EVALUATING DRUG-DRUG INTERACTIONS, POLYPHARMACY, THEIR ASSOCIATION WITH MORTALITY AND ASSESSING QUALITY OF LIFE AMONG HEMODIALYSIS PATIENTS IN LIBYA

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DEDICATION

To the spirit of my beloved father, you were the foundation upon which my character was built, the unwavering pillar of strength that supported my dreams and aspirations. Your wisdom, engraved within the corridors of my mind, continues to shape my choices and actions. Through your words of guidance and the lessons learned by your side, I have discovered the true meaning of integrity, compassion, and perseverance. Your love, like an eternal flame, warms my soul and illuminates my darkest moments. It is a love that transcends time and space, enveloping me with a sense of security and comfort. May Allah bless you.

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ADE	Adverse Drug Events
ADR	Adverse Drug Reaction
AKI	Acute Kidney Injury
APD	Automated Peritoneal Dialysis
AVF	Arteriovenous Fistula
AVG	Arteriovenous Graft
BIS	Berlin Initiative Study
BKD	Burden of Kidney Disease
BP	Blood Pressure
CAPD	Continuous Ambulatory Peritoneal Dialysis
CBC	Complete Blood Count
CDC	Centres for Disease Control and Prevention
C-G	Cockcroft–Gault Equation
CHF	Congestive Heart Failure
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMV	Cytomegalovirus
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CrCl	Creatinine Clearance
CRF	Chronic Renal Failure
CUA	Calcific Uremic Arteriolopathy
CVA	Cerebrovascular Accident
CVD	Cardiovascular Disease

DBP	Diastolic Blood Pressure
DCD	Donation after Circulatory Death
DDIs	Drug-Drug Interactions
DKD	Diabetic Kidney Disease
DM	Diabetes Mellitus
eGFR	Estimated Glomerular Filtration Rate
ESRD	End-Stage Renal Disease
FAS	Full Age Spectrum equation
GDP	Gross Domestic Product
GN	Glomerulonephritis
Hb	Hemoglobin
HBV	Hepatitis B Virus
Hct	Hematocrit
HCV	Hepatitis C Virus
HD	Hemodialysis
HICs	High-Income Countries
HLA	Human Leukocyte Antigens
HRQoL	Health-Related Quality of Life
HTN	Hypertension
ICES	Institute for Clinical Evaluative Sciences
ICU	Intensive Care Unit
IDU	Inappropriate Drug Use
ISN	International Society of Nephrology
ISN-GKHA	International Society of Nephrology Global Kidney Health Atlas
KDCS	Kidney Disease Component Summary

KDOQI	Kidney Disease Outcomes Quality Initiative
KDQOL-SF	Kidney Disease Quality of Life Short Form
KRT	Kidney Replacement Therapy
KT	kidney Transplantation
KT/V	Clearance, T time, V volume
LICs	Low-Income Countries
LMICs	Low- and middle-income countries
MBD	Mineral Bone Disease
MCS	Mental Composite Summary
MCV	Mean Corpuscular Volume
MDMA	3,4-Methylenedioxymethamphetamine
mGFR	Measured Glomerular Filtration Rate
MDRD	Modification of Diet in Renal Disease
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NKF	National Kidney Foundation
NKF-KDOQI	National Kidney Foundation-Kidney Disease Outcomes Quality Initiative
PC	Pharmaceutical Care
PCI	Percutaneous Coronary Intervention
PCS	Physical Composite Summary
PD	Peritoneal Dialysis
PD	Pharmacodynamic
PDA	Personal Digital Assistant
pDDI	Potential Drug-Drug Interactions
PK	Pharmacokinetic

PLT	Platelets
PLWH	People Living with Human immunodeficiency virus
Pmp	Per Million Population
PP	Pulse pressure
PTH	Parathyroid Hormone
QALY	Quality-Adjusted-Life-Year
QOL	Quality Of Life
RA	Rheumatoid Arthritis
RBC	Red Blood Cells
RBS	Random Blood Sugar
RRT	Renal Replacement Therapy
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SBP	Systolic Blood Pressure
SF-36	Short form 36
SLE	Systemic Lupus Erythematosus
SPSS	Statistical Packages for the Social Sciences
TD	Tardive Dyskinesia
USRDS	United States Renal Data System
WBC	White Blood Cells
WHO	World Health Organization
WHOQOL-BREF	World Health Organization Quality of Life Brief Version

LIST OF APPENDICES

MENILAI INTERAKSI UBAT-UBATAN, POLIFARMASI, HUBUNGAN MEREKA DENGAN KEMATIAN DAN MENILAI KUALITI HIDUP DALAM KALANGAN PESAKIT HEMODIALISIS DI LIBYA

ABSTRAK

Penyelidikan ini menangani jurang kritikal dalam memahami interaksi ubat-ubatan, polifarmasi, dan kualiti hidup berkaitan kesihatan dalam kalangan pesakit hemodialisis Libya, satu populasi yang mempunyai data yang terhad. Memandangkan risiko tinggi hasil buruk akibat interaksi ubat-ubatan dan polifarmasi dalam pesakit hemodialisis, kajian ini bertujuan untuk menilai prevalens dan peramalnya, serta mengkaji hubungannya dengan kematian di hospital. Tambahan pula, penyelidikan ini meneroka kualiti hidup berkaitan kesihatan populasi ini, mengenal pasti penentu utama yang mempengaruhi kualiti hidup pesakit penyakit ginjal peringkat akhir, satu bidang yang masih kurang diterokai dalam konteks penjagaan kesihatan Libya. Kajian ini dibahagikan kepada dua bahagian. Bahagian pertama membentangkan kajian retrospektif yang bertujuan untuk mengenal pasti prevalens dan peramal interaksi ubat-ubatan dan polifarmasi di Libya, serta mengkaji hubungannya dengan kematian di hospital. Bahagian kedua melibatkan kajian rentas seksyen yang dijalankan untuk menilai kualiti hidup berkaitan kesihatan dalam kalangan pesakit hemodialisis dan untuk mengenal pasti faktor-faktor yang mempengaruhi kualiti hidup berkaitan kesihatan. Kajian retrospektif mendedahkan bahawa prevalens interaksi ubat-ubatan antara pesakit hemodialisis adalah 71.1% dan polifarmasi adalah 74.1%, manakala kadar prevalens hiperpolfarmasi adalah 9.2%, masing-masing. Faktor bebas yang dikaitkan dengan interaksi ubat-ubatan adalah polifarmasi (OR 11.209, 95% CI 5.21–24.12; p = <0.001). Manakala faktor bebas yang dikaitkan dengan polifarmasi adalah

