ISSN: 2689-8616

Research Article

Advancements in Journal of Urology and Nephrology

Risk Factors of Chronic Kidney Disease Among Patients Attending at Dessie Comprehensive Specialized Hospital, Dessie, Amhara Region, Northeastern Ethiopia: Unmatched Case–Control Study

Abdusellam Yimer[1*], Bilal Mohammed[2], Welde Melese[3], Reta Dewau[3], Wondwosen Mebratu[3], Abel Endawkie[3], Jemal Seid[4] and Ali Hassen[5]

[1]*Department of Midwifery, College of Medicine and Health Sciences, Dire Dawa University, Ethiopia.*

[2]*Department of Epidemiology and Biostatistics, Amazon Medium Clinic, Ethiopia*

[3]*Department of Epidemiology and Biostatistics, School of Public Health, College of Medicine and Health Sciences, Wollo University, Ethiopia*

[4]*Department of Psychiatry Nursing, College of Medicine and Health Sciences, Wollo University, Ethiopia*

[5]*Department of Surgery, School of Medicine, Wollo University, Ethiopia*

[*]Corresponding Author
Abdusellam Yimer, Department of Midwifery, College of Medicine and Health Sciences, Dire Dawa University, Ethiopia.

Submitted: 2024, Apr 22; **Accepted:** 2024, May 23; **Published:** 2024, May 31

Citation: Yimer, A., Mohammed, B., Melese, W., Dewau, R., Mebratu, W., et al. (2024). Risk Factors of Chronic Kidney Disease Among Patients Attending at Dessie Comprehensive Specialized Hospital, Dessie, Amhara Region, Northeastern Ethiopia: Unmatched Case–Control Study. *Adv J Uro Nephro, 6*(1), 01-14.

Abstract

Introduction: *The incidence of chronic kidney disease is rising, primarily due to its asymptomatic nature of the disease and poor access to early detection and management services. In Ethiopia, little is known about the context-specific risk factors. This study aimed to identify the risk factors of chronic kidney diseases in Northeast Ethiopia, focusing on patients attending Dessie Comprehensive Specialized Hospital, in 2022.*

Methods: *A hospital-based unmatched case-control study was employed among chronic kidney disease patients at Dessie Comprehensive Specialized Hospital, from May 10 to July 15/2022. Cases were all patients who were diagnosed with chronic kidney diseases at Dessie Comprehensive Specialized Hospital while controls were patients without chronic kidney diseases. For each case, two controls were selected using a systematic random sampling technique. A semi-structured interviewer-administered questionnaire with the support of a document review was used to collect the data. The data were entered into Epi data version 4.6 and exported to Stata version 14 software for analysis. During bivariable logistic regression analysis, variables having p-value <0.2 were entered and analyzed by multivariable logistic regression analysis to identify risk factors associated with chronic kidney diseases. Statistical differences were considered at $P < 0.05$, and the strength of association was assessed by adjusted odds ratio and respective confidence intervals.*

Results: *A total of 78 cases and 156 controls were included in this study. This study revealed that factors such as being male [AOR: 2.54, 95%CI (1.125- 5.754)], the presence of hypertension [AOR: 5.33, 95%CI (2.107-13.489)], diabetic-mellitus [AOR: 3.64,95%CI (1.530- 8.671)], kidney stone [AOR: 3.91,95%CI (1.492-10.257)], and underground water source usage [AOR: 2.63,95%CI (1.108-6.262] were statistically significantly associated factors with chronic kidney diseases.*

Conclusion: *In our study, being male, the presence of hypertension, diabetic mellitus, diagnosis of a kidney*

stone, and underground water usage were independent risk factors for chronic kidney diseases. Therefore, policymakers, healthcare providers, and other stakeholders should emphasize the aforementioned factors to forestall the development and progression of the disease. Furthermore, routine urinalysis and glomerular filtration rates for all hospitalized patients with hypertension and diabetes-mellitus could help to detect chronic kidney diseases at an early stage.

Keywords: Chronic Kidney Disease, Risk Factors, Unmatched Case-Control Study, Dessie, Ethiopia

Abbreviations

CKD: Chronic Kidney Disease
CKD: Epi - Chronic Kidney Disease Epidemiology Collaboration
CVDs: Cardiovascular Disease,
DM: Diabetic Mellitus
DCSH: Dessie Comprehensive Specialized Hospital
ESRD: End Stage Renal Disease
GFR: Glomerular Filtration Rate
HIV: Human Immune Deficiency Virus
HTN: Hypertension
KDOQI: Kidney Foundation Disease Outcomes Quality Initiative
LMIC: Low- and Middle-Income Countries
NGOs: Non-Governmental Organizations
NCDs: Non-Communicable Disease
OPD: Outpatient Department
OTC: Over-counter Medications
RRT: Renal Replacement Therapy
SDG: Sustainable Development Goal
UTI: Urinary Tract Infections

1. Introduction

1.1. Background

Chronic kidney disease is defined as structural and functional kidney abnormalities or Glomerular Filtration Rate <60 ml/min/1.73m2 for more than 3 months [1]. When these structural changes, it become conspicuous and result in a decrease in the kidney's ability to process wastes in the blood and perform other functions. During early stages, patients may present with average or slightly decreased Glomerular Filtration Rate and albuminuria [2-6]. According to Kidney Foundation Disease Outcomes Quality Initiative (KDOQI) Chronic kidney disease is divided into five stages from mild kidney dysfunction to complete failure [7]. Generally, a person with stage 3 or 4 of chronic kidney disease (CKD) is considered to have moderate to severe kidney damage. Stage 3 is broken up into two levels of kidney damage: 3A) a level of Glomerular Filtration Rate (GFR) between 45 to 59 ml/min/1.73 m2, and 3B) a level of GFR between 30 and 44 ml/min/1.73 m2. In addition, GFR for stage 4 is 15–29 ml/min/1.73 m2 [7,8]. Later, it leads to end-stage renal disease. Once the kidneys are starting to fail, whichever of symptoms like itchy skin, vomiting, nausea, not feeling hungry, too much or inadequate urine, trouble catching breath and trouble sleeping, edema of feet and ankles, and muscle cramps will be manifested [9].

A diagnosis of CKD is defined as the presence of decreased GFR below 60 mL/min per 1.73m2, or GFR above 60 mL/min per 1.73 m2, but with markers of renal damage, as determined by the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) equation and at least one of the following: 1) Contracted kidneys, hypo-echoic kidneys or loss of corticomedullary differentiation on renal imaging; 2) Serum phosphate levels above 1.4mmol/l; 3) Serum calcium level below 2.2mmol/l; 4) History of kidney transplantation; 5) History of documented kidney dysfunction for more than 3 months; 6) Anemia of chronic disease (normochromic, normocytic, hyperproliferative picture), with a hemoglobin level of <10/dl [10,11].

Worldwide, the overall prevalence of CKD stages (1-5) ranges from 4.6% up to 15.8% in the general population [12]. The annual incidence rate is reached 8% [13]. Kidney disease is the ninth leading cause of death in the United States [14]. A meta-analysis report in Mexico revealed that between 1990 and 2017, the global standardized mortality rate increased by 41.5%, jumping from 11.4 to 16.1 deaths per 100,000 inhabitants [15]. A meta-analysis report in Africa revealed that of all the chronic non-communicable diseases, CKD has had one of the most rapid recent increases in Africa and its prevalence ranges from 6.1% up to 16% [16]. The burden of CKD has been increasing in sub-Saharan Africa, the overall prevalence is significantly higher compared to North Africa for CKD stages 1–5 [16]. Nearly a quarter (13.2%) of the sub-Saharan population has CKD [17]. Though the problem is preventable, the prevalence of CKD in our country Ethiopia has been increasing in the last few years following an increasing prevalence of diabetes, cardiovascular disease, and hypertension, and its prevalence is estimated to be 12.2% [18].

