61.4%)	1	1	
Stage	1	3(60%)	2(40%)	1	1	0.758
	2	13(68.4%)	6(31.6%)	8.2(1.224-54.919)	0.7(0.071-6.861)	
	3	65(71.4%)	26(28.6%)	5.7(1.775-18.152)	0.9(0.196-4.124)	
	4	123(92.5%)	10(7.5%)	4.9(2.236-10.828)	1.1(0.388-3.232)	
Co morbidity	Absent	22(66.7%)	11(33.4%)	1	1	0.694
	Present	182(84.5%)	33(15.5%)	0.4(0.161-0.818)	0.8(0.255-2.481)	
Complication	Absent	61(69.3%)	27(30.7%)	1	1	0.729
	Present	143(89.4%)	17(10.6%)	0.3(0.137-0.528)	1.2(0.419-3.461)	
ACEI use	No	147(72.1%)	9(20.5%)	1	6.6(2.202-19.634)	0.001*
	Yes	57(27.9%)	35(79.5%)	10(4.534-22.182)	1	
No of medication	≤ 3	86(74.8%)	29(25.2%)	1	1	0.849
	≥ 4	118(88.7%)	15(11.3%)	2.7(1.341-5.249)	1.1(0.434-2.760)	

4.7.Examples of medication related problems identified in the study participants

Table 7: Examples of medication related problems identified in chronic kidney disease patients having follow up at renal clinic of St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, June -August, 2019,

No	Description of the MRP	Types of MRP
1	A 50 years old male patient with stage 4 CKD and DM was on amlodipine 5mg, NPH 12/8, calcium carbonate 700 mg, furosemide 80mg bid, epo 400 mcg per week and iron sucrose 200mg. He stops taking his medication since the medication wasn't available.	Non-compliance to iron sucrose Unnecessary therapy of epo with Hg value of 14.7
2	A 55 years old female patient with stage 2 CKD was on enalapril 5mg and furosemide 20mg. sometimes she was taking her medication in every other day manner while she feels intermittent dry cough.	Need additional therapy of statin ADR due to enalapril Non-compliance
3	A 62 years old female patient with stage 3 CKD 2 nd to hypertensive sclerosis with furosemide 60mg, atorvastatin 40mg, vit-D 45,000 iu and amitriptyline 25mg. Her Bp was not controlled with furosemide alone.	Need additional therapy of ACEI
4	A 46 years old male patient with stage 4 CKD 2 nd to DM nephropathy was on furosemide 40mg tid, iron gluconate 300mg 2tab tid, calcium carbonate 500mg bid, omeprazole 20mg bid and NPH.	Unnecessary therapy of omeprazole Dosage too low with drug interaction
5	A 42 years old female patient with stage 4 CKD and HTN was on amlodipine 10mg, atenolol 50mg bid, furosemide 60mg bid and iron sulfate 325 mg bid.	Dosage too low of Feso ₄ (less frequent) Dosage too high of atenolol
6	A 53 years old male patient with stage 4 CKD + HTN nephropathy and DM was on furosemide 40mg, amlodipine 5mg, calcium carbonate 500mg bid and	ADR of metformin (unsafe drug) Need additional therapy of

	metformin 500mg bid. Unfortunately, he didn't took his medication especially night dose because of forgettness.	statin Non-compliance
7	A 56 years male patient with stage 2 CKD 2 nd to DM nephropathy was on nifedipine 40mg bid, metformin 500mg bid and aspirin 81mg. he was a chronic alcohol drinker.	Unnecessary therapy for recreation Ineffective therapy of nifedipine ADR due to drug interaction(aspirin + metformin)
8	A 22 years old male patient with stage 3 CKD + gout and hepatitis B was on enalapril 5mg, calcidilol 0.25mcg, calcium carbonate 500mg and TDF 300mg. He stopped his medication since he couldn't buy it.	Dosage too high of TDF ADR due to drug interaction(allopurinol +enalapril) Non-compliance
9	A 40 years old female patient with stage 4 CKD +DM and HTN was on furosemide 40mg bid, carvedilol 12.5mg bid, calcium carbonate 500mg bid, NPH, aspirin 81mg, amlodipine 5mg and hydrochlorothiazide 12.5mg.	ADR of HCT (unsafe drug) Ineffective therapy due to DDI (aspirin + furosemide)
10	A 35 years old female patient with stage 3 CKD and HTN was on calcium carbonate 500mg, iron sulfat 325mg tid and carvedilol 12.5mg bid. While he was on his medication he complaining of having burning sensation kind of pain on abdomen.	Dosage too low due to DDI feso ₄ + calcium carbonate ADR of iron sulfat

