EVALUATION OF CLINICAL OUTCOMES AND DIRECT MEDICAL COST OF ANEMIA MANAGEMENT AMONG END STAGE RENAL DISEASE PATIENTS IN KHARTOUM STATE HEMODIALYSIS CENTERS

by

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Thesis submitted in fulfillment of the requirements
for the degree of
Doctor of Philosophy

November 2017

DEDICATION

To

My parents…

My brother Abdelbagi…

My sister Samah…

For their unconditional love, support, encouragement, patience and sacrifice during my study

ACKNOWLEDGEMENT

(وَمَا تَوْفِيقِي إِلا بِاللهِ عَلَيْهِ تَوَكَّلْتُ وَإِلَيْهِ أُنِيبُ) (هود/88)

[My guidance depends totally on GOD; I have put my trust in Him. To Him I have totally submitted]. (11:88)

First of all, I express many thanks to Almighty Allah, the most merciful and my deepest gratitude for my blessings and great help to be successful in this work and in everything in life.

I would like to owe a deepest gratitude to my supervisor Prof. Dr. Azmi Sarriff, for his continuous support and kind encouragement and guidance. I greatly appreciate his unrestricted help, cooperation and enthusiasm. I would like also to express my gratitude to my co-supervisor Assoc. Prof. Dr. Mohamed Babikir, for his cooperation and invaluable help. My deepest gratitude also goes to my co-supervisor, Dr. Amer Hayat Khan for his helpful suggestions and great assistance and support.

My gratitude also goes to Dr. Norsa'adah Bachok, Unit of Biostatistics and Research Methodology, School of Medical Sciences, Universiti Sains Malaysia (USM), for her great help and guidance in statistical work that valuably enriched this thesis. My sincere gratitude to Prof. Dr, Abdalla Omer Elkhawad, Dean, Graduate College, University of Medical Sciences and Technology, Sudan, for his valuable help and guidance enriched this work. Also, I am gratefully indebted to Associate Prof. Dr. Habab Khalid El Kheir, Department of Pharmacology and Clinical Pharmacy, University of Science and Technology, Sudan, for her assistance in this study. I am greatly indebted to my colleague Mohamed Saaid, PhD candidate, Public Health,

Sudan, for his help and interesting discussions that valuably enriched this thesis. I am gratefully indebted to Dr. Omer Haj Hassan, the Director General, Health Insurance, Khartoum State, for his help and approval for the sabbatical leave to complete this work.

I would like to thank the National Center for Kidney Diseases and Surgery, Ministry of Health, Republic of Sudan for the approval to conduct the study. My gratitude goes to Dr. Wafa'a Obubid, Research Department. This work would not have been possible without the valuable help and assistance given by all staff in the Khartoum Dialysis Centers. I'm greatly indebted to all the center's staff members; consultant nephrologists, medical officers, and nursing staff. They really were cooperative and helpful.

I owe the deepest gratitude to my colleagues and friends in Sudan and Malaysia for their kindness, assistance and continuous support and I would like to express special sincere gratitude to my colleague Elbaleeq Adam, PhD candidate, School of Chemistry, USM, without his continuous help this work would not have been completed. Many great thanks also go to my colleague, Azam Khalid, PhD candidate, School of Management, USM, for his generous assistance and guidance regarding data analysis.

I would like to express my gratitude to my family for their sacrifice and support. Deepest thanks belong to my beloved mother and father for always continuous support; without their Dawat and prayers, this work would not have been completed. My great thanks go to my brothers and special thanks to my dear brothers Abdelmoneim and Abdelbagi, for their great help and moral support. My special thanks and love to my

sisters Samah, Salma and Sara, for their sympathy, deep love and incredible support, and their unwavering encouragement.

I would like to express my thanks to USM for the fellowship and financial support in the last year of my study. I am extremely thankful to all those who have contributed to the completion of this work.

"May Allah bless all"

الْحَمْدُ لِلَّهِ الَّذِي بِنِعْمَتِهِ تَتِمُّ الصَّالِحَاتُ"

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ACEI	Angiotensin Converting Enzyme Inhibitors
ACS	Acute Coronary Syndrome
AIDS	Acquired Immunodeficiency Syndrome
aORs	Adjusted Odd Ratios
ANCOVA	Analysis of Covariance
Ang II	Angiotensin II Receptor Blocker
ANOVA	Analysis of Variance
ANSWER	Spanish Study
APD	Automatic Peritoneal Dialysis
AURORA	A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events
B-blocker	Beta Blocker
BMI	Body Mass Index
BP	Blood Pressure
CAD	Coronary Artery Disease
CAD	Canadian Dollar
CAHPS	Consumer Assessment of Healthcare Providers and Systems Data
CAPD	Continuous Ambulatory Peritoneal Dialysis
CBA	Cost-Benefit Analysis
CBC	Complete Blood Count
Cbl	Cobalamin
CDC	Centers for Disease Control and Prevention
CEA	Cost-Effectiveness Analysis

CERA	Continuous Erythropoietin Receptor Activator
CHD	Coronary Heart Disease
CHF	Chronic Heart Failure
CHOIR	Correction of Hemoglobin and Outcomes in Renal Insufficiency Study
CI	Confidence Interval
CKD	Chronic Kidney Disease
CKD-MBD	Chronic Kidney Disease-Mineral and Bone Disorder
CMA	Cost-Minimization Analysis
CMS	Centers For Medicare and Medicaid Services
COI	Cost-of-Illness
CREATE	Cardiovascular Risk Reduction by Early Anemia Treatment Study
CRF	Chronic Renal Failure
CRI	Chronic Renal Insufficient
CSN	Canadian Society of Nephrology
CUA	Cost-Utility Analysis
CVD	Cardiovascular Disease
DARB	Darbepoetin Alfa
DBP	Diastolic Blood Pressure
DDDs	Defined Daily Doses
DOPPS	Dialysis Outcomes and Practice Patterns Study
DM	Diabetes Mellitus
DNA	Deoxyribonucleic Acid
DRIVE-II	Dialysis Patients Response to IV Iron with Elevated Ferritin II Study
4D	Die Deutsche Diabetes Dialyze Study

EBPG	European Best Practice Guidelines
E.coli	*Escherichia Coli*
EDTA	Ethylene Diamine Tetra Acetic Acid
eGFR	Estimated Glomerular Filtration Rate
EP	Erythropoietin Hormone
EPO	Epoetin Alfa
ERBP	European Renal Best Practice Guidelines
ERGO	Ergocalciferol
ESAM	European Survey of Anemia Management Study
ESAs	Erythropoietin-Stimulating Agents
ESRD	End-Stage Renal Disease
ET-1	Endothelin-1
Euro-DOPPS	European Countries in DOPPS Study
FDA	Food and Drug Administration
GFR	Glomerular Filtration Rate
G6PD	Glucose-6-Phosphate Dehydrogenises Enzyme
GMS	General Medical Supplies
GSH	Glutathione
H	Hour
Hb	Hemoglobin
HCB	Hepatitis B
Hct	Hematocrit
HCV	Hepatitis C
Hcy	Homocysteine