Prior researchers confirmed that age, sex, family history of kidney disease, primary kidney disease, urinary tract infections, cardiovascular disease, hypertension, diabetes mellitus, nephrotoxins (non-steroidal anti-inflammatory drugs, antibiotics), the consumption of energy drinks, drug misuse and adulteration of chemical substances into herbal medicines are Statically significant associated factors of CKD [14,16,19-22]. Nevertheless, in a study of CKD determinants like chat chewing, and HIV AIDS status, sources of water use-related variables were not well studied.

To address the CKD problem of Ethiopia sustained efforts from nongovernmental organizations (NGOs), governmental agencies, the pharmaceutical industry, and medical training programs are needed [23]. Even though there are shreds of evidence suggesting the high burden of CKD in Ethiopia it is concealed behind statistics [24]. Moreover, the existing data are hampered by the poor quality that limits inferences. Studies about CKD are almost non-existent and its determinants remain unknown Further, with the existence of low or no dialysis/kidney replacement infrastructure, strong evidence-based prevention interventions are recommended.

Hence, in Ethiopia prevention and early detection of CKD to slow its progression are of paramount importance. Therefore, this study aimed to identify the determinants of chronic kidney disease among patients attending Dessie's comprehensive specialized hospital.

2. Methods

2.1. Study Setting, Design, and Period

The study was conducted in Dessie Comprehensive Specialized Hospital, Dessie town, Amhara region, Northeast Ethiopia. A Hospital-based unmatched Case-control study was conducted during the study period from May 10 to July 15, 2022.

2.2. Sample Size Determination and Sampling Procedure

2.2.1. Sample Size Determination

The sample size was calculated by considering the following assumptions; 95% confidence level 80% power, 34.3% proportion of hypertension in a previous study, adjusted odds ratio of 2.39, 10% non-response rate, and 2:1 control to case ratio [25]. Using unmatched case-control in Epi info version 7.2.2.6 software Stat Calc. Based on the above assumptions the estimated optimal sample size used for this study was 234 (156 controls and 78 cases).

2.2.2. Sampling Technique and Procedure

All cases with confirmed CKD disease by urologist and full-filling case selection criteria as indicated from their medical record and at the time of data collection were included in the study until the total sample size was obtained. Primarily, patients with CKD in the hospital were small in number, thus all the available cases were considered to be included in the study. Controls were selected by a systematic random sampling method to get the required sample of controls. The average estimated total urological cases without including CKD in the total study period using average weekly urological patient flows of May 2022 was 333 and Kth interval from N/n = 333/156=2.13~ 2. Controls were selected by every 2 intervals and the first study subject of control was determined daily and selected by lottery method using the medical record number of patients. On a daily base, control was selected proportionally for cases based on control to-case ratio until the required number of cases was obtained.

2.2.3. Study Variables

Dependent Variable

• **Chronic Kidney Diseases** (Yes/No)

Independent variable

• **Socio-Demographic Characters:** like age of patients, sex, place of residence, educational level, occupation, and income

• **Comorbidities:** like diabetes mellitus, hypertension, CVD, HIV/AIDS, kidney stones, recurrent urinary tract infection, family history of chronic kidney diseases, history of burns, anemia

• **Behavioral and Lifestyle Factors:** Smoking, Alcohol drinking Chat chewing, physical exercise, consumption of unhealthy drinks and diet, and Consumption of over-the-counter medications.

2.2.4. Operational Definitions

• **Chronic Kidney Disease (CKD):** is defined as structural/functional abnormalities of the kidney or decreased GFR <60 ml/min/1.73m2 for more than 3 months [17]. According to the Kidney Foundation Disease Outcomes Quality Initiative (KDOQI), CKD is divided into five stages of kidney damage, from mild kidney dysfunction to complete failure [7]. Generally, a person with stage 1(GFR > 90 ml/min/1.73 m2) is considered to be normal, stage 2 (GFR between 60-89 ml/min/1.73 m2) which is mild, additionally CKD is considered as having moderate to severe kidney damage. Stage 3 is further broken up into two levels of kidney damage: 3A) a level of GFR between 45 to 59 ml/min/1.73 m2, and 3B) a level of GFR between 30 and 44 ml/min/1.73 m2. In addition, GFR for stage 4 is 15–29 ml/min/1.73 m2 later, it leads to end-stage renal disease (ESRD) [7,8].

• **End-Stage Renal Disease (ESRD):** kidney failure is defined as a GFR<15 mL/min/1.73 m^2 or very high albuminuria (>300 mg albumin/24 h) [12,13]. ESRD is irreversible and fatal unless treated by dialysis or kidney transplant [3-5]. Indicating that the kidney has stopped working permanently.

• **Glomerular Filtration Rate (GFR): i**s a measure of how well kidneys are cleaning blood-taking out extra water and waste. Specifically, it estimates how much blood passes through the glomeruli each minute [26]. It is central to the diagnosis and management of Chronic Kidney Disease and accepted as the best overall measure of kidney function. GFR can be calculated from standardized serum Creatinine and estimating equations, such as the Modification of Diet in Renal Disease (MDRD), Study equation CKD-EPI, or the Cockcroft-Gault formula [27]. The severity of kidney disease can be classified into five stages according to the level of GFR which is given as: According to Kidney Foundation Disease Outcomes Quality Initiative (KDOQI).

• **The CKD-EPI:** equation, expressed as a single equation, is: GFR = 141 * min(Scr/κ,1)α * max(Scr/κ, 1)-1.209 * 0.993Age * 1.018 [if female] * 1.159 [if black] Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1[10].

• **Diabetic Mellitus:** defined as random blood sager >200mg/dl or FBS> 126mg/dl and/or self-reported on anti-hyperglycemic medication [28].

• **Hypertension;** defined as a systolic (SBP) ≥140 mmHg and/or diastolic blood pressure of (DBP) ≥90 mmHg or self-reported on anti-hypertension drugs [28].

• **Renal Replacement Therapy:** a therapy that replaces the normal blood-filtering functions of kidneys are used when the kidneys are not working well [29].

• **Hemodialysis:** a type of treatment that filters the blood through a machine. It Removes harmful waste and extra fluids the body no longer needs. Also, hemodialysis helps control blood pressure, and balance potassium, sodium, calcium, and bicarbonate [30].

• **Over-The-Counter Medicine (OTC):** defined as nonprescription medicine, that can buy without a prescription including NSAID and some other commonly used drugs and herbal medications to treat aches and pains [31].

• **Ever Chat Chewer:** defined as a respondent who chewed chat

during his lifetime [32].

• **Sufficient Salt Intake**: individuals who take no more than 6g of salt a day (2.4g sodium) which is equivalent to one teaspoon [33].

• **Sufficient Fat Intake:** individuals who take up to 35% of the calories from fat that is equivalent to 97 grams in a 2500-calorie diet [33].

• **Sufficient Sugar Intake:** an individual who consumes no more than 150 discretionary calories of sugar is equivalent to 38 g or 9 teaspoons (tsp) of sugar per day for men and no more than 100 discretionary calories of sugar equivalent to 25 g or 6 tsp of sugar per day for women [34].