5. Discussion

Chronic kidney patients are at high risk having MRP, owing to the presence of comorbidity, complication and complexity of drug regimen. Presence of MRPs are of a major concern in health care delivery system because of increased burden in cost, morbidity and mortality. Identification of MRP and factors associated with them is critical for the prevention of this problems and improving health outcome. The present study would establish the extent and types of MRPs among adult patients with CKD at outpatient renal clinic, as well as identify various related risk factors contributing to MRPs among those population group.

In this study more than half of the patients were male, which was consistent with study conducted in Addis Ababa (Kore and Hm, 2018) and in India (Castelino, Sathvik, Parthasarathi, Gurudev Mbbs, Shetty Mbbs and Narahari, 2011). The mean ages of the patients were 53 years. This finding was similar with study conducted in Kenya (Njeri, William, Ogallo, Gitonga, Sylvia, Opanga, *et al.*, 2018) as well as India (Ahlawat, D'cruz and Tiwari, 2016).

In the current study, about 53.5% of study participant were under stage 4. However, this finding was higher than what was found in hospital based cross-sectional study in Kenya (Njeri, William, Ogallo, Gitonga, Sylvia, Opanga, *et al.*, 2018). The possible reason could be that early screening and diagnosis were poor in this country.

The present study showed that about 86.7% of the study participant had co-morbidities. But other study, conducted in Nigeria (Adibe, Igboeli and Ukwe, 2017) revealed that 100% of the study participant had co-morbidities. Such difference could be due to that individual prone to co-morbidity were included in Nigerian study. On the other hand those Nigerian study sum up both complication and co-morbidities together as co-comorbid.

In this study a total of 922 medication were used with a mean of 3.7 drugs per patients, which was comparable with other study results (Kefale, Tadesse, Alebachew and Engidawork, 2018)(Adibe, Igboeli and Ukwe, 2017) (Castelino, Sathvik, Parthasarathi, Gurudev Mbbs, Shetty Mbbs and Narahari, 2011). But finding of this study was different from other study conducted in Kenya, where a mean of 4.9 drugs per patient were prescribed. This discrepancy could be due to the fact that patients included in this study were only stage 3 and 4 which was most likely to have more comorbidities as well as complication and need complex regimen.

In our study, the most common documented co-morbidities in the study participant were HTN (37.5%) which was similar finding with studies conducted in India (Sibi, Shareef and Kamath, 2016) (36%). This finding also had consistent result with other research which was conducted in Indonesia (Ramadaniati, Anggriani, Wowor and Rianti, 2016)(Quintana-bárcena, Lord, Lizotte, Berbiche and Lyne Lalonde, 2018).The most likely reason for the hypertension as most commonly occurring co-morbidity is explained by the fact that the renin angiotensin system is affected in the patients of CKD which helps in controlling blood pressure.

This study showed that the most common prescribed class of drug among the study participants was diuretics (70%). This was higher than the study carried out in India (Ahlawat, D'cruz and Tiwari, 2016) which reported it to be as 8.2%. Small value of diuretics use report was seen in one research conducted in Nigeria 11.9% among chronic kidney patients (Onyedikachi, Ogochukwu and Chinwendu, 2017).