kemasukan ke hospital (OR 1.110, 95% CI 1.017–1.220; p = 0.020). Akhir sekali, faktor yang berkaitan dengan hiper-polifarmasi adalah kemasukan ke unit rawatan rapi (OR 6.165, 95% CI 1.475–25.767; p = 0.013). Mengenai kematian di hospital, ia dikaitkan secara bebas dalam model yang diselaraskan dengan polifarmasi diskret (bilangan ubat) (OR 1.287, 95% CI 1.099–1.508; p = 0.002), polifarmasi hiper (OR 3.776, 95% CI 1.302–10.950; p = 0.014), dan interaksi ubat-ubatan (OR 1.188, 95% CI 1.006–1.403; p = 0.042), masing-masing. Kajian rentas seksyen mendapati bahawa skor kualiti hidup berkaitan kesihatan dalam kalangan pesakit hemodialisis adalah rendah, dan Ringkasan Komponen Fizikal, Ringkasan Komponen Mental, dan Ringkasan Komponen Penyakit Ginjal masing-masing adalah 46.59, 47.87, dan 54.68. Ringkasan komponen fizikal adalah subskala yang terjejas. Dalam kalangan pesakit hemodialisis, jantina adalah peramal yang signifikan terhadap kualiti hidup berkaitan kesihatan, terutamanya bagi wanita, yang mendapat skor lebih rendah daripada lelaki pada semua subskala, seperti Ringkasan Komponen Fizikal (41.03±17.25; p = 0.018), Ringkasan Komponen Mental (39.17±18.23; p = 0.000), dan Ringkasan Komponen Penyakit Ginjal (43.79±16.51; p = 0.00). Prediktor lain adalah komorbiditi, terutamanya Diabetes Mellitus, yang mendapat skor terendah dalam semua subskala. Subskala-subskala ini termasuk Ringkasan Komponen Fizikal (32.44±16.20; p = 0.013), Ringkasan Komponen Mental (29.55±8.69; p = 0.043), dan Ringkasan Komponen Penyakit Ginjal (46.52±13.68; p = 0.031). Kesimpulannya, kajian ini mengenal pasti risiko tinggi interaksi ubat-ubatan (DDIs) dalam kalangan pesakit hemodialisis Libya, dengan tempoh tinggal di hospital berfungsi sebagai peramal yang signifikan. Interaksi ubat-ubatan dikaitkan dengan peningkatan kematian di hospital. Polifarmasi adalah perkara biasa, dan penunjuk-penunjuknya, bersama dengan kaitannya dengan kemasukan ke hospital, telah diketengahkan. Polifarmasi diskret,

hiperpolfarmasi dalam pesakit hemodialisis didapati meningkatkan risiko kematian di hospital. Tambahan pula, pesakit penyakit ginjal peringkat akhir di Libya menunjukkan kualiti hidup berkaitan kesihatan yang lebih rendah, terutamanya dalam skor ringkasan komponen fizikal (PCS), dengan jantina dan komorbiditi menjadi penentu penting HRQOL.

EVALUATING DRUG-DRUG INTERACTIONS, POLYPHARMACY, THEIR ASSOCIATION WITH MORTALITY AND ASSESSING QUALITY OF LIFE AMONG HEMODIALYSIS PATIENTS IN LIBYA

ABSTRACT

This research addresses the critical gaps in understanding drug-drug interactions, polypharmacy, and health-related quality of life among Libyan hemodialysis patients, a population for which limited data exist. Given the high risk of adverse outcomes due to drug-drug interactions and polypharmacy in hemodialysis patients, the study aims to evaluate their prevalence and predictors, and to examine their association with in-hospital mortality. Additionally, the research explores the health-related quality of life of this population, identifying key determinants that influence the quality of life in end-stage renal disease patients, an area that remains underexplored in the Libyan healthcare context. This study is divided into two parts. The first part presents a retrospective study aimed at identifying the prevalence and predictors of drug-drug interactions and polypharmacy in Libya, as well as examining their association with in-hospital mortality. The second part involves a cross-sectional study conducted to assess health-related quality of life among hemodialysis patients and to identify the factors influencing health-related quality of life. The retrospective study revealed that the prevalence of drug-drug interactions among hemodialysis patients is71.1% and polypharmacy is 74.1%, while hyper-polypharmacy prevalence rate is 9.2%, respectively. The independent factor associated with drug-drug interactions was polypharmacy (OR 11.209, 95% CI 5.21–24.12; p = <0.001). While the independent factor associated with polypharmacy was hospitalisation (OR 1.110, 95% CI 1.017–1.220; p = 0.020). Lastly, the associated factor with hyper-