HD	Hemodialysis
HDL	High-Density Lipoprotein
HDL-C	Higher-Density Lipoprotein Cholesterol
HF	Heart Failure
HIKS	Health Insurance Khartoum State
HMP	Hexose Monophosphate Shunt
H_2O_2	Hydrogen Peroxide
HR	Hazard Ratio
HTN	Hypertension
HyDRIT	Hypertension, Diabetes, Renal Insufficiency and Thyroid Derangement Pilot Study
IDA	Iron Deficiency Anemia
IDNT	Irbesartan Diabetic Nephropathy Trial
IHD	Ischemic Heart Disease
INTERHEART	A Global Study of Risk Factors for Acute Myocardial Infarction
IV	Intravenous
JDST	Japanese Society for Dialysis Therapy
KDIGO	Kidney Disease Improving Global Outcomes
K/DOQI	Kidney Disease Outcome Quality Initiative
KEEP	Kidney Early Evaluation Program Study
Kh	Khartoum City
Kh N	Khartoum North City
Kt/V	Dialyzer Clearance Expressed As a Fraction Of Urea or Body Water Volume=Indicate Dialysis Adequacy
LDL	Lower-density Lipoprotein

LDL-C	Lower-density Lipoprotein Cholesterol
LOO^{o}	Peroxyl Radicals
LVH	Left Ventricular Hypertrophy
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDRD	Modification of Diet in Renal Disease Equation
MI	Myocardial Infarction
MIA	Malnutrition Inflammation-Atherosclerosis Syndrome
MMA	Methyl Malonic Acid
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NCKD	National Center for Kidney Diseases and Surgery
ND	Non-Dialysis Dependent
NDD-CKD	Non-Dialysis Dependent Chronic Kidney Disease
NHANES	National Health and Nutrition Examination Survey
NHIS	Normal Hematocrit Study
NICE	National Institute for Health and Care Excellence
NIDDK	National Institute for Diabetes and Digestive and Kidney Diseases
NIDDM	Non-Insulin-Dependent Diabetes Mellitus
NIH	National Institute of Health
NKF	National Kidney Foundation
NKF-K/DOQI	National Kidney Foundation-Kidney Disease Outcome Quality Initiative
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
O_2^{O-}	Superoxide Anion

OH^{O}	Hydroxyl Radical
Om	Omdurman
ORs	Odds Ratios
PA	Pernicious Anemia
PD	Peritoneal Dialysis
PMPM	Per Member Per Month
PPPY	Per Patient Per Year
PRA	Plasma Renin Activity
PRCA	Pure Red Cell Aplasia
PRESAM	Pre-Dialysis Survey of Anemia Management Study
PTA	Post-Transplant Anemia
PTH	Parathyroid Hormones
PVD	Peripheral Vascular Disease
PS	Power and Sample Size Software
QOL	Quality of Life
RAAS	Renin-Angiotensin-Aldosterone System
RAMP	Renal Anemia Management Period Study
RBC	Red Blood Cell
RCT	Randomized Control Trial
RDW	Red Cell Distribution Width
RENAAL	Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus (NIDDM) with The Angiotensin II Antagonist Losartan Study
rHuEpo	Recombinant Human Erythropoietin
RNA	Ribonucleic Acid

ROD	Renal Osteodystrophy
ROS	Reactive Oxygen Species
RRT	Renal Replacement Therapy
SBP	Systolic Blood Pressure
SC	Subcutaneous
SES	Socioeconomic Status
SD	Standard Deviation
SDG	Sudanese Pound
SHHS	Southern Sudan Household Survey
SHPT	Secondary Hyperparathyroidism
SPSS	Statistical Package for Social Sciences
STD	Short-Term Disability
TIBC	Total Iron Binding Capacity
TREAT	Trial to Reduce Cardiovascular Events with Aranesp Therapy Study
TSAT	Transferrin Saturation
UF	Ultra Filtration
USD	United State Dollar
USM	Universiti Sains Malaysia
USRDS	U.S Renal Data System
UTI	Urinary Tract Infections
WBC	White Blood Cell
WHO	World Health Organization
WTP	Willingness to Pay

PENILAIAN HASIL RAWATAN KLINIKAL DAN KOS PERUBATAN LANGSUNG TERHADAP ANEMIA KALANGAN PESAKIT-PESAKIT MENGALAMI PENYAKIT RENAL TAHAP AKHIR DI PUSAT-PUSAT HEMODIALISIS DALAM NEGERI KHARTUM

ABSTRAK

Anemia adalah komplikasi biasa bagi penyakit renal tahap akhir (ESRD) yang dianggap suatu masalah kesihatan awam. Ia sangat prevalens dengan komplikasi teruk dan melibatkan perbelanjaan kesihatan yang tinggi. Justeru itu, dengan ketiadaan data tempatan, penyelidikan ini bertujuan untuk menilai prevalens anemia, keberkesanan regimen-regimen drug, menentukan faktor-faktor yang menyumbang kepada pengawalan paras haemoglobin, dan faktor-faktor yang menyumbang kepada peningkatan peristiwa kardiovaskular, hospitalisasi, kematian, serta kos rawatan tahunan dalam rawatan anemia di Pusat-pusat hemodialisis kerajaan, negeri Khartoum. Penyelidikan ini adalah suatu kajian pemerhatian secara prospektif jangkapanjang yang mana semua pesakit-pesakit di dua belas pusat dialisis di ikuti sejak Ogos 2012 sehingga Julai 2013. Sejumlah 1015 pesakit-pesakit telah di pilih dalam kajian ini. Sebahagian jumlah itu, 194 (19.1%) pesakit-pesakit telah dipindahkan ke pusat-pusat lain, 165 (16.3%) mengalami kematian, 84 (8.3%) telah hilang dalam susulan, dan 38 (3.7%) menjalankan perpindahan renal. Sejumlah 534 (52.6%) pesakit-pesakit mengikuti dan di analisiskan. Kebanyakkannya adalah lelaki (307; 57.5%), dalam julat umur 18-85, purata umur adalah 48.7 ±16.1 tahun, dengan umur median adalah 50 tahun. Purata tempoh dialysis adalah 1.61 ±1.20 tahun, 65.4% pesakit-pesakit