• **Significant Alcohol Intake:** individuals who take more than 2 standard drinks of alcohol for males and more than 1 per day for females. For E.g. 1 standard drink standard bottle of regular beer and the net alcohol content of a standard drink is approximately 10g of ethanol [35].

• **Sufficient Physical Exercise:** Adults doing at least 150–300 min of moderate-intensity aerobic physical activity per week [33].

• **Ever Smoker:** A person who has ever been a cigarette smoker or cigar smoker [34].

• **Underground Water:** These are sources of water found beneath the land surface it including springs and wells [36].

2.2.5. Data Collection Tools and Procedures

Data were collected using a semi-structured interviewer-administered questionnaire with support of medical records review to address all important variables using their medical record numbers when they return to the outpatient department for a checkup. The questionnaire was adapted from different literature and guidelines developed for a similar purpose by a different author.

Two data collectors and one supervisor were recruited and trained on how to collect data and check the completeness of data and training was given by the principal investigator for one day. There was continuous supervision by the principal investigator and trained supervisor.

2.2.6. Data Quality Control

The questionnaire was originally prepared in English and it was translated to local language (Amharic) for the purpose of data collection and then translated back to English by language experts to ensure its correctness and consistency. Two weeks before the commencement of the study, the semi-structured interviewer-administered questionnaires were pre-tested among 5% (4 cases and 8 controls) of a total of 12 samples in Kombolcha General Hospital by their local languages to prevent information leakage for the purpose of checking whether questions are clear or not, then after necessary corrections were done for unclear questions based on the pretesting findings. Internal consistency of the data was checked using Cronbach's alpha with a value of 0.75.

2.2.7. Data Management and Statistical Analysis

After the data were checked for completeness and consistency, coded and entered into Epi data version 4.6 software. Finally, the data were exported to and analyzed by STATA version 14 software. Descriptive statistics like frequencies and percentages were calculated to see the distribution of the variable.

To find out the risk factors of CKD, first bivariable logistic regression was conducted and variables having a P-value of < 0.2 were entered in multivariable logistic regression analysis to control the possible confounders. Finally, variables in the multivariable logistic regression analysis having a P-value of <0.05 and the corresponding AOR with 95% confidence level was declared as a statistically significantly associated variables with CKD. To check co-linearity between risk factors, tolerance and variance inflation factors (VIF) were used. The Hosmer–Lemeshow test for the model was checked to assess whether the necessary assumptions for the application of multiple logistic regression are fulfilled or not.

2.2.8. Ethical Consideration

Ethical clearance was obtained from the Institutional Research Ethical Review Committee (IRERC) of Wollo University, College of Medicine and Health Sciences ethically approved the study with a letter reference number (CMHS/345/2022 on the date of 23/04/20222). The procedure and purposes of the study were explained to Dessie's comprehensive specialized hospital. A letter of support was then obtained from Dessie Comprehensive Specialized Hospital with a letter reference number (DCSH-2/742/2022 on the date of 03/05/2022). Then permission and support letters were written to the medical ward department. Clients were asked for their consent verbally to confirm their willingness to participate in the study. Before enrolling any of the eligible study participants, the purpose, benefits, and confidential nature of the study were described and discussed with each participant. Confidentiality was ensured by omitting the names of the respondents from the questionnaire. Only those that consented and proved their willingness to take part in the study were enrolled in the study. The importance of medical check-ups, early detection, prompt medical management, nutrition relevance to CKD, and lifestyle modifications were provided by the data collectors during the data collection period.

3. Results

3.1. Socio-Demographic Characteristics

A total of 234 study participants (78 cases and 156 controls) were enrolled in the study making the response rate of 99% and 100% respectively. Of these, 26(33.33%) of the cases and 70(44.87%) of the controls were females. The mean age of cases and controls was 52(±14SD) and 47(±17SD) respectively. Twenty-six (33.33%) of the cases and 37 (23.72%) of the controls were above 60 years of age. Forty-two (53.85%) of case and 89 (57.05 %) of controls were live in rural area. Eighteen (23.08 %) of the cases and 28 (17.95 %) of the controls were unable to read and write. Four (5.13%) of the cases and 29(18.59%) of the controls had tertiary and above educational level. In regard to occupational status 37 (47.44 %) of cases and 58 (37.18%) of controls were self-employed, while 5 (6.41%) of cases and 20(12.82%) of controls were governmental workers. The mean monthly household income in ETB for cases and controls were 2588 and 3490 with standard deviations of ±

2243 and ± 2605 respectively (See Table 1 for detail).

Characteristics	CKD	
	Cases N (%)	Controls N (%)
Sex		
Male	52(66.67)	86 (55.13)
Female	26(33.33)	70 (44.87)
Age		
18-30	6 (7.69)	37 (23.72)
31-40	14 (17.95)	29 (18.59)
41-50	20 (25.64)	29 (18.59)
51-60	12 (15.38)	34 (21.79)
60+	26 (33.33)	27 (17.31)
Religion		
Orthodox	29 (37.18)	70 (44.87)
Muslim	47 (60.26)	76 (48.72)
Protestant	2 (2.56)	10 (6.41)
Residence		
Urban	36 (46.15)	67 (42.95)
Rural	42 (53.85)	89 (57.05)
Marital Status		
Single	3 (3.85)	31 (19.87)
Married	53 (67.95)	79 (50.64)
Divorced	13 (16.67)	20 (12.82)
Widow/widower	9 (11.54)	26 (16.67)
Educational Status		
Cannot read and write	18 (23.08)	28 (17.95)
Primary education (1-8)	46 (58.97)	73 (46.79)
Secondary education (9-12)	10 (12.82)	26 (16.67)
Tertiary education (>12)	4 (5.13)	29 (18.59)
Occupational Status		
Unemployed	36 (46.15)	78 (50.00)
Self employed	37 (47.44)	58 (37.18)
Governmental worker	5 (6.41)	20 (12.82)
Average Monthly Income		
<500	2 (2.56)	4 (2.56)
500-1000	32 (41.03)	34 (21.79)
1000+	44 (56.41)	118 (75.64)
Key: Average Monthly Income in Ethiopian Birr		

Table 1: Socio-Demographic Characteristics of Study Participants Who were Attending Dessie Comprehensive Specialized Hospital, Ethiopia, 2022

3.2. Comorbidity Related Variables

Among the study participants, 65(83.33%) of cases and 49(31.41%) of controls had anemia. The mean hemoglobin level of participants among cases and controls was 10.2(±2.5SD) and 13.6(±2SD) respectively. The mean creatinine level of study participants among cases and controls was 3.26 and 0 .88 with a standard deviation of ± 2.1 and ±0.5 respectively. About 52 (66.67%) of cases and 44 (28.21%) of controls had hypertension. Among the participants, 25(48.08%) cases and 21(47.73%) controls had hypertension of fewer than five-year duration. Thirty-two (41.03%) of the cases and 24(15.38%) of controls had diabetes mellitus, of which 14 (43.75%) of the cases and 14(58.33%) of controls had diabetes mellitus less than five years duration. About Fifth-nine (75.64%) of cases and 73(46.79%) of controls had cardio-respiratory diseases. Forty-two (53.85%) of cases and 95(60.90%) of controls had a history of burn. More than one-tenth (15.38) of cases and 26(16.67%) of controls live with HIV/AIDS. Roughly 64(82.05%) of the cases and 78(82.05%) of controls had a history of kidney stones. similarly, this study revealed that about twenty-five (32.05%) of cases and 32(20.51%) of controls had a family history of kidney disease (See Table 2 for details).