polypharmacy was intensive care unit admission (OR 6.165, 95% CI 1.475–25.767; p = 0.013). Regarding in-hospital mortality, it was associated independently in the adjusted model with discrete polypharmacy (number of medications) (OR 1.287, 95% CI 1.099–1.508; p = 0.002), hyper-polypharmacy (OR 3.776, 95% CI 1.302–10.950; p = 0.014), and drug-drug interactions (OR 1.188, 95% CI 1.006–1.403; p = 0.042), respectively. The cross-sectional study found that scores of health-related quality of life among hemodialysis patients are poor, and Physical Component Summary, Mental Component Summary, and Kidney Disease Component Summary were 46.59, 47.87, and 54.68, respectively. The physical component summary is the subscale that is affected. Among hemodialysis patients, gender was a significant predictor of health-related quality of life, especially for women, who scored lower than men on all subscales, such as Physical Component Summary (41.03±17.25; p = 0.018), Mental Component Summary (39.17±18.23; p = 0.000), and Kidney Disease Component Summary (43.79±16.51; p = 0.00). The other predictor was comorbidity, especially Diabetes Mellitus, which scored the lowest scores in all subscales. These subscales include Physical Component Summary (32.44±16.20; p = 0.013), Mental Component Summary (29.55±8.69; p = 0.043), and Kidney Disease Component Summary (46.52±13.68; p = 0.031). In conclusion, the study identified a high risk of drug-drug interactions (DDIs) among Libyan hemodialysis patients, with hospital stay length serving as a significant predictor. Drug-drug interactions were associated with increased in-hospital mortality. Polypharmacy was common, and its predictors, along with its correlation with hospitalization, were highlighted. Discrete polypharmacy, hyperpolypharmacy in hemodialysis patients were found to elevate the risk of in-hospital mortality. Furthermore, Libyan end-stage renal disease patients demonstrated

lower health-related quality of life, particularly in the physical component summary (PCS) scores, with gender, comorbidities, being significant determinants of HRQOL.

CHAPTER 1

INTRODUCTION

1.1 Chronic Kidney Disease

Damage to the kidney's structure and function over time from a variety of factors defines chronic kidney disease. Reduced kidney function, as measured by an estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1.73 m2, or markers of kidney damage, such as albuminuria, haematuria, or abnormalities detected through laboratory testing or imaging, present for at least 3 months, constitute a diagnosis of chronic kidney disease (Levey and Coresh 2012).

The Kidney Disease Outcomes Quality Initiative and the US National Kidney Foundation identify the following stages of chronic kidney disease: Stage 1 Kidney damage (pathological abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies) with a normal or elevated glomerular filtration rate (90 mL per minute per 173 square metres); Stage 2: Glomerular filtration rate 60–89 mL per min per 173 m2, with evidence of kidney damage; Stage 3: Glomerular filtration rate 30–59 mL per min per 173 m2; Stage 4: Glomerular filtration rate 15–29 mL per min per 173 m2; and Stage 5: End-stage renal failure; glomerular filtration rate 15 mL per min per 173 m2 (International Society of Nephrology 2024).

In the general population, hypertension, diabetes, hyperlipidemia, obesity, and smoking all of which have been recognised as potential risk factors or markers for the progression of chronic kidney disease (CKD) by a number of studies that were conducted using cohort designs. In more developed countries, it appears that the same risk factors and markers are connected to both renal disease and cardiovascular disease (CVD). Albuminuria is predictive not just of chronic kidney disease (CKD) but also

of the morbidity and mortality associated with CVD, as well as genetic susceptibility to CKD. This is in addition to the fact that albuminuria itself is a predictor of CKD(Go et al. 2004; Sarnak et al. 2003; Wang et al. 2018)

1.2 End Stage Renal Disease (ESRD)

End-stage renal disease (ESRD), also known as kidney failure, and death are two potential outcomes and prognoses associated with chronic kidney disease (CKD)(Haynes et al. 2014; de Nicola et al. 2011). End-stage renal disease, also known as ESRD, is characterized by a progressive and irreversible loss of kidney function in an individual that is severe enough to result in death in the absence of treatment with dialysis or a kidney transplant. People with an estimated glomerular filtration rate of less than 15 mL per minute per 1.73 m2 of body surface area or those who need dialysis even though they have a normal glomerular filtration rate are considered to have end-stage renal disease (ESRD) by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative. ESRD is considered to be a terminal stage of chronic kidney disease (Abbasi, Chertow, & Hall 2010)

People who have reached the end stage of kidney disease are candidates for renal replacement therapy (RRT), which can take the form of either dialysis or renal transplantation. RRT is a treatment that can save lives but comes at a high financial cost. It has been available in countries with high incomes for more than 50 years, and during this time period there has been a fast increase in the number of people who have been treated. The percentage of patients with end-stage kidney disease who are put on dialysis as a treatment varies greatly from one area to another, likely due to variations in population characteristics, the incidence of ESRD, and the availability and accessibility of renal replacement therapy. (Liyanage et al. 2015)

1.3 Global Prevalence of End Stage Renal Disease

Complexity surrounds the worldwide response to End Stage Kidney Disease (ESKD), as it is affected by the disease burden in a particular region, as well as by cultural and socioeconomic factors. In 2010, it is estimated that 2.6 million people all over the world received Kidney Replacement Therapy (KRT). On the other hand, it was estimated that between 4.9 and 9.7 million people needed KRT in 2010, This suggests that over 2,300,000 people perished because they could not afford this life-saving therapy. As a result, less than half of the population that required KRT around the world had access to it.

There were 79 nations with data on the incidence of treated ESKD, and the average number of new cases was 144 per million population (pmp). These findings are based on the findings of a cross-sectional survey conducted by the International Society of Nephrology (ISN) 2019 Global Kidney Health Atlas (GKHA), which included 160 participating countries. The incidence rates of treated ESKD that were reported by the United States Renal Data System (USRDS) in 2016 were extremely variable from country to country. The highest incidences of treated ESKD were reported in Taiwan, the United States of America, the Jalisco region of Mexico, and Thailand, in that order (493, 378, 355, and 346 pmp/year, respectively. The prevalence of ESKD is found to be at its lowest in high-income countries (HICs), specifically in countries from the Nordic region, other European countries, Australia, and New Zealand. In East and Southeast Asian countries like Thailand, Malaysia, the Republic of Korea, Singapore, the Philippines, and Taiwan, the treated ESKD incidence rates increased dramatically between 2003 and 2016.