mempunyai tahap pendidikan peringkat sekunder atau tertier, 57% mempunyai insuran kesihatan dan 56.4% adalah tidak bekerja. Kajian ini mendapati semua pesakit-pesakit mengalami anemia, dengan paras haemoglobin <12 g/dL, manakala lebih kurang 67% mempunyai paras hemoglobin level <10 g/dL dan hanya 20% sahaja mencapai paras Hb >12 g/dL. Namun demikian, telah didapati bahawa peningkatan ketara dalam paras HB purata bagi tujuh regimen-regimen drug. Anggarannya terdapat 61% pesakit-pesakit menerima drug ESA, purata dos mingguan adalah 8000 IU/kg dan 87.1 % menerima zat besi dextran. Corak drug-drug anemia kalangan 39.5% pesakit-pesakit adalah ESA, IV zat besi, zat besi oral, dan vitamins (vitamin B_{12} dan Folic acid). Terdapat hanya 27% pesakit-pesakit yang dilakukan ujian feritin dan saturasi transferin. Faktor-faktor yang mempunyai paras HB tinggi termasuk pesakit-pesakit yang mempunyai insuran kesihatan, yang mana penyelarasan nisbah odd (aORs) adalah 1.53, manakala dan gabungan drug-drug anemia yang merangkumi 'ESA, IV zat besi, zat besi oral dan vitamin' (OR = 1.87) dan 'ESA, zat besi oral dan vitamin', mempunyai nisbah odd 1.87 dan 6.67, masing-masingnya. Namun demikian, sejarah keluarga ESRD (OR=0.57) dan tempoh hipertensi yang melebihi 6 hingga 9 tahun (OR=0.47) menunjukkan perkaitan dengan paras Hb yang rendah. Manakala faktor-faktor yang mempengaruhi peristiwa-peristiwa kardiovaskular yang dilaporkan dalam 154 (28.8%) pesakit-pesakit berumur dalam julat 45 hingga 64 tahun (OR=1.94), umur melebihi 65 tahun (OR=10.88) dan mengalami uropati halangan (OR=2.33). Walau bagaimanapun, faktor-faktor yang meningkatkan risiko hospitalisasi dalam 206 (38.5%) termasuk usia lanjut (OR=5.01), hipertensi (OR=1.55), uropati halangan (OR=2.19), dan pielonefritis (OR=2.24). Faktor-faktor prognostik anemia terhadap bencana mortaliti adalah umur dalam julat 45 hingga 64 tahun, yang mana nisbah bencana (HR) adalah 1.65, usia lanjut (HR=2.30), diabetes (HR=1.43), hyperlipidemia

(HR=2.10) dan regimen drug anemia yang merangkumi “zat besi oral dan vitamin” (HR=2.30). Analisis kos rawatan tahunan menunjukkan kos purata tahunan bagi pesakit anemia yang menjalani ESRD hemodialisis adalah SDG 5,434.8 setiap pesakit. Pengubatan anemia menyumbangkan sebanyak 63% (SDG 1,904,122.7), ujian-ujian makmal sebanyak 31 % (SDG 952,632), dan 6% (SDG 171,434) berkaitan dengan kos personel perubatan. Regimen drug anemia yang menunjukkan purata kos perubatan langsung tahunan yang paling tinggi sebanyak SDG7802.6 ± 1191.10 adalah 'ESA, IV zat besi, zat besi oral, dan vitamin'. Pesakit-pesakit yang bekerja dan merokok serta corak penggunaan drug anemia yang mengandungi ESA merupakan faktor-faktor penyumbang terhadap kos tahunan langsung yang tinggi. Penyelidikan ini mengambarkan suatu senario tentang pengurusan anemia dalam pesakit-pesakit hemodialisis di negeri Khartoum, Sudan. Di perhatikan bahawa pesakit-pesakit memberikan respons yang pelbagai terhadap beberapa jenis-jenis drug anemia dan hanya peratus yang kecil sahaja mencapai paras Hb yang dikehendaki, yang mana ESA telah menyumbang pada peningkatan paras HB serta kos tahunan perubatan langsung. Justeru itu, penemuan dalam penyelidikan ini dapat memberikan suatu perancangan strategi klinikal dan ekonomi dalam pengurusan pesakit anemia di pusat-pusat hemodialisis yang dikaji.

EVALUATION OF CLINICAL OUTCOMES AND DIRECT MEDICAL COST OF ANEMIA MANAGEMENT AMONG END STAGE RENAL DISEASE PATIENTS IN KHARTOUM STATE HEMODIALYSIS CENTERS

ABSTRACT

Anemia is a common complication of end stage renal disease (ESRD), which is considered a public health problem. It is highly prevalent and associated with deleterious consequences and substantial health care expenditure. Therefore, in the absence of local data, this research aimed to evaluate the prevalence of anemia, effectiveness of drug regimens, factors contributing to the control of hemoglobin levels, and factors contributing to cardiovascular events, hospitalizations, deaths, as well as, the annual direct medical costs of anemia treatment at government hemodialysis centers in Khartoum State, Sudan. This research was an observational prospective longitudinal study where all patients at the 12 dialysis centers were followed from August 2012 to July 2013. A total of 1015 patients were recruited in this study. Out of these, 194 (19.1%) patients were transferred to other centers, 165 (16.3%) died, 84 (8.3%) were lost during follow-up, and 38 (3.7%) underwent renal transplantation. A total of 534 (52.6%) patients completed the study and were included in the analysis. The majorities were males 307 (57.5%), the age ranged from 18-85 years, mean age was 48.7±16.1 years, and the median age was 50 years. The study found anemia in all the patients, hemoglobin level (<12 g/dL), whereas about 67% had a hemoglobin level <10 g/dL and only 20% had achieved the target Hb level (≥12 g/dL) in the last month. However, a significant improvement in mean Hb levels in seven drug regimens was found. Approximately 61% of patients received

erythropoietin-stimulating agents (ESAs), and 87.1% received iron dextran. The most frequent anemia drugs regimen were 'ESA, intravenous (IV) iron, oral iron and vitamins (vitamin B_{12} and folic acid)' for 39.5% of the patients. Only 27% of the patients were tested for ferritin and transferrin saturation. The factors which influenced a higher Hb level were health insured patients, the adjusted odd ratios (aORs) was 1.53, while the combination of anemia drugs regimens comprised of 'ESA, IV iron, oral iron and vitamins', and 'ESA, oral iron and vitamins', had an odd ratios of (OR=1.87) and (OR=6.67), respectively. Nevertheless, factors related to the family history of ESRD (OR=0.57) and duration of hypertension for more than 6-9 years (OR=0.47) were associated with lower Hb level. The factors predicting the development of cardiovascular events reported in 154 (28.8%) patients, were age range from 45 to 64 years (OR=1.94), advanced age (≥ 65 year) (OR=10.88) and obstructive uropathy (OR=2.33). However, the factors associated with the risk of hospitalization in 206 (38.5%), were advanced age (OR=5.01), hypertension (OR=1.55), obstructive uropathy (OR=2.19), and pyelonephritis (OR=2.24). Anemia prognostic factors on mortality hazard were age range from 45 to 64 years, the hazard ratio (HR) was 1.65, advanced age (HR=2.30), diabetes mellitus (DM) (HR=1.43), hyperlipidemia (HR=2.10), and anemia drug regimen comprised of 'oral iron and vitamins' (HR=2.30). However, female gender (HR=0.55), smoking (HR=0.53), and pyelonephritis (HR=0.22), were inversely associated with mortality. Analysis of the annual direct medical cost for the treatment of hemodialysis anemic ESRD patients was Sudanese pound (SDG) 5,677.5 per patient. Anemia medications contributes about 63% (SDG 1,904,122.7), laboratory tests accounted for 31% (SDG 952,632), and 6% (SDG 171,434) cost of medical personnel. Anemia drugs regimen with highest mean annual direct medical cost of SDG7802.6 ±1191.10 was 'ESA, IV iron, oral iron and vitamins'.