About 82.3% of study participants had MRP and 1.6 MRP per patients. This finding was approximately similar to research result conducted in Jimma, which was 78.6% of the participants had MRP with an average 1.9 MRP per patients (Garedow, Bobasa, Wolide, Dibaba, Fufa, Tufa, *et al.*, 2019). The prevalence of MRP reported in the present study was lower than a study conducted in Kenya which stated that 100% of the study participant had MRP (Njeri, William, Ogallo, Gitonga, Sylvia, Opanga, *et al.*, 2018). Such discrepancy was due to first, difference in classification of MRP which includes eight categories which considers inappropriate lab monitoring as MRP, providing large number of MRP. Secondly, nature of study participant recruited in the Kenyan study (only individual with CKD stage 3 and 4 were included in the study). However, this result was higher than other studies done in Nigeria which was 70% (Adibe, Igboeli and Ukwe, 2017). The difference could be attributed to; first in study design (cross sectional vs prospective interventional), secondly difference in stage of CKD patients (in Nigerian study majority of study participants were under stage 3 in contrast to this study). The prevalence MRP with other studies conducted in India and Indonesia were 100% (Castelino, Sathvik, Parthasarathi, Gurudev Mbbs, Shetty Mbbs and Narahari, 2011)(Ramadaniati, Anggriani, Wowor and Rianti, 2016) showed higher result than this study. Such variation could be due to the nature of the study participants (admitted patients undergoing dialysis). Moreover in the Indonesian study more than 80% of the study participants were under

stage 5. In addition small sample size (105 vs 248) and different MRP classification system might be another reason for higher value in Indonesian study.

The commonest MRP encountered in the current study were need additional drug therapy 35.1%. Majority of need additional drug therapy mainly due to lack of preventive drug therapy and presence of untreated condition. This finding was consistent with study conducted in France 32% (Belaiche and Allenet, 2012). Study conducted in Jimma had also similar finding (31%) (Garedow, Bobasa, Wolide, Dibaba, Fufa, Tufa, *et al.*, 2019). However, other study conducted in Kenya, suggested that around 18% of indication without drugs (Njeri, William, Ogallo, Gitonga, Sylvia, Oponga, *et al.*, 2018). This discrepancy might be due to fear of Physician regarding the toxicity effect of drugs, small sample size and different in health care practices.

In the current study, the second most frequently identified types of MRP was non-compliance 16.6%. Around half of non-compliance mainly due to unaffordability (48%) of prescribed medication followed by lack of understanding about drug instruction. These findings can be attributed to failure of the patients to understand their disease process and the merit of compliance to medications as prescribed. This result was consistent with study conducted in Indonesia 19% (Ramadaniati, Anggriani, Wowor and Rianti, 2016). But the study result in this research was higher than the study result which was conducted in Nigeria 4.7% (Adibe, Igboeli and Ukwe, 2017). This might be due to presence of pharmacist service in the setup and low pill burden. Similarly, higher rate of non-compliance were reported in in one study in Saudi 36% (Ibrahim, Hossam and Belal, 2015). This was due to hemodialysis patients were included in the study.

Another MRP identified were unnecessary drug therapy 14.2%. Approximately, 39% of unnecessary drug therapy were due to patient use of medicine for recreation. Drug commonly prescribed without clear indication were proton pump inhibitors and analgesics. This finding was closely related with study conducted in France 12.8% (Belaiche and Allenet, 2012), Indonesia 15% (Ramadaniati, Anggriani, Wowor and Rianti, 2016) and Nigeria 12.2% (Njeri, William, Ogallo, Gitonga, Sylvia, Oponga, *et al.*, 2018). However, Prevalence of unnecessary drug therapy in India were 9.5% (Castelino, Sathvik, Parthasarathi, Gurudev Mbbs, Shetty Mbbs and Narahari, 2011). Such variation might be due to the study design (prospective interventional vs cross sectional) and they didn't include social drug as unnecessary drug therapy which in turn

lower the prevalence. Similarly, study in Kenyatta national hospital identified 9.2% unnecessary drug therapy which was lower than our finding (Njeri, William, Ogallo, Gitonga, Sylvia, Opanga, *et al.*, 2018). This discrepancy could be explained by small sample size (100 vs 248) and lack of follow up in our study.