The age-adjusted incidence rate of dialysis in China was estimated to be 122 pmp per year. Additionally, the prevalence of HD and PD in 2015 was estimated to be 402 and 40 pmp, respectively. The incidence of ESKD in India was estimated to be 232 per 100,000 people when adjusted for age. Analysis was performed in 2010 on 52,273 adult patients with CKD; While 32% of ESKD patients were receiving HD, 5% were receiving PD, and 2% were undergoing evaluation for a transplant, 61% were not receiving any form of KRT.

Despite having identical incidence rates, the prevalence of treated ESKD is lower in sub-Saharan Africa than it is in other developing countries (only 10% of people with incident ESKD remained on dialysis for 3 months), and this is likely due to the restricted access to KRT that is available in the region. Despite the fact that the incidence rates are comparable, this continues to be the case.(Thurlow et al. 2021)

1.4 Prevalence of End Stage Renal Disease in Middle East

The disease's prevalence and incidence varied across Middle Eastern countries. In Lebanon, there were 818 cases of pmp, while in Iraq, there were 55 cases of pmp. In 2008 and 2006, Turkey and Qatar had prevalences of 756 and 624 cases pmp, respectively. Iran had a prevalence of 49.9 cases pmp, while Turkey had 276 pmp. Egypt reported a prevalence of 330 pmp for ESRD. The Middle East reported an overall prevalence of ESRD of 150 pmp in 2001 and 430 pmp in 2008. It suggests that the prevalence of renal failure (commonly referred to as end-stage renal disease, or ESRD) in this region is less frequent compared to other countries (Malekmakan et al. 2018). It was reported that the prevalence of dialysis was 215 per pmp globally, and the prevalence of transplantation was 65 pmp. However, in the Middle East, the prevalence of dialysis was 140 pmp, and the prevalence of transplantation was 55 pmp

(Malekmakan et al. 2018). The projected prevalence of RRT in the Middle East, according to the "Global Perspective of Kidney Disease," indicates that 75% of patients are on dialysis and 25% have undergone transplantation. Kidney transplants in Middle Eastern nations mostly originate from live donors in the UAE, Algeria, Sudan, Egypt, Syria, Libya, Jordan, and Morocco (Shaheen et al. 2020).

1.5 Prevalence of End Stage Renal Disease in Libya

According to a comprehensive study published in 2012 on the epidemiology and etiology of dialysis-treated end-stage renal disease (ESRD) in Libya, there were 2417 adult patients undergoing maintenance dialysis for ESRD. This study is the only one conducted in Libya on this topic. With a total adult population of 3,873,000 in 2009, the prevalence of ESKD requiring dialysis was predicted to be 624 cases per pmp. Prevalence varied marginally throughout Libya's regions, with the North West area seeing the highest rate (628 per 100,000 people) which is also the most populous area of the country. Other regions recorded rates of 623 in the North East and 597 in the South of Libya.

During the one year of observation, there were a total of 1093 new patients who began dialysis treatment, which resulted in an incidence rate of 282 pmp. The incidence rates varied from region to region, with the South exhibiting a significantly higher rate than the other regions (Alashek, McIntyre, & Taal 2012a).

1.6 Regional Disparities in Kidney Replacement Therapy

The global reaction to end-stage kidney disease (ESKD) is intricate, shaped by socioeconomics, culture, and the local prevalence of the disease (Thurlow et al. 2021). The most significant disparities in treatment access were observed in low-income

nations, particularly in Asia and Africa. In Africa, the proportion of individuals requiring KRT who actually received treatment ranged from 9% to 16%, whereas in Asia, this proportion ranged from 17% to 34% (Liyanage et al. 2015).

1.6.1 Geographic variability and worldwide patterns in the incidence of treated end-stage kidney disease

Within High Income Countries (HICs), the incidence of end-stage kidney disease (ESKD) is the lowest in Nordic countries, as well as in other European countries, New Zealand, and Australia (Robinson et al. 2016). These countries have almost universally implemented health care systems that provide access to KRT. The lower rates could be because of dialysis commencement at lower glomerular filtration rates, slower progression of chronic kidney disease (CKD), health care reform strategies that prioritize cost containment, and a greater emphasis on conservative care management (Pippias et al. 2016). The occurrence of ESKD is significantly more prevalent in the United States and affluent countries in East and Southeast Asia. This is likely due to a larger burden of CKD and the presence of related risk factors such as hypertension, diabetes, glomerular disorders (such as IgA nephropathy in Asia), and obesity (Wu & Wu 2018).

1.6.2 Global Variation in Kidney Replacement Therapy Modality and Practice Patterns

Significant disparity exists in the availability and utilization of kidney transplantation. The transplantation rate for ESKD patients varied between 57-72% in Estonia, Netherlands, and Nordic nations in 2013, whereas it was less than 10% in certain eastern European and Asian countries (Robinson et al. 2016). Globally, HD is the prevailing method of renal replacement therapy (Himmelfarb et al. 2020), during

2016, the majority of countries had an in-center hemodialysis utilization rate of ≥80% for chronic dialysis patients. 9% and 17% of dialysis patients in Australia and New Zealand, respectively, received home HD therapy. Peritoneal dialysis was utilized by 71% of dialysis patients in Hong Kong. In the Mexican state of Jalisco, PD was used by 61% of dialysis patients. In Guatemala, 57% of dialysis patients worked as PD (Saran 2019).