Characteristics	CKD	
	Cases N (%)	Controls N (%)
Anemia		
Yes	65(83.33)	49(31.41)
No	13(16.67)	107(68.59)
Hypertension		
Yes	52(66.67)	44(28.21)
No	26(33.33)	112(71.79)
Durations of HTN		
<5 years	25(48.08)	21 (47.73)
5-10 years	12(23.08)	17(38.64)
>10 years	15(28.85)	6(13.64)
Diabetes Mellitus		
Yes	32(41.03)	24(15.38)
No	46(58.97)	132(84.62)
Durations of DM		
<5 years	14(43.75)	14(58.33)
5-10 years	8(25.00)	6(25.00)
>10 years	10(31.25)	4(16.67)
Cardio-Respiratory Diseases		
Yes	59(75.64)	73(46.79)
No	19(24.36)	83(53.21)
Burn		
Yes	42(53.85)	95(60.90)
No	36(46.15)	61(39.10)
HIV/AIDS		
Yes	12(15.38)	26(16.67)
No	66(84.62)	130(83.33)
Durations of HIV/AIDS		
<5 years	2(16.67)	8(30.77)
5-10 years	2(16.67)	5(19.23)
>10 years	8(66.67)	13(50.00)
Kidney Stone		
Yes	64(82.05)	78(50.00)

No	14(17.95)	78(50.00)
Recurrent UTI		
Yes	58(74.36)	90(57.69)
No	20(25.64)	66(42.31)
Family History of Kidney Disease		
Yes	25(32.05)	32(20.51)
No	53(67.95)	124(79.49)

Table 2: Comorbidity-Related Factors of Study Participants Who were Attending at Dessie Comprehensive Specialized Hospital, Dessie, North-East of Ethiopia, 2022

Among 78 cases who participated in this study, 32(13.67%) were in stage 3B (30-44) or had a moderate decrease in glomerular filtration rates. About 21(8.8%) of cases were on stage 4 or had a severe decrease in GFR. Ten (4.27%) of cases were on stage 3A (45-59) or had a mild to moderate ecrease in GFR. About 15(6.4%) of cases reached the end stages of renal diseases (ESRD) or had GFR < 15 with or without dialysis (See Figure for detail).

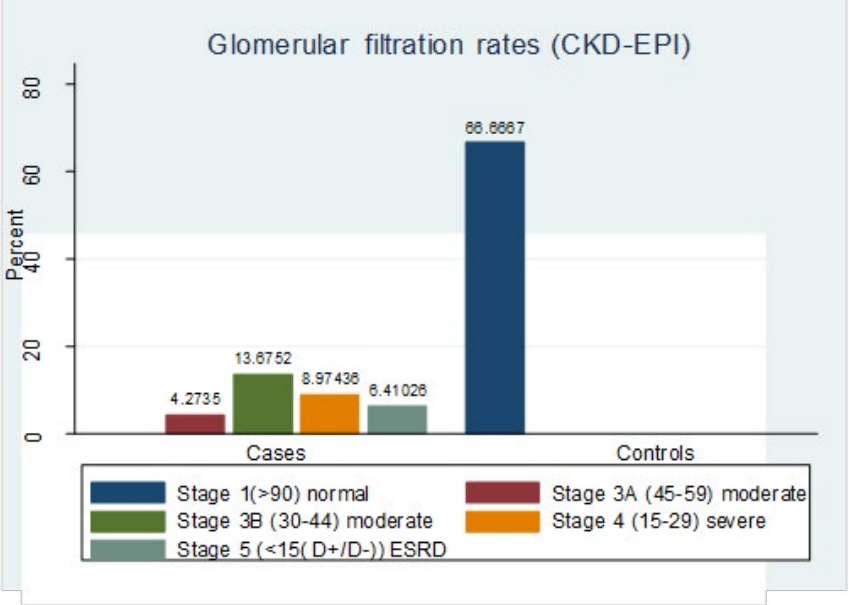

Figure: Distribution of CKD by CKD-EPI Stage Classification

3.3. Lifestyle and Behavioral Factors

Among interviewed study participants, 26(33.33 %) of cases and 20(12.82 %) of controls had a history of cigarette smoking. About 42(53.85%) of cases and 72(46.15%) of controls had a history of chat chewing. Seventy-five (96.15%) of cases and 111(71.15 %) of controls consumed high in salt foods, whereas 74(94.87%) of cases and 104(66.67%) of controls consumed high in fat foods. About 37 (47.44%) of cases and 58 (37.18%) of controls had a history of alcohol drinking. About 70(89.74%) of cases and 89(57.05%) of controls used Non-steroid Anti-inflammatory drugs as a means of controlling pain. Fifty-two (66.67%) of cases and 65(41.67%) of controls consumed or used herbal drugs s as a means of medication (See Table 3 for detail).

Characteristics	CKD	
	Cases N (%)	Controls N (%)
Cigarette smoking		
Yes	26(33.33)	20(12.82)
No	52(66.67)	136(87.18)
Chat chewing		
Yes	42(53.85)	72(46.15)
No	36(46.15)	84(53.85)
Consumption of High in Salt Foods		
Yes	75(96.15)	111 (71.15)
No	3(3.85)	45(28.85)
Consumption of High in Salt Foods		
Yes	74(94.87)	104(66.67)
No	4(5.13)	52(33.33)
Alcohol drinking		
Yes	37(47.44)	58(37.18)
No	41(52.56)	98(62.82)
Consumption of High Sugar/Carbonated Drinks		
Yes	68(87.18)	109(69.87)
No	10(12.82)	47(30.13)
Consumption of Caffeinated Drinks		
Yes	77(98.72)	139(89.10)
No	1(1.28)	17(10.90)
Types of Water Source Use		
Piped water	22(28.21)	82(52.56)
Underground water	34(43.59)	40(25.64)
Bottled water	22(28.21)	34(21.79)
Consumption of NSAID Drugs		
Yes	70(89.74)	89(57.05)
No	8(10.26)	67(42.95)
Consumptions of Herbal Medication		
Yes	52(66.67)	65(41.67)
No	26(33.33)	91(58.33)
Physical Activity		
Yes	25(32.05)	56(35.90)
No	53(67.95)	100(64.10)
Duration of Physical Activity		
<150 min per week	21(84.00)	33(58.93)
150-200 min per week	2(8.00)	12(21.43)
>200 min per week	2(8.00)	11(19.64)

Table 3: Life Style and Behavioral Factors of Study Participants Who Attending Dessie Comprehensive Specialized Hospital in Dessie Town, Amhara Region, North-East of Ethiopia 2022

3.4. Factors Associated with Chronic Kidney Disease

The chi-square assumption was tested for further analysis and to determine determinants of Chronic Kidney Disease (CKD). Bivariable and multivariable logistic regression analyses were conducted. In bivariable analysis variables with p-value <0.2 were selected for multivariable analysis and using average standard error those variables with average standard error of 2.0 and above were not analyzed in the final model (like Educational status, salt, fat, caffeinated drinks, NSAID drug usage, and anemia) finally 14 variables from 29 variables (Sex of the participants, Age, hypertension status, diabetes-mellitus, cardio-respiratory diseases, …. Herbal medication usage history) were analyzed in multivariable analysis. The Hosmer–Lemeshow goodness of fit test for the final model was conducted for multiple logistic regression (p-value = 0.3595) the model was good since the p-value was >0.05 and the odds ratios were adjusted for all other variables keeping constant in the final models and Significant was declared using 95% CI with chronic kidney disease.