In the current study, dosage too low accounted 14.2% of all MRP. Around two-third of dosage too low were due to drug interaction which was followed by less frequent administration. Drug commonly identified with dosage too low was iron supplement. This finding was approximately comparable with another study in France 19% (Belaiche and Allenet, 2012) and in Jimma 18% (Garedow, Bobasa, Wolide, Dibaba, Fufa, Tufa, *et al.*, 2019). Conversely, another study conducted in Kenya identified dosage too low accounted for 7% of all MRP (Njeri, William, Ogallo, Gitonga, Sylvia, Opanga, *et al.*, 2018). This difference could be explained by; different MRP classification system, inappropriate drug monitoring and failure of adjusting renal-dosed drugs as per the renal function could be the reason. 5% of dosage too low were identified in study conducted in Nigeria (Adibe, Igboeli and Ukwe, 2017). This variation could be due to less prevalence of anemia as complication (3.3% vs 36.7%). Because in our study medication for anemia treatment took high percentage as cause for dosage too low.

Ineffective drug therapy (11%) was the fourth commonly identified types of MRP. More than half of these problems were due to selection of less effective drugs followed by drug interaction. This was in line with another study conducted in Jimma 10% (Garedow, Bobasa, Wolide, Dibaba, Fufa, Tufa, *et al.*, 2019). But in Iraq higher prevalence of ineffective drug therapy were reported 27.7% (Dlear, Bushra and Kawa, 2015). This difference might be patients with end stage renal failure, on long-term hemodialysis were recruited in the study.

Another MRP identified in this study were adverse drug reaction 7.1%. From this greater than 40% of them were due to drug interaction followed by usage of unsafe drugs. Majority of these drug reactions were potentially harmful to the patient although some of them were documented in the patient's medical records and self-reported by the participants. Similarly, other study identified adverse drug reaction accounted for 9% (Njeri, William, Ogallo, Gitonga, Sylvia, Opanga, *et al.*, 2018). Conversely, around 19% of ADR were identified in other study in India (Castelino, Sathvik, Parthasarathi, Gurudev Mbbs, Shetty Mbbs and Narahari, 2011). The

possible explanation could be the fact that the study in India was carried over nine month period thus provide sufficient time for identifying more ADRs over time and patients on dialysis who were prone for ADR were recruited in the study. In comparison, this finding was lower than the studies conducted in USA 20.7% (Manley, Drayer and Muther, 2003). This variation could be due to long study period (ten months vs three months), good data collecting tool (electronic medical record) and patients on dialysis were recruited in the study.

The least occurring types of MRP were dosage too high which accounted for 1.5% of all MRPs in this study. The reason for the occurrence of dosage too high was due to the failure of adjusting the dose of renally excreted drugs as per renal function. To some extent similar finding were reported in one study conducted in Iraq 0.8% (Dlear, Bushra and Kawa, 2015). In contrast to this, another study conducted in USA identified 20.3% of dosage too high (Manley, Drayer and Muther, 2003). The difference in this prevalence could be explained by that study in USA recruit hemodialysis patients in the study. Because of dialysis treatment those individuals were challenged by pharmacokinetic and pharmacodynamics changes thus likely to have more burdens of dosage too high. And in another study conducted in Jimma, dosage too high accounted for a larger proportion of drug related problems 14.5% (Garedow, Bobasa, Wolide, Dibaba, Fufa, Tufa, *et al.*, 2019). This might be an underestimate due to lack of comprehensive documentation at ambulatory level in this study.