1.6.3 Global and Socioeconomic Disparities in the Burden of End Stage Kidney Disease

CKD poses a significant worldwide health challenge, particularly in low- and middle-income countries (LMICs). The majority of individuals residing in developing nations possess restricted salaries and are unable to acquire health insurance. Consequently, they face the potential of encountering personal financial hardships due to the high expenses associated with medical care for both KRT and CKD (Jha et al. 2013). Private companies predominately offer dialysis services in LMICs. However, the significant costs associated with these services sometimes result in households depleting their finances, leading to the suspension of treatment and eventual death after their resources are depleted. During a study conducted at a single center in Nigeria, 320 patients with ESKD who had started maintenance HD were examined. The study found that over 80% of the patients paid for their dialysis treatments using their own money within 12 weeks of starting the treatment. Additionally, 98% of the patients discontinued the program due to death or abandonment, while only 2% were able to continue funding their treatments beyond the initial 12 weeks (Luyckx et al. 2017).

US undocumented immigrants with ESKD are ineligible for Medicare, which is decided by states or municipalities. Emergency only hemodialysis (EOHD) and continuous outpatient dialysis collide with justice and society. Different EOHD patients get weekly or monthly dialysis. EOHD is associated with psychosocial distress, life-threatening medical symptoms, and poor outcomes, with a mean 16-month dialysis duration at death. A retrospective cohort analysis of 211 undocumented patients in 3 states indicated EOHD had a 14-fold higher 5-year mortality risk than chronic outpatient dialysis. Undocumented patients' 1-year mortality and expenditures decrease with private health insurance and thrice-weekly dialysis. Other states offer outpatient dialysis through private insurance or county-funded safety-net hospitals. Poor health outcomes result from variable ESKD care for undocumented patients between states (Cervantes et al. 2018).

1.7 Aetiology of End Stage Renal Disease

Patients with HD who have diabetes, hypertension, improper drug use, hereditary disorders, urine retention, or obstruction of the urinary system are the most likely to develop end-stage renal disease (ESRD) (Qadhi et al. 2021).

Other causes may include chronic tubulointerstitial nephritis, primary glomerulonephritis, plasma cell dyscrasias, hereditary or cystic diseases, secondary glomerulonephritis and sickle cell nephropathy (Al-Naqeeb et al. 2009; Morovatdar et al. 2019).

Both unknown etiologies and environmental factors, which may sometimes contribute to the advancement of end-stage renal disease (ESRD), are regarded as causes of the diseases (Bragg-Gresham et al. 2020).

1.8 Drug-drug Interactions (DDIs)

When the effects of one drug are altered by the presence of another drug, this is known as a drug-drug interaction (DDI). Interactions are typically categorised as pharmacokinetic or pharmacodynamic based on the method by which they occur, with the exception of pharmaceutical interactions, which occur before medications are introduced to the patient (Hammar et al. 2021; Magro, Moretti, & Leone 2012).

Both pharmacokinetic and pharmacodynamic drug interactions are possible. Pharmacokinetic drug interactions occur when the object drug's transport to its site of action is influenced by the precipitant drug, while pharmacodynamic drug interactions occur when the object drug's response is modified by the precipitant drug without changes in drug concentrations.

When two medications with a known interaction are prescribed to the same patient, regardless of whether or not adverse effects occur, the result is a potential DDI (PDDI) (Hines, Malone, & Murphy 2012).

It is predicted that between 0.02 and 0.17 percent of the over 130 million annual emergency department visits in the United States are caused by clinically significant events attributed to PDDI exposure in inpatients (Ayvaz et al. 2015).

DDIs may lead to adverse drug responses (ADRs). ADRs are considered significant health risks that could potentially affect patient well-being or lead to mortality; for example, patients who simultaneously administer ceftriaxone and lansoprazole may develop life-threatening arrhythmias. According to statistics from the U.S. Centers for Disease Control and Prevention, approximately 300,000 people die from ADR each year in the United States and Europe. Moreover, it is believed that over 10% of individuals concurrently use five or more medications. Significantly, 20% of the aged

population consumes a minimum of 10 medications, which may substantially elevate the risk of adverse drug reactions (ADRs). This problem presents a significant barrier for pre-marketing clinical research (Zhang, Leng, and Liu 2020).

1.9 Global Prevalence of Drug-drug Interactions

There is a notable incidence of hospitalisation due to interactions (>1%), and epidemiological estimates place the prevalence of probable DDIs in the elderly between 35 and 60%. Of these, 5–15% are responsible for adverse effects that are mostly avoidable or treatable (Burato 2021).

It is important to note that people of advanced age were also classified as high-risk for DDIs (major or severe). For example, in France, 60% of cancer patients aged 65 and more and in India, 21% of geriatric cases, experienced severe DDIs. Prevalence of DDIs varied, ranging from 0.8% in Albania to 90.6% in Croatia (Zhao et al. 2022).

1.10 Prevalence of Drug-drug Interactions in Middle East

The term Middle east is most commonly used to depict the triangle from the Nile valley to the Muslim area of central Asia to the Persian Gulf, an area containing 120 million people and the lands of Egypt, the Fertile Crescent, Iran, Saudi Arabia, and Persian Gulf countries (Curtis 2023).

A systematic review of DDI in the Middle East concluded that errors involving drug-to-drug interactions were the least prevalent type of prescription medication. According to reports, Iran has the highest rate of interaction errors in the Middle East, at 1.54% Saudi Arabia ranked second with a reported rate of 1.08%, while with regard

to Libya, there is no evidence in the literature that describes the prevalence of DDIs in Libya (Aidah 2021).

1.11 Drug-drug Interactions Risk Factors

Age, multimorbidity, and polypharmacy increase DDI risk. Age-related sociodemographic factors (such as gender and ethnicity), clinical and treatment factors, prescriber factors, and healthcare system factors may potentially increase this risk (Hughes et al. 2021).

acute medical condition (for example, alcoholism, alcohol dehydration (alcohol can cause dehydration by increasing urine production so dehydration can affect the pharmacokinetics of drugs) , infection, a reduction in renal and/or hepatic function, the use of medications with a limited therapeutic range, Conditions related to metabolism or the endocrine system (such as hypothyroidism, obesity, or fatty liver), as well as pharmacogenetics, are additional contributory risk factors for DDIs (Elliott & Irving 2012).