Male, smoker, employed patients and anemia drug regimens containing ESA were factors associated with higher annual direct medical anemia costs. This research portrays a scenario of the management of anemia in patients undergoing hemodialysis at the studied centers in Khartoum State, Sudan. Patients demonstrated variable responses to the different types of anemia drug regimens and only small percentages had achieved a target hemoglobin level, of which ESA had contributed to the increased in Hb levels as well as the annual direct medical costs from patients' perspective. Therefore, the research findings may provide an important clinical and economic strategic planning for the management of anemic patients undergoing hemodialysis at the studied centers.

CHAPTER ONE

INTRODUCTION

1.1Background

Chronic kidney disease (CKD) is a worldwide public health problem, particularly in developing countries, with increasing incidence and prevalence, poor outcomes, and high costs (Levey *et al.*, 2007). CKD is defined as either kidney damage or glomerular filtration rate (GFR) < 60 ml/min/1.73m^2 for ≥ 3 months. Kidney damage can include pathologic abnormalities and markers of damage, resulting in reduced kidney function (Levey *et al.*, 2003). CKD manifests as either pathologic abnormalities or markers of kidney damage, including abnormalities in the composition of the blood or urine or abnormalities in imaging tests, with or without a supplementary reduction in glomerular filtration rate (GFR) (Kidney Disease Outcome Quality Initiative (K/DOQI) National Kidney Foundation (NKF), 2002).

1.1.1 Prevalence of end stage renal disease

The prevalence of CKD was estimated to be 8-16% worldwide (Jha *et al.*, 2013). However, according to the United States (US) Renal Data System (USRDS) the prevalence of CKD increased from 12% in 1988-1994 to 14% in 1999-2004, largely due to the increase prevalence rate of hypertension (HTN) and DM, but has remained stable at 13.6% in 2007-2012 (USRDS, 2015). The prevalence of CKD in Asian countries ranged from 1.7%- 20% (Zhang *et al*., 2012, McCullough *et al*., 2012, Zhang *et al*., 2008, Hosseinpanah *et al*., 2009, Imai *et al*., 2007).

Higher incidence and prevalence of CKD was documented in recent years in developed and developing countries as well as in sub-Sahara Africa. The frequency of CKD in Africa is at least 3-4 times more than in other developed countries (Naicker, 2009). About 70% of the least developed countries of the world are in sub-Saharan Africa. Hence, the prevalence of CKD suggested to range between 200-300 per million of the

general population (Naicker, 2010). The meta-analysis of 21 studies found the prevalence of CKD was 13.9% in sub-Saharan Africa (Stanifer *et al.*, 2014). In Sudan, according to the results of the cross-sectional community-based survey of the Hypertension, Diabetes, Renal Insufficiency and Thyroid Derangement (HyDRIT) pilot study, the prevalence of overall CKD was 11% when using standardized Cockroft-Gault equation and 7.7% using the four variable MDRD equation (Abu-Aisha *et al.*, 2009).

The end stage renal disease (ESRD) is defined as stage five CKD or kidney failure with GFR <15 ml/min/1.73m^2. It is associated with significant reduction in kidney function that is not compatible with life and accompanied by a combination of signs and symptoms of uremia, and increased risk of mortality, morbidity and others complications (National Kidney Foundation, 2002).

ESRD is highly prevalent and has become a major public health problem. In the USRDS there were 661,648 and 678,383 prevalent cases of ESRD in 2013 and 2014, respectively (USRDS, 2015b, USRDS, 2016a). While, in China the prevalence of ESRD was 102,863 patients at 2008 (Zuo *et al.*, 2010). A cross-sectional Iranian study found that the prevalence of CKD was 18.9% and only 0.1% in the stage 5 (Hosseinpanah *et al.*, 2009). In Japan, the prevalence of ESRD was more than 2,000 per million populations (Iseki, 2008). However, in Malaysia, the prevalence of ESRD was found to be 88.7% (Al-Ramahi, 2012).

Although, there was a lack of reliable statistics about the prevalence of ESRD in the majority of African countries (Naicker, 2009). However, in Sudan, the estimated incidence was 70-140 per million inhabitant per year in 1995 (Suliman *et al.*, 1995),

and in 2009 the prevalence of treated ESRD was 106 patients per million population (Elamin *et al.*, 2010).

1.1.2 Causes and risk factors of end stage renal disease

The etiologies of ESRD are related to several factors, the most important being HTN, DM, glomerulonephritis, and chronic interstitial nephritis (Barsoum, 2002). Risk factors for CKD can be classified into three categories;

1.1.2(a) Susceptibility factors

Susceptibility factors include advanced age, reduced kidney mass, low birth weight, family history of kidney disease, low income or education, and systemic inflammation (Ouseph, 2007, Chisholm-Burns *et al.*, 2008, National Kidney Foundation, 2002). Generally, these factors cannot be regulated by pharmacological therapy or lifestyle modifications. Although, these factors do not directly cause CKD, they are associated with an increased risk of CKD development (Ouseph, 2007,Chisholm-Burns *et al.*, 2008,National Kidney Foundation, 2002).

1.1.2(b) Initiation factors

Initiation factors are conditions that directly cause kidney damage and include DM, HTN, autoimmune diseases, polycystic kidney disease, systemic infections, urinary tract infections, urinary stones, lower urinary tract obstructions, and drug toxicity (Chisholm-Burns *et al.*, 2008, National Kidney Foundation, 2002). These factors are regulated by pharmacological therapy. The key risk factors for CKD are DM and HTN (Atkins, 2005, Yousif and Nahas, 2010).

1.1.2(c) Progression factors

These factors are associated with a rapid decline in kidney function and worsening of CKD. They include proteinuria, poor blood glucose control in patients with DM, elevated blood pressure, and tobacco smoking (Chisholm-Burns *et al.*, 2008, National Kidney Foundation, 2002). As with initiation factors, progression factors may be modified by pharmacological therapy or lifestyle modifications that slow the progression of CKD. About 30% of patients with diabetic nephropathy progress to ESRD (Atkins, 2005). DM was the largest single cause of ESRD in the United States in 2007-2012, being present in 39.2%-40.4% of patients with ESRD. In comparison, HTN was present in 26%-31% of these patients, cardiovascular disease (CVD) was present in 39.5% and obesity in about 17% (USRDS, 2015a).

1.1.3 Classification of chronic kidney disease

GFR is the best indicator of kidney function. Normal GFR varies by age, gender, and body size, ranging from 120-130 ml/min/1.73 m^2 in young adults and declining slightly with age (National Kidney Foundation, 2002).

Table 1.1Classification of stages of chronic kidney disease and clinical action plan for each stage

Stage	Description	GFR (ml/min/1.73m^2)	Action*
1	Kidney damage with normal or ↑ GFR	≥ 90	Diagnosis and treatment Treatment of comorbidities Slowing progression CVD risk reduction
2	Kidney damage with mild ↓GFR	60-90	Estimating progression
3	Moderate ↓ GFR	30-59	Evaluating and treating complications
4	Severe ↓ GFR	15-29	Preparation for kidney replacement therapy
5	Kidney failure (ESRD)	< 15 (or dialysis)	Replacement (if uremia present)

* Includes actions from the preceding stages,
GFR: glomerular filtration rate, CVD: cardiovascular disease, ESRD: end-stage renal disease

Classifications of the stages of CKD are based on the level of kidney function, regardless of the specific diagnosis. The KDOQI classification system has defined five stages of CKD and has recommended a clinical action plan for each stage Table 1.1 (National Kidney Foundation, 2002). According to the Kidney Disease Improving Global Outcomes (KDIGO) system, CKD can be classified into five stages, based on GFR and serum albumin concentration, as shown in Table 1.2.