In this study a total of 56 drug-drug interactions were identified. This was lower than study results conducted in India which identified 365 drug-drug interaction (Sibi, Shareef and Kamath, 2016) and in Nigeria (898) (Onyedikachi, Ogochukwu and Chinwendu, 2017). This difference could be explained that Indian study carried out for a long period time (eight months) and majority of the study participants recruited in the study were above the age of 60 years and with CKD stage of 5. Similarly, Nigerian study carried out for a long period of time (four years). Drug interaction is a major factor that may affect patient's clinical outcomes by contributing the increase risk of ineffective drug therapy, suboptimal dose, adverse drug events related hospitalization and a higher health care cost. Based on severity three class of DI were identified in this study, from this 19% of them were major DI, 25% moderate and 46.5% minor. Related to major DI this finding was consistent with study conducted in India which identified major DDI as 20% (Sibi, Shareef and Kamath, 2016). Likewise, other studies also indicated drug-drug interaction as the most prevalent MRPs (Njeri, William, Ogallo, Gitonga, Sylvia, Opanga, *et al.*,

2018). In the current study majority of DDI was Iron supplement + Calcium carbonate followed by Aspirin + Metformin.

Identification of the risk factors for MRPs is important, as it helps to identify the most susceptible patient and put recommendation for those who need close monitoring of drug therapy. The result of this study showed that occupation and ACEIs use have statistical association with the occurrence of MRP among CKD patients which is different from most findings (Garedow, Bobasa, Wolide, Dibaba, Fufa, Tufa, *et al.*, 2019)(Njeri and Fulfilment, 2018b) where occupation and ACEIs use were not an independent predictor of MRPs. Previous study identified different factors that are associated to occurrence of MRPs among those populations. For example, one study in Jimma identified that marital status, polypharmacy and number of complication had significant association with occurrence of MRP. Another study Kenya identified; number of co morbidities, stage of CKD, and number of medication as a predictors of MRP. This discrepancy might be due to difference in health care delivery system, factors related to disease (average number of co morbidities; 4.9 vs 1.25), average number of medication (9.3 vs 3.7), and factors related to the participants.

6. Limitation of the Study

- This was a cross-sectional study that didn't allow to follow patient condition prospectively.
- When identifying ADR no causal relationships were established. It was retrieved from medical records and patients interview
- Since laboratory values were not updated in regular basis, it was very difficult to assess disease progress.

7. Conclusion

Our study identified that medication related problems experienced by each chronic kidney disease patients were high. In terms of types of MRPs, need additional drug therapy was frequently identified types of MRP followed by non-compliance, ineffective drug therapy, dosage too low, unnecessary drug therapy, adverse drug reaction and dosage too high. Majority of need additional drug therapy problems were due to absence of preventive drug therapy whereas unaffordability of medication was the main cause for non-compliance. In the other hand selection of less effective drugs was the common cause for ineffective drug therapy problem. Drug interaction was mostly identified cause for both ADR and dosage too low. There was a significant association between occupation and ACEIs use with the occurrence of MRP.

8. Recommendation

- There should be clinical pharmacy service for provision of pharmaceutical care in this clinic to make sure that early prevention, detection and resolution of MRPs.
- There should be patient education program to improve continuous patient compliance to their medication
- Potential drug-drug interaction should be checked
- Comprehensive guideline should be prepared for management of chronic kidney disease
- Further studies with a follow up of patients with intervention should be considered

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10. Annex

Annex 1: English version of information sheet

Dear participant, Good Morning/Afternoon

Introduction

My name is----- I am a member of the study that is carried out at St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, entitled "Assessment of medication related problems and contributing factors among ambulatory Chronic Kidney Disease patients in St's Paul's Hospital Millennium Medical College" The study is being conducted by Mr. Eshetu Shiferaw from Addis Ababa University, school of Pharmacy, department of clinical Pharmacy and Pharmacology, post graduate program.

Objective

The main purpose of this study is to assess medication related problems and contributing factors among ambulatory Chronic Kidney Disease patients in St's Paul's Hospital Millennium Medical College. Your input will be extremely valuable as the information will be used to identify medication related problem

Significance

The result of the study will provide valuable insights for the healthcare professionals and policy makers about the prevalence of medication related problems and predictive factors and can also be used as base line information for further similar studies.

Expected Outcomes and/or Benefits

At the end of the study, medication related problems and associated factors will be evaluated. Therefore, the study will identify and investigate the main gaps associated with prevalence of such problem and will propose possible recommendations that may benefit you directly or indirectly by improving chronic kidney disease treatment.