After keeping the other variables constant the odds of developing CKD among males was 2.54 [AOR; 2.54, 95% CI (1.125- 5.754)] times higher than females. Similarly, the odds of developing CKD were 5.33 [AOR; 5.33, 95% CI (2.107-13.489)] times higher for patients who had hypertension compared to those who had not. Furthermore, the odds of developing CKD among patients who had diabetes- mellitus was 3.64 [AOR; 3.64, 95% CI (1.530- 8.671)] times higher compared to their counterparts. Patients with kidney stones had 3.91 times the odds of developing CKD compared to those without kidney stones [AOR; 3.91, 95% CI (1.492-10.257)]. This study also confirmed that the use of underground water was a positive factor in CKD development [AOR; 2.63, 95% CI (1.108-6.262)] (See Table 4 for details).

Characteristic	CKD			
	Cases (n=78)	Controls (n=156)	COR (95%CI)	AOR (95%CI)
Sex				
Male	52	86	1.63(.923- 2.871)	2.54(1.125-5.754) *
Female	26	70	1	1
Age				
18-30	6	37	1	1
31-40	14	29	2.97(1.018-8.703)	2.65(.684- 10.302)
41-50	20	29	4.25(1.512-11.957)	1.72(.492- 6.026)
51-60	12	34	2.17(.735-6.440)	1.12(.295- 4.25)
60+	26	27	5.93(2.147-16.417)	2.28(.644 8.109)
Hypertension				
Yes	52	44	5.09(2.833-9.145)	5.33(2.107-13.489) **
No	26	112	1	1
Diabetic –Mellitus				
Yes	32	24	3.82(2.044-7.160)	3.64(1.530 8.671) **
No	46	132	1	1
Cardio-Respiratory Disease				
Yes	59	73	3.53(1.927- 6.466)	1.33(.520-3.431)
No	19	83	1	1
Kidney Stone				
Yes	64	78	4.57(2.367-8.826)	3.91(1.492 - 10.257 *
No	14	78	1	1
Recurrent Urinary Tract Infections				
Yes	58	90	2.12(1.167-3.872)	1.67(.678-4.143)
No	20	66	1	1
Family History of Kidney Diseases				

Yes	25	32	1.82(.989-3.377)	1.33(.570-3.140)
No	53	124	1	1
Smoking				
Yes	26	20	3.4(1.748-6.609)	1.82(.694-4.803)
No	52	136	1	1
Chat				
Yes	42	72	1.36(.789 -2.347)	1.06(.492- 2.317)
No	36	84	1	1
Alcohol				
Yes	37	58	1.52(.879-2.643)	84(.381-1.865)
No	41	98	1	1
Carbonated Drinks				
Yes	68	109	2.93(1.389-6.187)	1.94(.708-5.323)
No	10	47	1	1
Water Sources				
Piped water	22	82	1	1
Underground				
water	34	40	3.16(1.643- 6.105)	2.63(1.108-6.262) *
Bottled water	22	34	2.41(1.18-4.92)	1.44(.550- 3.774)
Herbal Medication Usage				
Yes	52	65	2.79(1.586-4.942)	1.60(.761-3.388)
No	26	91	1	1

COR: Crude Odds Ratio; **AOR**: Adjusted Odds Ratio; **UTI**: Urinary Tract Infection; **CKD**: Chronic Kidney Disease; **CKD EPI**: Chronic Kidney Disease Epidemiology Collaboration; **CVD**: Cardiovascular Disease; **GFR**: Glomerular Filtration Rate; NCD, Non-Communicable Disease. Note: Statistically Significant at *P<0.05, **P<0.01.

Table 4: Multivariable Binary Logistic Regression on Risk Factors of CKD Among Patients Attending Dessie Comprehensive Specialized Hospital, Dessie, Amhara Region, North-East Ethiopia, 2022

4. Discussion

The aim of this study was to identify risk factors of chronic kidney diseases among patients attending Dessie Comprehensive Specialized Hospital, Dessie Town, Amhara region, Northeastern Ethiopia, 2022.

The study found that males had higher odds of developing CKD than females did. It is consistent with other research conducted in Taiwan, Yemen, and Mexico [14,21,37]. The explanation could have something to do with testosterone's negative effects on males and estrogen's protective effects on females. Additionally, gender norms or social practices related to physical mobility may limit females' opportunities for different behaviors, as evidenced by the differences between male and female behavioral activity levels because males tend to be more active, mobile, and involved in various behaviors like chat chewing, smoking, drinking alcohol, and involvement in war and accidents than females. Males are therefore more likely to develop lung cancer, physical impairments, and drug addictions, which can lead to non-communicable diseases like hypertension, diabetes mellitus, and cardiovascular disease, which can then result in the development of CKD [1,38,39]. However, studies conducted in Indonesia, Iran, and India showed that sex has no association with CKD [40-42]. These controversies might be due to the great variation of population by gender in the current study (66.67 % of cases and 55.13 % of controls) were males. Additionally, prior studies on the diagnosis of NCDs have focused more on men than on women [34].

In this study, those with a history of hypertension had five times the odds of developing CKD than those without. This finding is coherent with several related studies [17,19,21,40,42,43]. Meanwhile, there is a cyclical relationship between hypertension and CKD. One possible explanation is that hypertension is one of the leading causes of CKD due to the negative effects that elevated blood pressure has on kidney vasculature. Uncontrolled high blood pressure causes high intra-glomerular pressure, which impairs glomerular filtration. Damage to the glomeruli causes an increase in protein filtration, resulting in abnormally high levels of protein in

the urine (microalbuminuria or proteinuria), which leads to renal vascular nephropathy, which gradually leads to a decrease in glomerular filtration rate and allows enough time for other renal diseases to develop; alternatively, nephrons in the kidney are supplied by a dense network of blood vessels, and a large volume of blood flows through them; uncontrolled high blood pressure can cause arteries surrounding the kidney to narrow, weaken, or harden over time. These damaged arteries are unable to deliver enough blood to the kidney tissue, resulting in CKD [2,20,28,44,45]. As a result, hypertensive patients have a high probability of developing CKD compared to non-hypertensive patients. Nonetheless, an Indian study found no statistically significant link between hypertension and CKD [41]. This disagreement could be attributed to the small sample size (61 cases and 50 controls), study population differences, and study settings.

In the current study, a history of diabetes was associated with higher odds of developing CKD. This finding is in line with the findings of other related studies [14,21,28,46]. It is not surprising that individuals with diabetes have a higher risk of developing CKD because diabetes is a significant risk factor for kidney function and approximately 40% of individuals with diabetes end up with CKD [17,44]. One possible explanation could be Diabetes mellitus is a risk factor for the onset and progression of diabetes, characterized by high blood glucose (sugar) levels. High levels of sugar in the blood cause damage to the arteries leading to the kidneys over time. Poor glycemic control leads to a variety of renal structural alterations, including the thickening of the glomerular basement membrane, which parallels the thickening of the capillary and tubular basement membranes. Then there will be increased peripheral artery resistance due to vascular remodeling and increased body fluid volume associated with insulin resistance-induced hyperinsulinemia and hyperglycemia, which will lead to complications such as diabetic nephropathy, secondary hypertension, and eventually CKD [41,47]. As a result, patients with diabetes have a high probability of developing CKD compared to their counterparts. Nonetheless, a study conducted in Nepal revealed that diabetes has no statistically significant relationship with CKD [48]. This disagreement may be due to differences in the study setting, methods, and sample size.