Table 1. 2 Classification of stages of chronic kidney disease based on GFR and serum albumin concentration*

Stage	Description (G, A)	GFR (ml/min/1.73m^2)	Albuminurea (mg/mmol)
1 (G1, A1)	Normal or ↑, normal to mildly ↑	≥ 90	< 3
2 (G2, A1)	Mildly ↓, normal to mildly ↑	60-89	< 3
3a (G3a, A2)	Mildly to moderately ↓, moderately ↑	45-59	3–30
3b (G3b, A3)	Moderately to severely ↓, severely ↑	30-44	>30
4 (G4, A3)	Severely ↓, very severely ↑	15-29	>30
5 (G5, A3)	kidney failure, very severely ↑	< 15	>30

***Kidney Disease: Improving Global Outcomes (KDIGO), CKD Work Group, 2013,
G, glomerular filtration rate; A, Albuminurea

1.1.4 Treatment of end stage renal disease

The ESRD is the irreversible loss of kidney function, to a point at which the kidneys fail to sustain life. The main treatment for ESRD is renal replacement therapy (RRT) using dialysis or kidney transplantation (Meade *et al.*, 2009). In 2006, the National Kidney Foundation recommended that patients with stage 4 CKD (eGFR < 30 ml/ min/1.73m^2), as well as their family members and caregivers, receive timely education about kidney failure and treatment options, including kidney transplantation, peritoneal dialysis (PD) and hemodialysis (HD).

1.1.4(a) Peritoneal dialysis (PD)

The peritoneum is a membrane located in the abdomen, across which blood moves to remove waste products. In PD, a permanent tube is inserted into the abdomen and flushed out with fluid, either every night while the patient sleeps (automatic peritoneal dialysis [APD]) or via regular exchanges throughout the day (continuous ambulatory peritoneal dialysis [CAPD]) (Obrador *et al.*, 1999).

1.1.4(b) Hemodialysis (HD)

Dialysis is the process by which the blood is cleansed and excess fluids are removed artificially with special equipment called a dialysis unit (Obrador *et al.*, 1999). HD as a routine treatment for renal failure was initiated in the 1960s and has become the routine treatment for ESRD. HD has two main functions: the ultra-filtration (UF) of excess fluid and the diffusion of waste solutes and electrolytes across a semi permeable membrane.

The USRDS estimated that, in 2013, of all patients newly diagnosed with ESRD, 88.4% began renal replacement therapy with HD, 9.0% with PD, and 2.6% received a preemptive kidney transplant (USRDS, 2015b). Patients usually undergo HD 2-3 times per week, during which uremic nitrogen waste, phosphate, potassium, and magnesium are removed from the blood down a concentration gradient, and calcium and bicarbonate move into the circulation (Venkat *et al.*, 2006). HD also corrects fluid overload. In Sudan, PD was introduced as dialysis therapy in 1968 and HD in 1985 (Suliman *et al.*, 1995). In 2013, the National Center for Kidney Diseases and Surgery (NCKD) reported that there were 56 dialysis centers across the country, including 24 centers in Khartoum State, directly supervised by the government.

1.1.4(c) Kidney transplantation

A kidney transplant is an operation in which a person with kidney failure receives a new kidney. There are two types of kidney transplants: those from living donors and those that come from unrelated deceased donors (National Kidney Foundation, 2007).

1.2 Complications of end stage renal disease

1.2.1 Malnutrition

Nutrition during HD is very important in reducing complications and improving patient's quality of life. The higher risk of mortality in HD patients is frequently due to higher malnutrition rates, which have been estimated to range from 18%-75% (Dwyer *et al.*, 2005). Malnutrition is usually of long duration in HD patients, despite adequate dialysis dose and protein intake (Chazot *et al.*, 2001).

Two types of malnutrition can occur in dialysis patients: The first type consists of uremic syndrome and a reduction in serum albumin levels resulting from reductions in energy and protein intake. Malnutrition due to poor nutrition can lead to chronic volume overload, congestive heart failure (CHF), and systemic HTN, uremic bone disease and extra-skeletal metastatic calcification due to the development of hypophosphatemia and other adverse conditions encountered as a result of the diet incompatibility (Güneş, 2013). Protein-energy malnutrition is a common problem among patients on HD with inflammation, the most potent non-traditional cardiovascular risk factor in these patients, due to the development of atherosclerosis (Stenvinkel *et al.*, 1999, Kalantar-Zadeh *et al.*, 2005). This condition can be improved by adequate energy and protein intake.

The second type of malnutrition, which is associated with inflammation, atherosclerosis, and high cardiovascular mortality, is called the malnutrition inflammation-atherosclerosis (MIA syndrome). Prominent features of this type of malnutrition include the production of proinflammatory cytokines, increased oxidative stress, increased protein catabolism, increased resting energy expenditure, and hypoalbuminemia (Stenvinkel *et al.*, 2000). The MIA syndrome is associated with very high cardiovascular morbidity and mortality rates in patients undergoing HD (Dukkipati and Kopple, 2009,Chan *et al.*, 2012).

1.2.2 Renal osteodystrophy

Renal osteodystrophy (ROD) is a systemic disorder of mineral and bone metabolism due to CKD, which manifests as disturbances in bone physiological processes. ROD begins early during the course of kidney disease and worsens as kidney function declines, becoming essentially universal in patients with ESRD. ROD reduces quality of life and increases morbidity in patients with ESRD. Moreover, ROD is regarded as a musculoskeletal abnormality, the long-term effects of which may include altered cardiovascular function related to extra-skeletal calcification (National Kidney Foundation, 2007).

1.2.3 Anemia

Anemia is the clinical manifestation of a decline in circulating red blood cell mass and is commonly diagnosed by low blood hemoglobin (Hb) concentrations (Joy, 2002). The World Health Organization (WHO) defines anemia as Hb <13 g/dL in adult men and non-menstruating women, and <12 g/dL in menstruating women (WHO, 1993). The National Kidney Foundation defined anemia in 2000 as Hb <12 g/dL in adult men and post-menopausal women and < 11 g/dL in pre-menopausal women (National

Kidney Foundation, 2001). In 2006, updated National Kidney Foundation criteria defined anemia as Hb < 12 g/dL in women and <13.5 g/dL in men. More recently, in 2012, the KDIGO Anemia Work Group defined anemia in adults and children >15 years with CKD as Hb concentration <13 g/dL in men and <12 g/dL in women.