If you have any questions concerning the study, please call Eshetu Shiferaw (+251) 913651239.

Thank you for your time

Annex 2: English version of informed consent form

The study is being conducted by Mr. Eshetu Shiferaw from Addis Ababa University, College of Health Sciences, School of Pharmacy, department of clinical Pharmacy and Pharmacology, post graduate program. The study will be conducted by interviewing and reviewing your medical chart. Therefore I am kindly requesting you to take part in this study by allowing your medical data to be included in the study. The interview will take 5-10 minutes. Your name will not be written in the data collection form and will never be used in connection with any information you tell us. There is no risk associated with participating in this study. All information regarding your medical condition will be kept strictly confidential. Your participation is voluntary and you are not obligated to participate in the study. If you feel discomfort with study, it is your right to drop it anytime you want. If you have questions regarding this study, please feel free to contact the principal investigator via her address.

Eshetu Shiferaw, Tell: +251- 913651239

e-mail: eshe.j19@gmail.com

Signature of respondent:

Signature of interviewer:

Thanks for your time

Annex 3: Data abstraction format from patient interviews

Code of Participant.....

I. Socio demographic Data

A. Age -----

B. Gender : Male Female

C. Weight: -----

D. Height: -----

E. Marital Status:

Single separated married divorced widowed

II. Family History

F. What is the patient’s relevant family history?

.....

III. Social History

G. What is the patient’s social history? Please fill in the space below

Occupation	Unemployed <input type="checkbox"/> employed <input type="checkbox"/> retire <input type="checkbox"/>
Income/month	<500 <input type="checkbox"/> 500-1000 <input type="checkbox"/> 1000-3000 <input type="checkbox"/> 3000-6000 <input type="checkbox"/> >6000 <input type="checkbox"/>
Education	Illiterate <input type="checkbox"/> primary <input type="checkbox"/> secondary <input type="checkbox"/> college and more <input type="checkbox"/>
Religion	Orthodox <input type="checkbox"/> Muslim <input type="checkbox"/> catholic <input type="checkbox"/> protestant <input type="checkbox"/>
Alcohol intake	Yes <input type="checkbox"/> No <input type="checkbox"/>
Smoking	Yes <input type="checkbox"/> No <input type="checkbox"/>

IV. MRP reported by the patients

H. Does the patient have trouble using his/her medicine? Yes No

If yes, briefly state their concern below

.....

I. Does the patient have trouble in understanding or remembering how to take his/her medicine? Yes No

If yes, please list the problems they encounter in the space below

.....
.....

J. Do any patient's medication make him/her feel unwell? Yes No

If yes, please indicate how they feel when they take medicine below

.....
.....

K. Does he/she sometimes stop taking his/her medicine? Yes No

If yes, please indicate when they cease, lead them to stop taking medicine

.....
.....

L. Does the patient feel like he/she is taking too many drugs? Yes No

If yes, please indicate their major concern in the space below

.....
.....

M. Does the patient feel like the medicine he/she is taking is making him/her feel better?

Yes No

If No, please indicate what they feel and which medicine make them feel that way in the space below

.....
.....

N. Does the cost of patient's medicine make it hard for his/her to take it as prescribed?

Yes No

If yes, please state which medicine they have missed because they find them expensive below

.....
.....

Annex 4: Data abstraction format from patient medical chart

V. Chief Complaint

O. What is the patient’s chief complaint?

.....

.....

.....

VI. History of Present Illness

P. What is the patient’s history of present illness? (pertinent)

.....

.....

.....

VII. Past Medical History

Q. What is the patient past medical history? State briefly below

.....

.....

VIII. Medication History

R. What is the patient past medical history? Please conduct comprehensive past medication history and fill in the table below

Medicines /dose	Indication	Duration (date)		Comment (outcomes, allergy. ADR)
		Start	Stop	
Allergy:				
Current medication history: prescription and non-prescription				

Past medication history: prescription and non-prescription				
Home remedies/herbal preparation/dietary supplements				

S.