When compared to those who did not have kidney stones, those who had kidney stones had roughly four times the odds of developing CKD. This result agrees with other studies conducted in Yemen, England, Kenya, and Ambo town [14,22,27,49]. This might be due to insufficient water intake or a lack of access to clean water services, as more than half of the study participants (53.85 percent of cases and 57 percent of controls) lived in rural areas, where the primary source of water was underground water, as well as living in hot climates and eating foods high in protein, salt, and sugar. These conditions may impair renal function. As a result, patients with kidney stones have a high probability of renal function impairment as it likely involves multiple different pathways [15,41]. Stones that obstruct urine flow have the potential to cause kidney damage. Moreover, unilateral ureteral obstruction has been shown to cause severe renal vasoconstriction, and the reduction in renal blood flow can result in significant ischemia and permanent renal parenchymal damage. As a result, nephropathy can cause inflammation and fibrosis in the kidneys, resulting in severe kidney damage [33]. Nevertheless, studies conducted in Indonesia and Taiwan revealed that kidney stone has no statistically significant association with CKD [37,40]. These discrepancies may be the result of variations in the study area, including environmental factors, dietary practices, or the study environment.

Chronic kidney diseases were positively linked to groundwater source usage compared to those who used piped water sources. This finding is in line with other studies on the same subject [36,46,50,51]. The possible reason might be a large number of water quality studies to date investigated a range of harmful constituents in these ground waters as potential causative agents of the disease and were insufficient to ensure the microbial safety of the product water, moreover, there is high demand for product water, lack of technical capacity of the local communities, poor maintenance practices, and lack of rules and regulations for water treatment could lead to numerous environmental and public health problems [36,51]. As a result, the groundwater's alkalinity, hardness, and microbiological parameters exceeded the maximum allowable levels (MALs) for drinking. Furthermore, the total dissolved solids (TDS) and magnesium levels exceeded the MALs. There were no significant seasonal differences in groundwater quality or chemical composition. The best examples of such contaminants are iconicity (primarily related to Ca2+, Mg2+, and Na+), some toxic heavy metals and metalloids (e.g., cadmium, lead, arsenic, and silica), agrochemical residues, organic matter, bacterial toxins, and certain viruses. As a result of the synergistic effect of these chemicals, the water becomes hard, contaminated, and nephrotoxic, and these conditions may reduce renal function, leading to chronic kidney diseases of unknown etiology (CKDU) [36,50]. Nevertheless, studies employed in Indonesia, and Taiwan revealed that sources of water have no static association with CKD [37,40]. These discrepancies might be explained by variations in the study area, study setting, and sample size.

4.1. Limitation

Since it is a facility-based study and mainly on governmental health facilities, this may overlook the whole community and those who have served in private health facilities. Hence, the conditions might underrate or overrate the conclusion. Since the study did not use the appropriate measurement for some variables like the presence of anemia, kidney stone size, and HIV test during data collection rather than using documented information and history, this may distort the information.

5. Conclusion

This research was conducted to identify determinants of chronic kidney disease (CKD). Study participants, who were male, had a history of hypertension, diabetes, and kidney stones, and those who used underground water sources were prone to developing CKD. Therefore, the need for increased emphasis on screening and managing the modifiable risk factors early enough so as to forestall the development and progression of the disease, Further-

more, Routine urinalysis and estimation of glomerular filtration rate (GFR) for all patients, especially those with hypertension, diabetes, kidney stones and underground water source users, could help detect CKD at an earlier stage for a better prognosis, given that the disease's course is irreversible

Declarations

Ethics Approval and Consent to Participate

An ethical clearance letter was obtained from the ethical committee of the Department of Public Health, Wollo University. Before delivering the questionnaire, written consent was obtained from every participant. No names and possible identifying issues were written on the questionnaire to ensure the data was confidential.

Authors' Contribution

Conceptualization: Abdusellam Yimer and Bilal Mohammed
Data Curation: Abdusellam Yimer and Bilal Mohammed
Formal Analysis: Abdusellam Yimer and Bilal Mohammed
Funding Acquisition: Abdusellam Yimer, Bilal Mohammed, Welde Melese, Reta Dewau, Wondwosen Mebratu, Abel Endawkie, Jemal Seid, Dr. Ali Hassen
Investigation: Abdusellam Yimer, Bilal Mohammed, Welde Melese, Reta Dewau, Wondwosen Mebratu, Abel Endawkie, Jemal Seid, Dr. Ali Hassen
Methodology: Abdusellam Yimer and Bilal Mohammed
Project Administration: Abdusellam Yimer, Bilal Mohammed, Welde Melese, Reta Dewau, Wondwosen Mebratu, Abel Endawkie, Jemal Seid, Dr. Ali Hassen
Resources: Abdusellam Yimer, Bilal Mohammed, Welde Melese, Reta Dewau, Wondwosen Mebratu, Abel Endawkie, Jemal Seid, Dr. Ali Hassen
Software: Abdusellam Yimer and Bilal Mohammed
Supervision: Abdusellam Yimer, Bilal Mohammed, Welde Melese, Reta Dewau, Wondwosen Mebratu, Abel Endawkie, Jemal Seid, Dr. Ali Hassen
Validation: Abdusellam Yimer, Bilal Mohammed, Welde Melese, Reta Dewau, Wondwosen Mebratu, Abel Endawkie, Jemal Seid, Dr. Ali Hassen
Visualization: Abdusellam Yimer, Bilal Mohammed, Welde Melese, Reta Dewau, Wondwosen Mebratu, Abel Endawkie, Jemal Seid, Dr. Ali Hassen
Writing – Original Draft: Abdusellam Yimer and Bilal Mohammed
Writing – Review & Editing: Abdusellam Yimer, Bilal Mohammed, Welde Melese, Reta Dewau, Wondwosen Mebratu, Abel Endawkie, Jemal Seid, Dr. Ali Hassen. All authors approved the final draft of the manuscript.

Availability of Data and Materials

The dataset containing all the required data is found at the primary author which can be accessed with a justifiable request.

Acknowledgments

The authors would like to acknowledge the staff of Wollo University, Dessie Comprehensive Specialized Hospital s' staff members, study participants, and data collectors for their welcome and assistance. Finally, we should give our genuine appreciation to our accomplices for their best regards and encouragement during this research thesis work.

References

1. Siegel, R. L., Miller, K. D., Fuchs, H. E., & Jemal, A. (2022). Cancer statistics, 2022. *CA: a cancer journal for clinicians, 72*(1).
2. Rossi, S. H., Klatte, T., Usher-Smith, J., & Stewart, G. D. (2018). Epidemiology and screening for renal cancer. *World journal of urology, 36,* 1341-1353.
3. Linehan, W. M., & Ricketts, C. J. (2019). The Cancer Genome Atlas of renal cell carcinoma: findings and clinical implications. *Nature Reviews Urology, 16*(9), 539-552.
4. Graham, J., Dudani, S., & Heng, D. Y. (2018). Prognostication in kidney cancer: recent advances and future directions. *Journal of Clinical Oncology, 36*(36), 3567-3573.
5. Hsieh, J. J., Purdue, M. P., Signoretti, S., Swanton, C., Albiges, L., Schmidinger, M., ... & Ficarra, V. (2017). Renal cell carcinoma. *Nature reviews Disease primers, 3*(1), 1-19.
6. Chen, Y., Liu, Q., Chen, Z., Wang, Y., Yang, W., Hu, Y., ... & Zhang, H. (2019). PD-L1 expression and tumor mutational burden status for prediction of response to chemotherapy and targeted therapy in non-small cell lung cancer. *Journal of experimental & clinical cancer research, 38,* 1-14.
7. Rini, B. I., Powles, T., Atkins, M. B., Escudier, B., McDermott, D. F., Suarez, C., ... & Motzer, R. J. (2019). Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial. *The Lancet, 393*(10189), 2404-2415.
8. Motzer, R. J., Penkov, K., Haanen, J., Rini, B., Albiges, L., Campbell, M. T., ... & Choueiri, T. K. (2019). Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *New England Journal of Medicine, 380*(12), 1103-1115.
9. McDermott, D. F., Huseni, M. A., Atkins, M. B., Motzer, R. J., Rini, B. I., Escudier, B., ... & Powles, T. (2018). Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma. *Nature medicine, 24*(6), 749-757.
10. Choueiri, T. K., Larkin, J., Oya, M., Thistlethwaite, F., Martignoni, M., Nathan, P., ... & Rini, B. I. (2018). Preliminary results for avelumab plus axitinib as first-line therapy in patients with advanced clear-cell renal-cell carcinoma (JAVELIN Renal 100): an open-label, dose-finding and dose-expansion, phase 1b trial. *The lancet oncology, 19*(4), 451-460.
11. Sharma, P., Retz, M., Siefker-Radtke, A., Baron, A., Necchi, A., Bedke, J., ... & Galsky, M. D. (2017). Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. *The lancet oncology, 18*(3), 312-322.
12. Motzer, R. J., Rini, B. I., McDermott, D. F., Frontera, O. A., Hammers, H. J., Carducci, M. A., ... & Tannir, N. M. (2019). Nivolumab plus ipilimumab versus sunitinib in first-line treat-

ment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. *The Lancet Oncology, 20*(10), 1370-1385.
13. Motzer, R. J., Tannir, N. M., McDermott, D. F., Arén Frontera, O., Melichar, B., Choueiri, T. K., ... & Escudier, B. (2018). Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *New England Journal of Medicine, 378*(14), 1277-1290.
14. Clark, J. I., Wong, M. K., Kaufman, H. L., Daniels, G. A., Morse, M. A., McDermott, D. F., ... & Aung, S. (2017). Impact of sequencing targeted therapies with high-dose interleukin-2 immunotherapy: an analysis of outcome and survival of patients with metastatic renal cell carcinoma from an on-going observational IL-2 clinical trial: PROCLAIMSM. *Clinical genitourinary cancer, 15*(1), 31-41.
15. Rizvi, N. A., Hellmann, M. D., Snyder, A., Kvistborg, P., Makarov, V., Havel, J. J., ... & Chan, T. A. (2015). Mutational landscape determines sensitivity to PD-1 blockade in non–small cell lung cancer. *Science, 348*(6230), 124-128.
16. Hugo, W., Zaretsky, J. M., Sun, L. U., Song, C., Moreno, B. H., Hu-Lieskovan, S., ... & Lo, R. S. (2016). Genomic and transcriptomic features of response to anti-PD-1 therapy in metastatic melanoma. *Cell, 165*(1), 35-44.
17. Van Allen, E. M., Miao, D., Schilling, B., Shukla, S. A., Blank, C., Zimmer, L., ... & Garraway, L. A. (2015). Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. *Science, 350*(6257), 207-211.
18. Le, D. T., Uram, J. N., Wang, H., Bartlett, B. R., Kemberling, H., Eyring, A. D., ... & Diaz Jr, L. A. (2015). PD-1 blockade in tumors with mismatch-repair deficiency. *New England Journal of Medicine, 372*(26), 2509-2520.
19. Yu, G., Wang, L. G., Han, Y., & He, Q. Y. (2012). clusterProfiler: an R package for comparing biological themes among gene clusters. *Omics: a journal of integrative biology, 16*(5), 284-287.
20. Jia, Q., Wu, W., Wang, Y., Alexander, P. B., Sun, C., Gong, Z., ... & Zhu, B. (2018). Local mutational diversity drives intratumoral immune heterogeneity in non-small cell lung cancer. *Nature communications, 9*(1), 5361.
21. Yoshihara, K., Shahmoradgoli, M., Martínez, E., Vegesna, R., Kim, H., Torres-Garcia, W., ... & Verhaak, R. G. (2013). Inferring tumour purity and stromal and immune cell admixture from expression data. *Nature communications, 4*(1), 2612.
22. Becht, E., Giraldo, N. A., Lacroix, L., Buttard, B., Elarouci, N., Petitprez, F., ... & De Reynies, A. (2016). Estimating the population abundance of tissue-infiltrating immune and stromal cell populations using gene expression. *Genome biology, 17,* 1-20.
23. Vicari, A. P., Figueroa, D. J., Hedrick, J. A., Foster, J. S., Singh, K. P., Menon, S., ... & Zlotnik, A. (1997). TECK: a novel CC chemokine specifically expressed by thymic dendritic cells and potentially involved in T cell development. *Immunity, 7*(2), 291-301.
24. Krueger, A., Willenzon, S., Łyszkiewicz, M., Kremmer, E., & Förster, R. (2010). CC chemokine receptor 7 and 9 double-deficient hematopoietic progenitors are severely impaired in seeding the adult thymus. *Blood, The Journal of the American Society of Hematology, 115*(10), 1906-1912.
25. Hippe, A., Braun, S. A., Oláh, P., Gerber, P. A., Schorr, A., Seeliger, S., ... & Homey, B. (2020). EGFR/Ras-induced CCL20 production modulates the tumour microenvironment. *British journal of cancer, 123*(6), 942-954.
26. Harlin, H., Meng, Y., Peterson, A. C., Zha, Y., Tretiakova, M., Slingluff, C., ... & Gajewski, T. F. (2009). Chemokine expression in melanoma metastases associated with CD8+ T-cell recruitment. *Cancer research, 69*(7), 3077-3085.
27. Ritter, J. L., Zhu, Z., Thai, T. C., Mahadevan, N. R., Mertins, P., Knelson, E. H., ... & Barbie, T. U. (2020). Phosphorylation of Rab7 by TBK1/IKKϵ regulates innate immune signaling in triple-negative breast cancer. *Cancer research, 80*(1), 44-56.
28. Zhou, Q., Qi, Y., Wang, Z., Zeng, H., Zhang, H., Liu, Z., ... & Xu, J. (2020). CCR5 blockade inflames antitumor immunity in BAP1-mutant clear cell renal cell carcinoma. *Journal for immunotherapy of cancer, 8*(1).
29. Margaillan, G., Rouleau, M., Fallon, J. K., Caron, P., Villeneuve, L., Turcotte, V., ... & Guillemette, C. (2015). Quantitative profiling of human renal UDP-glucuronosyltransferases and glucuronidation activity: a comparison of normal and tumoral kidney tissues. *Drug Metabolism and Disposition, 43*(4), 611-619.
30. Tang, D., Zhao, Y. C., Liu, H., Luo, S., Clarke, J. M., Glass, C., ... & Wei, Q. (2020). Novel genetic variants in PLIN2, SULT2A1 and UGT1A9 genes of the Ketone metabolism pathway are associated with survival of non-small cell lung cancer. *International journal of cancer, 147*(6), 1559.
31. Yang, Z. Z., Li, L., Wang, L., Yuan, L. M., Xu, M. C., Gu, J. K., ... & Zeng, S. (2017). The regioselective glucuronidation of morphine by dimerized human UGT2B7, 1A1, 1A9 and their allelic variants. *Acta Pharmacologica Sinica, 38*(8), 1184-1194.
32. De Mattia, E., Cecchin, E., Polesel, J., Lupo, F., Tiribelli, C., Crovatto, M., ... & Toffoli, G. (2017). UGT1A polymorphisms as genetic biomarkers for hepatocellular carcinoma risk in Caucasian population. *Liver International, 37*(9), 1345-1353.
33. Calvo, N., Shabaka, A., Cubillo, B. R., de la Manzanara, V. L., Pérez-Flores, I., de la Higuera, M. M., ... & Sánchez-Fructuoso, A. I. (2016, November). Presence of T-275A and C-2152T Polymorphisms of the Promoter Region of Uridine Diphosphate-Glucuronosyltransferase 1A9 Increases Mortality From Digestive Tumors: Results After 10 Years of Follow-up in a Renal Transplant Population. In *Transplantation Proceedings* (Vol. 48, No. 9, pp. 2947-2949). Elsevier.
34. Siska, P. J., Beckermann, K. E., Mason, F. M., Andrejeva, G., Greenplate, A. R., Sendor, A. B., ... & Rathmell, J. C. (2017). Mitochondrial dysregulation and glycolytic insufficiency functionally impair CD8 T cells infiltrating human renal cell carcinoma. *JCI insight, 2*(12).
35. Giraldo, N. A., Becht, E., Pages, F., Skliris, G., Verkarre, V., Vano, Y., ... & Sautes-Fridman, C. (2015). Orchestration and prognostic significance of immune checkpoints in the microenvironment of primary and metastatic renal cell cancer. *Clinical Cancer Research, 21*(13), 3031-3040.

36. Mariathasan, S., Turley, S. J., Nickles, D., Castiglioni, A., Yuen, K., Wang, Y., ... & Powles, T. (2018). TGFβ attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells. *Nature, 554*(7693), 544-548.
37. Rini, B. I., Plimack, E. R., Stus, V., Gafanov, R., Hawkins, R., Nosov, D., ... & Powles, T. (2019). Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *New England Journal of Medicine, 380*(12), 1116-1127.
38. Koshkin, V. S., Barata, P. C., Zhang, T., George, D. J., Atkins, M. B., Kelly, W. J., ... & Rini, B. I. (2018). Clinical activity of nivolumab in patients with non-clear cell renal cell carcinoma. *Journal for immunotherapy of cancer, 6*, 1-7.
39. McKay, R. R., Bossé, D., Xie, W., Wankowicz, S. A., Flaifel, A., Brandao, R., ... & Choueiri, T. K. (2018). The clinical activity of PD-1/PD-L1 inhibitors in metastatic non–clear cell renal cell carcinoma. *Cancer immunology research, 6*(7), 758-765.
40. Shields, J. D., Kourtis, I. C., Tomei, A. A., Roberts, J. M., & Swartz, M. A. (2010). Induction of lymphoidlike stroma and immune escape by tumors that express the chemokine CCL21. *Science, 328*(5979), 749-752.
41. Balsam Rizeq, Mohammed Imad Malki(2020) The Role of CCL21/CCR7 Chemokine Axis in Breast Cancer Progression. *Cancers (Basel)* 12:1036.
42. Niu, Y., Tang, D., Fan, L., Gao, W., & Lin, H. (2020). CCL25 promotes the migration and invasion of non small cell lung cancer cells by regulating VEGF and MMPs in a CCR9 dependent manner. *Experimental and Therapeutic Medicine, 19*(6), 3571-3580.
43. Le, D. T., Uram, J. N., Wang, H., Bartlett, B. R., Kemberling, H., Eyring, A. D., ... & Diaz Jr, L. A. (2015). PD-1 blockade in tumors with mismatch-repair deficiency. *New England Journal of Medicine, 372*(26), 2509-2520.
44. Rizvi, N. A., Hellmann, M. D., Snyder, A., Kvistborg, P., Makarov, V., Havel, J. J., ... & Chan, T. A. (2015). Mutational landscape determines sensitivity to PD-1 blockade in non–small cell lung cancer. *Science, 348*(6230), 124-128.
45. Huang, A. C., Postow, M. A., Orlowski, R. J., Mick, R., Bengsch, B., Manne, S., ... & Wherry, E. J. (2017). T-cell invigoration to tumour burden ratio associated with anti-PD-1 response. *Nature, 545*(7652), 60-65.
46. Samstein, R. M., Lee, C. H., Shoushtari, A. N., Hellmann, M. D., Shen, R., Janjigian, Y. Y., ... & Morris, L. G. (2019). Tumor mutational load predicts survival after immunotherapy across multiple cancer types. *Nature genetics, 51*(2), 202-206.
47. Yarchoan, M., Hopkins, A., & Jaffee, E. M. (2017). Tumor mutational burden and response rate to PD-1 inhibition. *New England Journal of Medicine, 377*(25), 2500-2501.
48. Wang, L., Liang, Y., Li, P., Liang, Q., Sun, H., Xu, D., & Hu, W. (2019). Oncogenic activities of UBE2S mediated by VHL/HIF-1α/STAT3 signal via the ubiquitin-proteasome system in PDAC. *OncoTargets and therapy,* 9767-9781.
49. Li, P., Huang, T., Zou, Q., Liu, D., Wang, Y., Tan, X., ... & Qiu, H. (2019). FGFR2 promotes expression of PD-L1 in colorectal cancer via the JAK/STAT3 signaling pathway. *The Journal of Immunology, 202*(10), 3065-3075.
50. Shen, J., Ju, Z., Zhao, W., Wang, L., Peng, Y., Ge, Z., ... & Peng, G. (2018). ARID1A deficiency promotes mutability and potentiates therapeutic antitumor immunity unleashed by immune checkpoint blockade. *Nature medicine, 24*(5), 556-562.
51. Huang, Y., Wang, J., Jia, P., Li, X., Pei, G., Wang, C., ... & Zhang, B. (2019). Clonal architectures predict clinical outcome in clear cell renal cell carcinoma. *Nature communications, 10*(1), 1245.
52. Miao, D., Margolis, C. A., Gao, W., Voss, M. H., Li, W., Martini, D. J., ... & Van Allen, E. M. (2018). Genomic correlates of response to immune checkpoint therapies in clear cell renal cell carcinoma. *Science, 359*(6377), 801-806.
53. Naito, T., Udagawa, H., Umemura, S., Sakai, T., Zenke, Y., Kirita, K., ... & Goto, K. (2019). Non-small cell lung cancer with loss of expression of the SWI/SNF complex is associated with aggressive clinicopathological features, PD-L1-positive status, and high tumor mutation burden. *Lung Cancer, 138*, 35-42.
54. Youn, H. G., Matsumoto, J., Tanaka, Y., & Shimotohno, K. (2003). SR-related protein TAXREB803/SRL300 is an important cellular factor for the transactivational function of human T-cell lymphotropic virus type 1 Tax. *Journal of virology, 77*(18), 10015-10027.