1.12 Clinical Manifestations of Drug-drug Interactions

In hospitals, DDIs pose a serious threat to patients' health. Polypharmacy and complex pharmacotherapy are common among hospitalised patients, and they can worsen clinical outcomes like deterioration and lengthen the length of stay, if not lead to death altogether (de Andrade Santos et al. 2020). The DDIs between warfarin-aspirin and digoxin-atenolol were associated with primary intracerebral haemorrhage and cardiac rhythm disorders, respectively, in a study of hospitalised patients (Hart, Tonarelli, & Pearce 2005). Recent research found that all high-risk pregnant women studied had an increase in systolic blood pressure (BP) after experiencing a recurring

clinically apparent DDI of methyldopa with ferrous sulphate, in which one treatment rendered the other less effective. Patients' blood pressure (BP) dropped after they stopped using ferrous sulphate (de Oliveira-Filho et al. 2017).

According to one study, DDIs can cause cardiovascular and neurological complications, bleeding, a decline in renal function, hyperkalemia (which can cause severe myopathy and rhabdomyolysis), hematologic toxicity, and other rare but serious side effects (Zerah et al. 2021).

1.13 Mortality Associated with Drug-drug Interactions

The causes of discharges due to death in the elderly hospital population are high, and pDDIs are common in this population (García-Peña et al. 2011).

Among intensive care unit (ICU) patients, DDIs accounted for 10–16% of all preventable adverse events, and roughly 5% of all ICU patients were expected to encounter an adverse drug reaction (ADR) due to a DDI during hospitalisation (Wang et al. 2022).

ADRs are a significant cause of morbidity, affecting approximately 10% of patients in ambulatory care settings, 10% to 20% of hospital inpatients, and 5% of all hospital admissions (Montané et al. 2018).

An increased documented mortality risk was seen when 3,4-Methylenedioxymethamphetamine (MDMA) was administered along with eight different drug classes (opioids, antidepressants, benzodiazepines, amphetamines and stimulants, anaesthetics, ethanol, MDMA metabolites or analogues, and muscle relaxants), four different antidepressants (bupropion, citalopram, sertraline, and

venlafaxine), and two dopamine antagonists (olanzapine and metoclopramide) (Cohen et al. 2021).

1.14 Cost Associated with Drug-drug Interactions

Not all drug-drug interactions (DDIs) result in harmful or severe health effects. However, some can lead to diminished treatment efficacy, adverse drug reactions (ADRs), or even toxicity. These consequences may cause failure to achieve treatment goals, worsening of the patient's condition, or, in extreme cases, death. Moreover, DDIs have a significant impact on healthcare utilization, particularly through increased hospitalization rates and extended hospital stays. This, in turn, leads to considerable financial burdens, driving up healthcare costs for both individuals and governments (Kardas et al. 2021).

It is reasonable to hypothesize that increased hospital stays and associated costs can often be attributed to adverse drug interactions. For example, a DDI-related complication may require additional laboratory tests or symptomatic treatments, prolonging the hospital stay and escalating healthcare expenses (Moura, Acurcio, & Belo 2009).

A study on DDIs and associated costs among people living with HIV (PLWH) found that during a one-year follow-up, the costs attributed to DDIs in the propensity score-matched sub-cohort (make two similar groups: those who were exposed to DDIs and those who were not) amounted to $2,693 (Demessine et al. 2019). This highlights the significant financial implications that DDIs can have across different patient populations.

1.15 Polypharmacy

Many definitions of polypharmacy can be found in published literature; however, the one provided by World Health Organization (WHO) is the one that is generally accepted “Polypharmacy is the concurrent use of multiple medications. Although there is no standard definition, polypharmacy is often defined as the routine use of five or more medications. This includes over-the-counter, prescription and/or traditional and complementary medicines used by a patient” (World Health Organization n.d.).

The definitions mostly use numbers and a variety of words and phrases to show the different levels of severity of polypharmacy. For example, minor (Guillot, Maumus-robert, & Bezin 2020; Khezrian, Mcneil, et al. 2020; Lee et al. 2020; Masnoon et al. 2017; Santos et al. 2019). The majority of those are numerical definitions and are heterogenous and include terms like minor (> 4 medications) (Jorgensen et al. 2011; Lu et al. 2014), mild (> 3 medication) (Trevisan et al. 2019), moderate (5–9 medicines) (Gallagher et al. 2020), major (> 5 medications) (Ljg et al. 2000), and excessive polypharmacy (> 9 medications) (Walckiers, Heyden, & Tafforeau 2015) are all used to show different levels of severity.

Additionally, in certain studies, polypharmacy was defined as "hyperpolypharmacy" when the number of medications exceeded ten (Guillot et al. 2020). Literature sometimes refers to hyperpolypharmacy as excessive polypharmacy (Toh et al. 2023).

1.16 Prevalence of Polypharmacy in Middle East:

The prevalence rate of polypharmacy was found to be 51.5% in a community-based study conducted in Saudi Arabia (Aljawadi et al. 2022). On the other hand, the prevalence rate of polypharmacy was found to be 89.1% in Saudi Arabia (Salih et al., 2013), 89% in the United Emirate (Ameri et al. 2014), 85.3% in Egypt (Eltaher & Araby 2019), and 75.5% in Qatar (Id et al. 2020), according to other hospital-based studies. There is a lack of information regarding the prevalence rate of polypharmacy in Libya, according to the statistics currently available.

1.17 Health-related Quality of Life

Health-related quality of life (HRQOL) is defined as ‘‘how well a person functions in their life and his or her perceived wellbeing in physical, mental, and social domains of health’’ (Karimi & Brazier 2016; Yin et al. 2016). More research is being done on the effects of HRQoL on people with end-stage renal disease (ESRD) as treatment and methods of RRT are looked at (Valderrabano, Jofre, & Lopez-Gomez 2001). Additionally, exploring HRQoL in this population may aid in identifying individuals who are at a higher risk of experiencing unfavourable outcomes(Mawhinney et al. 1999; Stull, Clough, & Van Dussen 2001). Several studies conducted among patients undergoing hemodialysis have reached the conclusion that a low HRQOL is a significant risk factor for both mortality and hospitalization (DeOreo 1997; Kalantar-Zadeh et al. 2001).

HRQOL instruments can be easily divided into two categories: generic instruments and disease-specific assessments. Disease-specific measures of HRQOL, such as the Kidney Disease Quality of Life Short Form (KDQOL-SF), highlight the effects on people's health and functioning that arise directly from a particular ailment

or therapy. Generic measures of HRQOL encompass profiles such as the SF-36, which aim to offer insights into the overall functioning and well-being of individuals (Juniper 1997; Manns et al. 2002). The rationale for choosing disease-specific instruments over general ones is as follows: If comparison to general populations is not paramount, a disease-specific measure may more effectively capture data pertinent to individuals with ESRD. Such a measure is crucial, as generic measures lack the specificity required to describe and analyze changes over time related to dialysis modality and dosage. Furthermore, disease-specific measures exhibit superior reliability, validity, and internal consistency (Cagney et al. 2000).

The presence of polypharmacy exhibited a negative correlation with the physical aspect of health-related quality of life (HRQoL) in individuals suffering from chronic illnesses. However, no significant association was observed between polypharmacy and the mental domain of HRQoL in the same patient population. The observed correlation between this association and HRQOL remained statistically significant even after controlling for multimorbidity, indicating that polypharmacy had an independent impact on HRQOL (Wilder et al. 2022).

A systematic review and meta-analysis were undertaken with a primary focus on the United States, the United Kingdom, and Australia to examine the relationship between quality of life (QoL) and mortality rates. The research investigation revealed a significant correlation between higher quality of life (QoL) and a reduced risk of mortality, indicating that QoL assessments have the potential to serve as effective screening instruments in routine clinical settings. The research encompassed a sample size of around 1,200,000 individuals, and its findings indicate a significant correlation between health-related quality of life (HRQOL) and a reduced risk of mortality. This

implies that employing quality of life (QoL) metrics may serve as a means to identify demographic groups that are most susceptible to mortality (Phyo et al. 2020).

A previous study revealed a positive correlation between reduced HRQOL ratings and increased hospitalization rates. The study findings indicate that there is a positive correlation between a decline in the Physical Component Summary (PCS) score and an increased risk of hospitalization. Specifically, for each decrement of 10 points in the PCS score, there was a corresponding 15% increase in the likelihood of hospitalization (Mapes et al. 2003).

1.18 Problem Statements

Patients undergoing hemodialysis in Libya encounter the difficulty of treating several comorbidities, due to limited health care resources and patients need to visit multiple physicians that lead to multiple prescription require them to take a wide variety of drugs and possibility of DDI and polypharmacy. In order to successfully treat a wide variety of medical disorders, this population frequently engages in polypharmacy, which refers to the practise of simultaneously administering many medications. On the other hand, the proposed approach raises a substantial issue over drug-drug interactions (DDIs), which may result in adverse drug reactions, decreased therapeutic efficacy, and greater healthcare use.

There is absolute dearth of studies in Libya on the prevalence of polypharmacy and DDIs among hemodialysis patients as well as the clinical implications of these conditions. The inability of healthcare practitioners to optimise treatment and ensure patient safety is hampered by a lack of detailed data on medication regimens and the interactions that occur between those medications in this vulnerable population.

This research aims to address the following key questions:

i- Prevalence and Patterns of Drug Use

- How common is the practice of taking multiple medications among hemodialysis patients in Libya?
- Which medicine combinations are most frequently associated with the development of possible hemodialysis drug interactions (DDIs)?

ii- Clinical Impact of Drug-Drug Interactions (DDIs)

- In hemodialysis patients, how does the presence of DDIs affect therapeutic outcomes and overall, in-hospital mortality?

iii- Prevalence of polypharmacy and hyperpolypharmacy

- What is the prevalence of polypharmacy and hyperpolypharmacy among Libyan hemodialysis patients, and what are the key demographic, clinical, and treatment-related factors that predict their occurrence?

iv- Clinical Impact of polypharmacy and hyperpolypharmacy

- What is the impact of polypharmacy and hyperpolypharmacy on in-hospital mortality among Libyan hemodialysis patients, and how do these conditions contribute to an increased risk of adverse clinical outcomes?

v- Health-Related Quality of Life (HRQOL)

- How do health-related quality of life (HRQOL) scores, including physical, mental, and kidney disease component summary scores, vary among Libyan hemodialysis patients, and what factors are associated with lower HRQOL scores in this population?

This research intends to increase patient care, reduce mortality, and improve the overall quality of life for the vulnerable population it focuses on by investigating the incidence of polypharmacy and the potential dangers associated with DDIs among hemodialysis patients in Libya. In the context of hemodialysis therapy in Libya, the findings of this study will provide invaluable insights to healthcare practitioners, policymakers, and researchers, opening the way for evidence-based interventions and guidelines to optimise drug use and maintain patient safety.

1.19 Objective of The Study

General Objective

To evaluate the medication-related factors and health outcomes among hemodialysis patients, including the frequency, determinants, and impact of drug-drug interactions, polypharmacy, in-hospital mortality, and health-related quality of life.

Specific Objectives

1. To examine the frequency, and determinants of drug-drug interactions among hemodialysis patients.

2. To investigate the prevalence and determinants of polypharmacy among hemodialysis patients.

3. To assess the association of drug-drug interactions and polypharmacy with in-hospital mortality among hemodialysis patients.

4. To evaluate health-related quality of life and assess the factors associated with it among hemodialysis patients.

1.20 Significance of The Study

The increasing prevalence of end-stage renal disease (ESRD) worldwide has posed a significant challenge to healthcare systems. Hemodialysis (HD), the most common renal replacement therapy for ESRD, is a life-sustaining treatment for these patients. However, HD patients often face a range of comorbidities, which leads to the frequent use of multiple medications, commonly referred to as polypharmacy. The complexity of their medical regimen raises concerns regarding drug-drug interactions (DDIs), polypharmacy, and their potential impact on patient outcomes, particularly mortality. Additionally, as ESRD and its treatments severely affect a patient's quality of life, there is a growing need to assess and improve the health-related quality of life (HRQOL) in these patients. This study focuses on evaluating DDIs and polypharmacy, examining their association with in-hospital mortality, and assessing HRQOL among hemodialysis patients.

The evaluation of DDIs and polypharmacy is particularly significant in the context of hemodialysis due to the unique physiological changes experienced by ESRD patients. Altered drug metabolism and excretion in these patients increase the likelihood of adverse drug reactions and interactions, which can contribute to poor

clinical outcomes. DDIs are a critical concern because they may exacerbate existing health problems, reduce the efficacy of essential medications, or lead to harmful side effects, thereby jeopardizing patient safety. This study aims to identify the most frequently occurring DDIs in the hemodialysis population and evaluate their contribution to mortality. Identifying specific drug combinations that pose the highest risk will provide healthcare professionals with actionable data to optimize medication regimens, minimize risks, and improve patient outcomes.

Polypharmacy is also a common phenomenon among hemodialysis patients due to their multiple comorbidities, such as cardiovascular disease, diabetes, and hypertension. This study will assess the prevalence of polypharmacy and hyperpolypharmacy and their predictors, contributing to a better understanding of the scale of the problem. The findings will help identify vulnerable subgroups and provide insight into whether existing prescribing practices contribute to poor outcomes, including increased mortality.

One of the objectives of this study is to evaluate the relationship between polypharmacy, DDIs, and in-hospital mortality among hemodialysis patients. Previous studies have suggested that excessive medication use and potential interactions may increase the risk of adverse outcomes, including death. This study will provide crucial data on the extent to which polypharmacy and DDIs influence mortality in the Libyan hemodialysis population, offering evidence that can guide clinical decision-making and policy development aimed at reducing preventable deaths.

In addition to clinical outcomes, the study will assess HRQOL, an important measure that reflects the physical, mental, and kidney disease component summary of patients. Hemodialysis has a profound impact on quality of life, and by identifying the

key factors influencing HRQOL in Libyan hemodialysis patients, this study will contribute to improving patient care. This knowledge will enable healthcare providers to develop strategies to enhance quality of life, considering the broader spectrum of health outcomes beyond survival.

Overall, this study will address critical gaps in knowledge regarding DDIs, polypharmacy, and HRQOL in the hemodialysis population, contributing to more effective management and better health outcomes for these patients.

CHAPTER 2

LITERATURE REVIEW

2.1 Renal Replacement Therapy

Patients with chronic kidney disease who have developed end-stage kidney disease (ESKD) can choose between conservative therapy and renal replacement therapy (RRT) to continue their treatment. Symptom management, complication prevention, and palliative care all fall under the umbrella of "conservative therapy." Renal replacement therapy (RRT) is a generic name for a variety of treatments for kidney failure. These include hemodialysis, peritoneal dialysis, kidney transplantation, and hemodiafiltration. These patients have a combination of chronic kidney disease and acute kidney damage, a condition known as ESKD. Patients with ESKD who chose conservative therapy instead of renal replacement therapy got worse more quickly because conservative therapy was linked to worse clinical symptoms and biochemical changes.(Okyere et al. 2022)

Given a willingness to pay threshold of $4,766 USD, a study indicated that HD-first is not cost-effective when compared to PD-first. This resulted from comparing the economics of PD and HD and finding that HD-first is less cost-effective than PD-first. On the other hand, current data show that the Quality-Adjusted Life Year (QALY) obtained from HD is greater than that acquired from PD (Assanatham et al. 2022; Putri et al. 2022). The expense of dialysis remains prohibitive for many people living in Cambodia, Myanmar, Laos, Vietnam, Mongolia, and Bhutan, among other lower-middle-income Asian countries. (Hyodo et al. 2022)

2.1.1 Peritoneal Dialysis

Peritoneal dialysis (PD) accounts for 11% of all dialysis and 9% of all kidney replacement treatment (KRT) globally. According to data compiled for the 2018 edition of the International Society of Nephrology Global Kidney Health Atlas (ISN-GKHA), the median worldwide prevalence of PD was 38.1% per million people (pmp), with rates as low as 0.1% in Egypt and as high as 531% in Hong Kong. This represents a variation of over 5,000-fold. PD has a number of benefits that should be appealing to LICs, such as being easier to use technically, requiring less trained staff, and having a lower nurse-to-patient ratio. It is also easier to use in rural and remote areas, easier to manage during natural disasters, has more cost-effectiveness, and is more fair for everyone who needs dialysis. All of these advantages should make PD more appealing to LICs and possibly better survival in the first few years. It is common knowledge that PD is linked to superior clinical results, as well as those reported by patients, in comparison to HD. This association is firmly rooted in place. In addition to reducing the risk of blood-borne and respiratory viruses like the novel SARS-CoV-2, these advantages include better preservation of regenerative kidney function, higher patient satisfaction, higher quality of life, improved kidney transplantation outcomes (in transplant recipients), delayed need for vascular access (especially in small children), and better management of anaemia (Bello et al. 2022).

Inadequate patient education regarding options for KRT, paucity of well-trained clinical personnel, large number of elderly, frail patients for whom self- care is difficult, fear of machines or unwillingness to be tethered into place, use of HD as the default for urgent dialysis, abundance of small PD programs with poor outcomes, and variability in definitions of incident and prevalent patients contributes to the lower prescription rates of PD compared to HD (Teitelbaum and Finkelstein 2023).