1.3 Causes of anemia in end stage renal disease

Erythropoietin (EP) is important for the production of red blood cells (RBCs) (Nurko, 2006). In healthy persons, release of erythropoietin is a response to a decline in Hb concentration or hematocrit. However, CKD patients are unable to produce erythropoietin in response to decreases in Hb or hemotocrit (Hct) (Erslev 1991). Anemia in ESRD is a multi-factorial disease, with anemia due to erythropoietin deficiency being a primary and frequent complication of ESRD.

Anemia in ESRD is mostly due to erythropoietin deficiency, inhibition of erythropioesis by uremic solutes, and reduction in RBCs life span caused by deficiencies in iron, vitamin B_{12}, and folic acid, and by blood loss (Eschbach, 2002, Levin *et al.*, 1999). However, non-renal and non-dialysis factors, including drug-induced bleeding, infection and inflammation, can also contribute to anemia in patients with CKD (Besarab and McCrea, 1993, Rice *et al.*, 1999).

1.4 Prevalence of anemia in end stage renal disease worldwide

The prevalence of anemia and Hb concentrations in patients with CKD vary according to race or ethnicity. Although the prevalence of anemia in both men and women increases as kidney function declines, the rates depend on the Hb concentration chosen to define anemia (Hsu *et al.*, 2002, Astor *et al.*, 2002, National Kidney Foundation, 2006, McFarlane *et al.*, 2008). An American study carried out among 8.3 million

patients with stages 3,4, and 5 CKD, in which anemia was defined as a Hb concentration < 12 g/dL, found that 4 million of these patients were anemic (McClellan *et al.*, 2004).

A cross sectional study in Nepal found that the prevalence of anemia was 100% in both pre and post dialysis patients (Bhatta *et al.*, 2011), and a study in India found that the prevalence of anemia in ESRD HD patients was 92% (Aditya *et al.*, 2014). A study in Saudi Arabia of a large cohort of patients with different stages of CKD showed that the prevalence of anemia in patients with stage 5 CKD was 82% (Shaheen *et al.*, 2011).

1.5 Prevalence of anemia in end stage renal disease in Africa

ESRD and its' associated anemia are highly prevalent in both developed and developing countries. A prospective study in Nigeria found that all 20 adult patients with CKD had anemia, but that this condition was more severe in patients on maintenance HD than in pre-dialysis patients (Abdu *et al.*, 2009). A cross sectional study in Tanzania showed that the prevalence of anemia, defined using WHO criteria, in patients with stages 4 and 5 CKD was 97% (Juma, 2012). A prospective cohort study in Cameroon found that 79% of the patients had anemia, primarily microcytic hypochromic anemia (Kaze *et al.*, 2015).

1.6 Prevalence of anemia in end stage renal disease in Sudan

Relatively little is known about the prevalence of anemia in different stages of CKD in Sudan. A study of patients with chronic renal failure (CRF), defined as serum creatinine concentrations ≥ 124 μmol/L for women and ≥ 133 μmol/L for men, showed that 28.6% of these patients had anemia, defined as an Hb concentration <12 g/dL (Fathelrahman, 2011). Another study reported that the prevalence of late post renal

transplant anemia (PTA) was 39.5% (Banaga *et al.*, 2011). However, the prevalence of anemia among ESRD patients undergoing HD in Sudan has not yet been determined.

1.7 Effectiveness of treatment of anemia in end stage renal disease hemodialysis patients

Early treatment of anemia in patients with CKD can delay the progression of renal disease and prevent costly consequences. Moreover, the management of anemia during ESRD is very important due to the strong associations between anemia and cardiovascular complications, as well as morbidity, mortality and patient quality of life (Pisoni *et al.*, 2004, Finkelstein *et al.*, 2009, Boudville *et al.*, 2009). The National Kidney Foundation has recommended treating anemia to maintain a target Hb range of 11-12 g/dL. The KDIGO has recommended that Hb concentrations be no higher than 13 g/dL for general adult patients using erythropoietin-stimulating agents (ESAs) and not higher than 11.5 g/dl for patients with ESRD.

The management of anemia in ESRD has been transformed since the licensing of recombinant human erythropoietin (rHuEpo) in 1988 in the US. Prior to 1989, dialysis patients were transfusion-dependent and suffered the debilitating symptoms consistent with Hb levels chronically in the 6-7 g/dL range (Lankhorst and Wish, 2010). Epoetin alfa (EPO) and darbepoetin alfa (DARB) are erythropoietic agents indicated in the United States for the treatment of anemia in patients with CKD. However, treatment of anemia with erythropoietin requires concomitant treatment of iron deficiency (Auerbach *et al.*, 2008).

Iron supplementation is necessary in more than half of patients with advanced CKD, particularly patients who receive ESAs. However, patients not receiving ESAs may

also require iron supplementation (Locatelli *et al.*, 2009, Francisco and Angel, 2010). Various anemia practice guidelines, including the 2004 European Best Practice Guidelines (EBPG), the 2006-2007 National Kidney Foundation guidelines, the 2008 European Renal Best Practice (ERBP) guidelines, and the 2012 KDIGO guidelines, recommend oral iron therapy for non-dialysis CKD patients and kidney transplant recipients, particularly those not on ESAs. Although oral iron may be used in patients undergoing ESA treatment, parenteral iron is more effective and better tolerated (Locatelli *et al.*, 2009, Francisco and Angel, 2010).

A prospective, randomized study showed that epoetin therapy achieved target Hb levels in ESRD HD patients with anemia and a history of CVD, while adverse outcomes were associated with higher Hb levels (Besarab *et al.*, 1998). In contrast, clinical trials have shown that ESAs corrected anemia and improved quality of life in ESRD patients by eliminating the need for blood transfusion and the risk of immunologic sensitization, infections, and iron overload (Eschbach *et al.*, 1987, Eschbach *et al.*, 1989b). Indeed, a previous randomized control trial (RCT) showed that epoetin improved patients' quality of life while, partially correcting Hb level, but adverse effects, including death, were observed in some dialysis patients (Furuland *et al.*, 2003).

Iron supplementation is essential for patients with CKD-related anemia and can be administered orally or intravenously. The 2005 USRDS Annual Report found that approximately 70% of ESRD HD patients in the U.S. receive intravenous (I.V) iron supplements (USRDS, 2005).

1.8 Economic burden of anemia management in end stage renal disease

Anemia is an ESRD-specific complication that contributes to the cost of ESRD. The economic burden of anemia in ESRD patients is a global dilemma. Greater understanding of the burden of anemia in ESRD patients is needed to evaluate the potential benefits of treatment. Anemia in ESRD HD patients places a high burden on these individuals and on society, being both a major public health problem and placing an economic burden on the health care system. The results of burden of illness analysis are usually used to help set priorities for healthcare expenditures (Lissovoy, 2007). This burden is associated with both direct health care costs and indirect costs, including loss of productivity from disability and premature mortality.

In the USA, the burden of anemia was estimated to be US$110 million, with direct medical costs twice as high for anemic than for non-anemic patients with CKD (Nissenson *et al.*, 2005). The lowest burden from iron deficiency anemia (IDA) was found in high income North America (2.9%), whereas low income regions had a very high burden, including Central Asia (64.7%), South Asia (54.8%), and Andean Latin America (62.3%). However, for the higher life expenditures and cost of health care services, the burden of CKD anemia tend to be higher in high-than in low-income regions (Kassebaum *et al.*, 2014).

Factors associated with the cost of anemia management included numbers and lengths of visits to dialysis centers and low Hb concentration, with ESA accounting for 90% of the total cost (Rottembourg *et al.*, 2015). Large savings may be achieved by using the ESA once per month (Schiller *et al.*, 2008). An observational study showed that using the ESA once per week can save time and costs, by converting from traditional ESA regimens to once monthly long acting ESA and reducing the amount of health

care staff time associated with ESA administration. The current mean annual cost of anemia management with ESA in 100 patients is €4,786 in Germany and €7,696 in the UK (Saueressig *et al.*, 2008).

Increased costs of anemia in ESRD patients have been associated with increased morbidity and mortality, decreased quality of life, and substantial health care costs. Direct costs include those of visits to the physician, medications, hospital stay, diagnostic procedures and others. Indirect costs can include the time taken off from work for treatment and to treat side effects of treatment, as well as for transportation (Cox and Hesselgrave, 1998).

1.9 Direct medical costs of anemia in end stage renal disease

Several factors must be included in economic analyses of costs related to the treatment of anemia in patients with ESRD without complications. These factors include both direct and indirect costs. Drug acquisition costs and hospitalization costs are the two largest components of direct health care costs for patients with CKD**.** Frequent anemia among privately insured population results in greater health care utilization and costs (Nissenson *et al.*, 2005). Anemia management markedly increased the annual direct medical costs in insured patients with CKD; the costs per patient were found to be $78,209 in anemic patients (Ershler *et al.*, 2005). Administration of drugs to treat anemia, including intravenously administered iron, vitamin D and ESA, accounted for sustained increases in Medicare expenditures in the U.S. for ESRD HD patients. For example, in 2002 Medicare paid more than US$1billion for ESA (Pizzi *et al.*, 2006).

1.10 Health economic studies

The goal of the healthcare system is to provide qualified health services to patients, despite limitations in available resources. Economic analysis includes both inputs and outputs, and involves costs, consequences and choices (Gold *et al.*, 1996). Because of limited resources and the inability to achieve all target outputs, healthcare managers and physicians require equilibrium in choices of therapy, based on both clinical and economic criteria. Therefore, economic evaluations can enable physicians and administrators to make decisions, providing outlines that account for the clinical and economic consequences related to their choices (Drummond *et al.*, 1997).

Economic evaluation has been defined as the comparative analysis of alternative courses of action, considering both their costs and consequences (Drummond *et al.*, 2005). There are four types of pharmacoeconomic analyses tools depending on clinical outcomes, which enable economic evaluation and the ability to choose the optimal utilization of scarce resources (Goodacre and McCabe, 2002, Drummond *et al.*, 1997). These are cost-benefit analysis (CBA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-minimization analysis (CMA), and cost-of-illness (COI) analysis.

1.10.1 Cost-of illness analysis

Cost-of-illness (COI) analysis consider the costs of a given disease without considering the outcomes. COI was the first economic evaluation technique in healthcare, being used to measure the economic burden of a particular disease to society (Tarricone, 2006). However, the aim of a COI study is to identify and measure all the costs of a particular disease, including direct, indirect, and intangible costs (Bootman *et al.*, 1996, Rice, 1994).

COI analysis estimates the cost of a disease based on its prevalence or incidence. Prevalence studies refer to the total number of cases in a determined period of time (usually a year), estimating the direct costs and production losses attributable to all cases of any disease or group of diseases within that time period (Tarricone, 2006). Incidence-based costs represent the lifetime costs resulting from a disease or illness, based on all cases with onset of disease in a given base year (Byford *et al.*, 2000). COI studies are used by policymakers to justify budgets, to prioritize funding for biomedical research, and to develop intervention programs to ameliorate or prevent a disease (Rice, 2000).

Several perspectives can be considered in economic evaluations, including those of the patient, hospital, government, insurer, employer, or society, thereby reflecting different levels of a healthcare system (Robinson, 1993).

1.11 Problems statement

There are several problems to be examined by this study including; the prevalence of anemia among ESRD HD patients and the anemia drugs regimen that can achieve the target Hb levels. In addition to determining the factors affect control of Hb levels, this study also attempts to determine factors that could enhance the development of adverse clinical outcomes that may be associated with uncontrolled Hb levels, namely new-onset cardiovascular events, hospitalization, and death. Moreover, the study examined the estimated annual direct medical costs of anemia management in ESRD HD patients.

1.12 Rationale of the study

Anemia is a well-known complication of ESRD that contributes to higher morbidity and mortality rates and affects the quality of life of ESRD patients undergoing HD. Moreover, it has severe impact on patients and health care systems. The economic burden of illness is important in the allocation of health care resources and evaluation of research and programs (Rice *et al.*, 1985). In spite of the high prevalence of anemia in ESRD worldwide, no previous study has assessed the prevalence of anemia and the direct medical costs of anemia management in Sudan. On the other hand, the management of anemia among patients undergoing HD is inadequate (Elamin and Abu-Aisha, 2012). Therefore, this study was designed to provide baseline data about the status of anemia in ESRD patients undergoing HD in Khartoum State and the use of drug regimens based on clinical practice guidelines to achieve target Hb levels. The study was also performed to identify the factors that contribute to adverse clinical outcomes related to uncontrolled Hb levels. The study was also conducted to estimate the direct medical cost of anemia management among the patients. The results of this study may provide health care system planners with evidence enabling the design of optimal treatment plans to maximize the effectiveness of anemia medications, along with other factors, to control Hb levels and to avoid the development of complications and the burden of anemia management.

1.13 Significance of the study

This study evaluated the effects of anemia medications and direct medical costs in anemic ESRD patients undergoing HD over a period of one year. Its results can enable stakeholders and policy makers to design a sustainable plan to improve health care and quality of life. Its results may also help appraise the economic burden of anemia in ESRD patients undergoing HD in governmental dialysis centers in Sudan.

There is no previous study in Sudan on the prevalence of anemia and factors affecting anemia management, cardiovascular events, hospitalization, and death. Moreover, this study adopted both clinical and economic perspectives, which may be important in designing a plan associated with the costs of anemia treatment in ESRD patients. The main significance of this study is that it outline anemia management in ESRD patients undergoing HD in Khartoum governmental dialysis centers and roughly estimate the direct medical costs involved in treating ESRD-related anemia from the patient perspective. The study also provides data about the prescribing pattern of drugs, which can help predict future consumption regimens.

1.14 Study objectives

1.14.1 General objective

To evaluate clinical outcomes and annual direct medical costs of anemia treatment in ESRD patients undergoing HD at governmental hemodialysis centers in Khartoum State, Sudan.

1.14.2 Specific objectives

1. To determine the prevalence of anemia among ESRD patients undergoing HD.
2. To assess the anemia drug regimens that achieve Hb target levels in anemic ESRD patients undergoing HD.
3. To evaluate the factors that affect control of Hb levels. These include *patient factors, clinical factors,* such as *comorbidities, etiologic factors for ESRD, duration of HTN and DM,* in addition to *anemia medications.*
4. To determine factors contributing to the development of the *new onset cardiovascular events, hospitalization, and death.*
5. To estimate the annual direct medical costs among anemic ESRD HD patients.

CHAPTER TWO

LITERATURE REVIEW

2.1 Background

This research highlights anemia in ESRD patients undergoing HD and its management. The results of this study documented the prevalence of anemia, utilized anemia drug regimens, factors affecting Hb levels, adverse clinical outcomes, and factors contributing to these outcomes. As well as, the background information for the cost of anemia, and the estimated direct medical cost in these patients. Therefore, this literature review will focus on the; background of anemia in ESRD patients undergoing HD, clinical variable characteristic of anemia in ESRD patients, factors affecting anemia control, effectiveness of anemia medications, anemia adverse clinical outcomes, the factors which contribute to their development, and the annual direct medical cost including cost of anemia medications, laboratory tests, and medical personnel.

Anemia is a well-recognized complication of CKD. It is one of the clinical and laboratory manifestation of a decrease in circulating red blood cell mass identified by low blood Hb concentration. It begins when the GFR falls below 30-35% of normal level (Levin, 2001). The degree of anemia is proportional to the severity of azotemia, which increases morbidity and mortality among dialysis and pre-dialysis ESRD patients (Radtke *et al.*, 1979, Kovesdy *et al.*, 2006). Despite the advances in dialysis care and the use of the ESAs drug, anemia continues to be a clinical problem in patients with ESRD.

2.2 Definitions of anemia in end stage renal disease patients

Anemia is a common severe outcome in patients with CKD, with reported prevalence rates of 9-64% depending on CKD stage and definition, and is associated with increased morbidity and mortality (Knight *et al.*, 2010). Anemia is defined by a

decrease in Hct or Hb. The NKF-K/DOQI clinical practice guidelines defined anemia when Hb levels are maintained between 11-12 g/dL for all stages of CKD (National Kidney Foundation, 2001). This is inconsistent with its definition in the NKF-K/DOQI, 2006 and 2007 as Hb value < 12 g/dL in females and Hb value < 13.5 g/dL in males, whilst, the EBPG in 2004 defined anemia as Hb levels < 11.5 g/dL in women, Hb levels < 13.5 g/dL in men ≤ 70 years old and Hb levels < 12 g/dL in men >70 years old. In 2008, EBPG updated anemia definition as Hb < 12 g/dL in females and Hb < 13.5 g/dL in males (Locatelli *et al.*, 2009). Nevertheless, it updated according to the KDIGO Anemia Work Group, 2012, as mentioned earlier.

2.3 Epidemiology of anemia in end stage renal disease hemodialysis patients

Anemia is a common and severe complication of advanced kidney disease and its incidence increases as GFR declines. In general population, the prevalence of anemia in 2010 was 32.9% worldwide (Kassebaum *et al.*, 2014). In the US analysis of cross-sectional data from the National Health and Nutrition Examination Survey (NHANES), 2007-2008 and 2009-2010, prevalence of anemia ranged between 15.4% and 53.4% in ESRD (Stauffer and Fan, 2014). However, when anemia is defined according to the KDOQI definition as Hb < 13.5 g/dL for males and Hb < 12 g/dL for females, the prevalence was greater in the Kidney Early Evaluation Program (KEEP) study than in the NHANES study, 13.9% vs. 6.3%, respectively (McFarlane *et al.*, 2008).

A US multi-center cross-sectional study found that the prevalence of anemia in CKD patients who had not received the ESAs therapy was 47.7% when anemia was defined as Hb ≤ 12 g/dL and 8.9% when Hb level ≤ 10 g/dL (McClellan *et al.*, 2004). Moreover, the high anemia prevalence of Hb value <11 g/dL in maintenance patients

undergoing HD in Brazil was documented as 73.7% (Matos *et al.*, 2013). Moreover, the findings of the Dialysis Outcomes and Practice Patterns Study (DOPPS) study revealed that the prevalence of anemia of Hb <11 g/dL in patients undergoing HD ranges between countries from 23% to 77% (Pisoni et al., 2004). Furthermore, Zuo *et al.* (2016) documented that in China-DOPPS patients the prevalence of anemia of Hb < 9 g/dL was 21% compared with 10% in Japan and 3% in North America.

In the Iranian cross-sectional study on HD and pre-dialysis CKD patients noted that the prevalence of anemia among the patients was 85% and 75%, respectively. The mean Hb level was 10.27g/dL and 11.11 g/dL, respectively (Afshar *et al.*, 2007). However, a high prevalence of anemia defined as Hb level < 13 g/dL in males and < 12 g/dL in females ESRD HD patients was found in Korea as 93% (Hwang *et al.*, 2009). Moreover, a retrospective study conducted in North Africa revealed a higher prevalence of anemia of 88% in ESRD (Maïz *et al.*, 2002). The prevalence of anemia in lower-income regions of sub-Saharan Africa increased from 16.4% to 23.9% of the total anemia prevalence worldwide. However, the higher-income regions had the lowest prevalence (Kassebaum *et al.*, 2014).

2.4 Causes of anemia in end stage renal disease hemodialysis patients

Anemia is considered as a complication or uremic syndrome related to a decline in the level of GFR (National Kidney Foundation, 2002). The primary cause of renal anemia is decreased EP-producing capacity related to renal disorder (Tsubakihara *et al.*, 2010). Furthermore, causes of renal anemia which include uremic toxin or endotoxin, malnutrition, shorter life span of RBCs due to inflammation and other factors, poor responsiveness of erythroid progenitor cells to EP, and residual blood in the HD circuit of patients undergoing HD (Tsubakihara *et al.*, 2010). This is in addition to

deficiencies in EP, vitamins, iron, and blood loss (Eschbach *et al.*, 1989a, Nurko, 2006). In general, malaria, schistosomiasis, and CKD are the common diseases which contribute to higher prevalence of anemia worldwide (Kassebaum *et al.*, 2014).

2.5 Risk factors for anemia in end stage renal disease hemodialysis patients

CKD-related anemia is associated with several risk factors that are also more prevalent among patients undergoing HD. Identification of these factors is necessary for both the prevention and management of anemia. The risk factors can be divided into, the socio-demographic and clinical factors:

2.5.1 Socio-demographic factors

2.5.1(a) Gender

Gender differences are considered as an important factor in the cause and control of anemia in ESRD. In US, the retrospective studies showed that females were more likely to have anemia than males for all conditions (Nissenson *et al.*, 2005, Ershler *et al.*, 2005). However, the previous NHANES III (1988-1994) study, demonstrated that adult males had a greater decrease in Hb concentration than females (McFarlane *et al.*, 2008).

A review study documented that previous studies had revealed that anemia was more prevalent among male than female population (Beghé *et al.*, 2004). On the other hand, a study suggested that anemia was common in both males and females in CKD patients (Hsu *et al.*, 2002). It could be that the disparity in the prevalence of anemia between the sexes may relate to differences in the Hb cut-off point used for the definition of anemia, as well as, the fact that the normal range in females may be used for defining