T. Please conduct a comprehensive review of systems. Are there any significant findings on the review of systems in relation to pharmacotherapy?

Yes

No

If yes, briefly clarify it below

.....

.....

.....

.....

IX. Investigation

U. Have any investigation been carried out? Please fill the result below

Test/investigation	Date carried out	Value	Comment (normal vs abnormal)
Vitals			
HR			

BP			
RR			
Body T ^o			
Blood analysis			
RBC			
Hb			
MCV			
WBC			
Neutrophils			
Lymphocytes			
Monocytes			
Eosinophils			
Coagulation			
Prothrombin time			
APTT			
INR			
Electrolyte			
Na ⁺			
K ⁺			
Mg ²⁺			
Cl ⁻			
Urea			
Cr			
Clcr			
Ca ²⁺			
PO ₄ ⁻			
LFTs			
AST			
ALT			
GGT			

ALP			
Alb			
Total bilirubin			
BGA			
PH			
PO2			
PCO2			
HCO-3			
Blood glucose			
RBS			
FBS			
HbA1c			
Lipid profile			
LDL			
HDL			
Triglyceride			
Others			
CxR			
ECG			
Urinalysis			
HIV			
HBV			
HCV			

X. Diagnosis

V. What is the current working diagnosis or confirmed diagnosis? Briefly state below

Diagnosis	Comment
.....
.....
.....

.....
-------	-------

Annex 5: MRPs Registration Format

I. Prevalence of MRP

A. Did the patient have any MRPs? Yes No

If yes, please elaborate by filling the section below

II. Classification

B. Please classify the MRP(s) in the categories provided below. Please justify by providing comment. Also state the medicine involved.

Classification of MRP	Comment	Medicine involved	
Unnecessary Drug Therapy			Medicine for recreation
			Medicine for treating side effect
			Drugs without indication
			Duplicate therapy
Need Additional Drug Therapy			Preventive drug therapy needed
			Untreated condition
			Synergistic therapy
Ineffective Drug Therapy			Not the most effective drugs
			Drug interaction
Dose Too Low			Drug interaction
			Less frequent administration
			Low dose
			Short duration
Adverse Drug Reaction			Cause undesirable effect
			Unsafe drugs
			Drug interaction
			Incorrect administration
Dose Too Low			High dose
			More frequent

የአወሳሰድና የአጠቃቀም ክህሎትና

የእርስዎን እርካታን ይጠናሉ። በተጨማሪም ከጥናቱ በሚገኙ ግኝቶች የልብሀክምና ዉጤትን በተወሰነ መልኩ ለማሻሻል

እንደሚቻል በመገመት፤ እርስዎ የጥቅሙ ቋሚ ስህተት ይሆናሉ ብለን እናምናለን። ጥናቱ የሚከሄደው የህክምና ካርድዎንና

በመከለስና በቃለ መጠይቅ ነው። ስለዚህ የእርስዎ ቅንና ሓቀኛ መረጃ ለጥናቱ እጅግ በጣም ወሳኝ ነው።

ቅጽ 2: በቃለ መጠይቅ ለመሳተፍ የፈቃደኝነት ቃል መቀቢያ ቅጽ

በዚህ ጥናት የእርስዎ መረጃ መላ በመላ በምስጢር የተጠበቀና ለምርምር አላማብቻ የሚውል ነው። በተጨማሪም የእርስዎ

ተሳታፊነት በፈቃደኝነት የተመሠረተ ነው። የጥናቱ አላምውን ተረድተውና ጊዜዎን ሰውተው፤ ከ 5-10 ደቂቃ ለሚፈጅ ቃለ -

መጠይቅ መረጃ ለመስጠት ፍቃደኛ በመሆንዎ በቅድሚያ አመሰግናለሁ።

በየትኛውም ጊዜ ጥያቄ ካለዎት በስ.ቁ +251913651239 ወይም

በኢ-ሜይል: eshe.j19@gmail.com

ቅ ጽ 3: