Article

Not peer-reviewed version

Factors Contributing to Negative Outcomes Associated with Medications and Drug-Related Problems in Kidney Replacement Therapy. A Hospital-Based Prospective Observational Study

Alfonso Pereira-Céspedes *, Alberto Jiménez-Morales, Aurora Polo-Moyano, Magdalena Palomares-Bayo, Fernando Martínez-Martínez, Miguel Ángel Calleja-Hernández

Posted Date: 16 January 2024

doi: 10.20944/preprints202401.1186.v1

Keywords: kidney replacement therapy; medication review; drug-related problems; negative outcomes associated with medication.

Article

Factors Contributing to Negative Outcomes Associated with Medications and Drug-Related Problems in Kidney Replacement Therapy. A Hospital-Based Prospective Observational Study

Alfonso Pereira-Céspedes [1,2,3,4,*], Alberto Jiménez-Morales [1,2], Aurora Polo-Moyano [4], Magdalena Palomares-Bayo [4], Fernando Martínez-Martínez [1] and Miguel Ángel Calleja-Hernández [1,5]

1 Pharmaceutical Care Research Group, Pharmacy Faculty, University of Granada, 18071 Granada, Spain; alberto.jimenez.morales.sspa@juntadeandalucia.es (A.J.-M.); femartin@ugr.es (F.M.-M.); mangel.calleja.sspa@juntadeandalucia.es (M.Á.C.-H.)
2 Pharmacy Department, Hospital Universitario Virgen de las Nieves, 18014 Granada, Spain
3 Centro Nacional de Información de Medicamentos, Instituto de Investigaciones Farmacéuticas, Pharmacy Faculty, University of Costa Rica, San José 11501-2060, Costa Rica
4 Nephrology Department, Hospital Universitario Virgen de las Nieves, 18014 Granada, Spain; mapalomabayo@gmail.com (M.P.-B.); auroreja2002@yahoo.es (A.P.-M.)
5 Pharmacy Department, Hospital Universitario Virgen Macarena, 41009 Seville, Spain
* Correspondence: alfonsopereira@correo.ugr.es (A.P.-C.).

Abstract: Background: Negative outcomes associated with medications (NOM) and drug-related problems (DRP) significantly impact individuals with kidney replacement therapy (KRT) given the complexities of managing kidney disease and associated comorbidities. The present study aims to assess the frequency of NOMs/DRPs among KRT patients and identify contributing factors. Methods: A cross-sectional study was conducted at Virgen de las Nieves University Hospital (Granada, Spain), involving 117 outpatient adults with KRT. Data were collected from February 2021 to July 2023 using electronic records, semi-structured interviews (Dáder Method), and discussions with nephrology specialists. NOMs/DRPs were identified following treatment guidelines. Binary logistic regression determined associated factors (p-value < 0.05). Results: Across 117 patients, 2,436 NOMs and 3,303 DRPs were identified, averaging 20.82 NOMs and 28.23 DRPs per patient. Prevalent NOMs included untreated conditions (58.95%), quantitative ineffectiveness (35.43%), and non-quantitative safety problems (5.13%). Dominant DRPs were undertreated conditions (37.63%), wrong dose/posology/length (33.00%), risk of adverse drug reactions (ADR) (16.14%), and non-adherence (6.87%). Patients with ADR, undertreated conditions, and anemia were associated with quantitative ineffectiveness. Risk of ADR and vitamin D deficiency/insufficiency correlated with non-quantitative safety problems. Conclusions: KRT patients exhibited a substantial prevalence of NOMs/DRPs. Further research is needed to deepen our understanding of these complexities for improved patient care.

Keywords: kidney replacement therapy; medication review; drug-related problems; negative outcomes associated with medication

1. Introduction

Chronic kidney disease (CKD) is a significant global public health issue, necessitating early identification and intervention to delay its progression [1–5]. Once the disease reaches a stage leading to end-stage renal disease (ESRD), patients necessitate kidney replacement therapies (KRT), which may involve hemodialysis (HD), peritoneal dialysis (PD), and kidney transplant (KT) [1,5]. The projected number of individuals experiencing ESRD requiring KRT is estimated to fall between 4.902 and 7.083 million [1].

 doi:10.20944/preprints202401.1186.v1

The KRT pose intricate medical challenges, necessitating the use of numerous medications to manage their associated comorbidities (6). These healthcare conditions impose substantial financial burdens on the healthcare system. Individuals afflicted with these ailments face potential issues related to medication, known as drug-related problems (DRP), which can elevate the risk of heightened morbidity, mortality, and healthcare expenses [1,4,5,7,8]. DRPs can lead to negative outcomes associated with medications (NOM) [1,7,8].

Few published studies on NOMs and associated factors in KRT are available [7]. Recognizing NOMs and DRPs is a responsibility that pharmacists can manage in collaboration with other healthcare professionals by conducting medication reviews with follow up [1,3,7–9].

Assessing NOMs/DRP in the KRT population in Spain holds significance for various reasons. This includes the rising prevalence of CKD in the local community, which could potentially diminish quality of life, extend hospitalization durations, and elevate the likelihood of both mortality and morbidity [10].

The aim of this study is to determine the frequency of NOMs/DRPs and associated factors among patients undergoing KRT.

2. Materials and Methods

2.1. Design and Setting

A cross-sectional and prospective observational study was carried out at the nephrology department of Virgen de las Nieves University Hospital (Granada, Spain). The research spanned from February 2nd, 2021, to July 31, 2023, encompassing a period of 29 months, and focused on patients with ESRD.

2.2. Study Population and Eligibility Criteria

All outpatient individuals meeting the following criteria were considered for inclusion in the study: being over 18 years old, undergoing RRT such as HD, PD, or KT at nephrology department during the study period, and expressing willingness to participate. The stage of kidney disease was determined by categorizing patients using the estimated Glomerular Filtration Rate, calculated from serum creatinine levels employing the CKD EPI formula, as documented in the electronic medical records. Patients with cognitive impairment were excluded from the study.

2.3. Methods

Data collection involved two main sources: electronic medical records and semi-structured interviews following the Dáder Method developed by the Pharmaceutical Care Research Group at the University of Granada [11]. Additionally, discussions with nephrology experts were facilitated by pharmacists.

The pharmacist conducted a thorough review of electronic medical records and conducted semi-structured interviews. These interviews aimed to assess the number of prescribed medications and identify baseline demographics, comorbidities, clinical laboratory data, allergies, and the number of NOMs/ DRPs.

2.4. Study Outcomes

The primary outcome was the prevalence of NOMs/ DRPs and associated factors among outpatients undergoing KRT. These included different types of NOMs/ DRPs, as was reported in previous studies according to the Granada Third Consensus [11], and associated factors such as: age, sex, number of comorbidities, number of medications, age, clinical laboratory data, time in KRT, time in KT and number of hospitalizations.

Additional secondary outcomes include types of medications and comorbidities.

 doi:10.20944/preprints202401.1186.v1

2.5. Sample Size

We included all patients consulting the nephrology department of the Virgen de las Nieves University Hospital and meeting the eligibility criteria.

2.6. Operational Definitions

2.6.1. NOMs

A NOM is a result affecting the health of the patient that is or may be associated with the use of medications [11].

2.6.2. DRPs

A DRP is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes [11].

2.7. Statistical Analysis

The prevalence of NOMs/ DRPs is presented as percentage, with a 95% confidence interval using an exact binomial test. We tabulated descriptive statistics by a count or percentage for categorical variables, and the mean ± standard deviation (SD), median, or interquartile range (IQR), when appropriate, were used for continuous data.

Spearman's Rank correlation (r_s) was used to measure the association or correlation between the number of NOMs, as the dependent variable and the following independent variables: number of DRPs, number of comorbidities, number of medications, age, clinical laboratory data, time in KRT, time in KT and number of hospitalizations. A chi-square test of independence was performed to examine the relation between categorical variables.

Binary logistic regression was used to analyze the association between independent and dependent variables, and variables with a p value <0.05 were a candidate for multivariate analysis.

Statistical tests were conducted using a 5% level of significance. All analyses were conducted using SPSS 29.0.1.1(171) (IBM Corporation, USA, 2023) and R software version 4.3.2 (2023-10-31).

2.8. Ethics

Institutional review board approval was obtained from Andalusian Biomedical Research Ethics Committee (FIS-IRB-2020-01) on July 28, 2020. The written informed consent was obtained from each study participant.

3. Results

3.1. Sociodemographic and Clinical Characteristics of the Study Population

Throughout 29 months study period, 117 KRT patients were included in the study. Eleven patients died throughout the study due to complications of kidney disease (Table 1).

Table 1. Characteristics of KRT patients at the Virgen de las Nieves University Hospital (Granada, Spain).

1. **Baseline Characteristics**	**N=117[a]**
Age, mean (SD)	63 (14) years
Age >75 years	31 (26.50)
Age > 60 years	71 (60.68)
Sex (Males)	62 (52.99)
Current renal replacement therapy	
• Hemodialysis	72 (61.54)
• Deceased donor	28 (23.93)

 doi:10.20944/preprints202401.1186.v1

• Peritoneal dialysis	16 (13.68)
• Living donor	1 (0.85)
Personal history of renal transplant	23 (19)
Personal history of hemodialysis	35 (29.91)
Personal history of peritoneal dialysis	28 (23.93)
Number of renal transplants, mean (SD)	0.55 (0.71)
Time in dialysis, median (IQ)	41 (85.50-19) months
Time in kidney replacement therapy, median (IQ)	50 (105-31) months
Time in kidney transplant, mean (SD)	26 (91) months
Number of hospitalizations, mean (SD)	0,20 (0.44)
Number of comorbid conditions per patient, mean (SD).	18.64 (4.35)
Number of medications per patient, median (IQ)	12 (13-10)
Number of medications per patient, median (IQ) (end of study)	12 (15-10)
Number of medications administered at dialysis per patient, median (IQ)	2 (3-0)
Number of medications administered at dialysis per patient, median (IQ) (end of study)	1 (3-0)
Number of medications administered at home per patient, median (IQ)	10 (12-8)
Number of medications administered at home per patient, median (IQ) (end of study)	10 (14-9)
Allergies to medications	34 (29.06)
2. Underlying cause of End-Stage Renal Disease	
• Unknown	31 (26.50)
• Glomerulonephritis	28 (23.93)
• Diabetic nephropathy	16 (13.68)
• Polycystic kidney disease	12 (10.26)
• IgA nephropathy	9 (7.69)
• Systemic disease	5 (4.27)
• Vascular nephropathy	5 (4.27)
• Reflux nephropathy	4 (3.42)
• Pyelonephritis	3 (2.56)
• Nephrotoxicant-induced nephropathy	1 (0.85)
• Interstitial nephropathy	1 (0.85)
• Congenital anomalies of the kidney and urinary tract	1 (0.85)
• Tuberous sclerosis	1 (0.85)
3. Serum clinical laboratory data	
• Glucose mg/dL, mean (SD)	108.22 (29.87)
• Urea mg/dL, mean (SD)	104.85 (35.62)
• Creatinine mg/dL, mean (SD)	6.86 (3.89)
• Uric acid mg/dL, mean (SD)	5.79 (1.18)
• Total Proteins g/L, mean (SD)	6.32 (0.56)
• Albumin g/L, mean (SD)	3.61(0.44)
• Sodium mEq/L, mean (SD)	138.55(2.54)
• Potassium mEq/L, mean (SD)	4.83(0.54)
• Calcium mg/dL, mean (SD)	8.81(0.62)
• Phosphorus mg/dL, mean (SD)	4.33(1.09)
• Magnesium mg/dL, mean (SD)	2.06(0.33)
• intact parathyrin pg/mL, mean (SD)	307.42 (212.44)
• Vitamin D (25OH) ng/mL, mean (SD)	23.99 (9.81)
• Iron ug/dL, mean (SD)	71.33 (20.49)

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 16 January 2024 doi:10.20944/preprints202401.1186.v1

• Ferritin ng/mL, mean (SD)	460.59 (368.64)
• Transferrin mg/dL, mean (SD)	190.94 (43.13)
• Transferrin (saturation index) %, mean (SD)	31.53 (9.89)
• Folic acid ng/mL, mean (SD)	10.34 (6.62)
• Vitamin B12 pg/mL, mean (SD)	485.90 (262.88)
• Total cholesterol mg/dL, mean (SD)	152.58(36.43)
• HDL cholesterol mg/dL, mean (SD)	55.81(18.57)
• LDL cholesterol mg/dL, mean (SD)	95.04(25.43)
• Triglycerides mg/dL, mean (SD)	126.64(54.66)
• C-reactive protein mg/L, mean (SD)	16.86 (25.50)
• Erythrocytes (count) $x10^6$/uL, mean (SD)	3.73 (0.54)
• Hemoglobin g/dL, mean (SD)	11.57(1.35)
• Hematocrit %, mean (SD)	35.43(3.83)
• Leukocyte (count) $x10^3$/uL, mean (SD)	7.13 (3.65)
• Platelet (count) $x10^3$/uL, mean (SD)	188.66 (63.88)
4.Comorbilities/Risk factors for CKD[b]	
• Diabetes	32 (27.35)
• Hypertension	101 (86.32)
• Autoimmune diseases	7 (5.98)
• Other Systemic infections (e.g., HIV, hepatitis B virus, hepatitis C virus)	53 (45.30)
• Cytomegalovirus	6 (5.13)
• Exit-site infection	6 (5.13)
• Recurrent urinary tract infection	24 (20.51)
• Nephrotoxic medications (e.g., nonsteroidal anti-inflammatory drugs, herbal remedies, lithium)	5 (4.27)
• Kidney stones	9 (7.69)
• Malignant neoplasms	25 (21.37)
• Obesity and other hyperalimentation	26 (22.22)
• Smoking or personal history of smoking	44(37.61)
• Other cardiovascular diseases	71(60.68)
• Dyslipidemia	83(70.94)
• Personal history of COVID-19	30(25.64)
• Family history of kidney disease	26 (22.22)
• Anemia	105 (89.74)
• Mineral and bone disorder	107 (91.45)
• Hyperphosphatemia	98 (83.76)
• vitamin D deficiency/ insufficiency	79 (67.52)
• secondary hyperparathyroidism	98 (83.76)
• Hypocalcemia	64 (54.70)
• Hypomagnesemia	47 (40.17)
• Hyponatremia	45(38.46)
• Hypoalbuminemia	65(55.56)
• Hyperkalemia	83 (70.94)
• Metabolic acidosis.	18 (15.38)
• Hyperuricemia	52 (44.44)
• Diseases of the nervous system	35 (29.91)
• Diseases of the respiratory system	64 (54.70)
• Diseases of the digestive system, number (%)	95 (81.20)
• Diseases of the skin and subcutaneous tissue	32 (27.35)
• Diseases of the musculoskeletal system and connective tissue	46 (39.32)

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 16 January 2024 doi:10.20944/preprints202401.1186.v1

• Other diseases of the genitourinary system	8 (6.87)
• Other diseases of the blood and blood-forming organs	44(37.61)
• Mental and behavioral disorders	41 (35.04)
• Disorders of thyroid gland	31 (26.50)

[a] Unless otherwise indicated: Numbers present n (%); [b] The list of comorbidities is exhaustive for our cohort and was identified as documented in the medical records. Chronic kidney disease (CKD).

3.2. Types of NOMs/DPRs

During the study duration, 117 patients with KRT exhibited a total of 2,436 NOMs (Table 2) and 3,303 DRPs (Table 3). This equates to an average rate of 20.82 NOMs and 28.23 DRPs per patient.

Table 2. Types of uncontrolled health problems' treatment identified as NOMs among KRT patients.

Types NOMs	**N=2,436[a] NOMs**		**N=117[a] patients**			
	mean (SD)	n	HD	PD	KT	Total
Untreated health problem (requiring additional drugs)	12.27(7.52)	1,436 (58.95)	71(60.68)	16(13.68)	29(24.79)	116(99.15)
Effect of unnecessary medicine	0	0	0	0	0	0
Non-quantitative ineffectiveness	0.10(0.36)	12 (0.49)	3(2.56)	0	4(3.42)	7(5.98)
Quantitative ineffectiveness (prescribed quantity or dosage of a medication is insufficient)	7.38(5.21)	863 (35.43)	70(59.83)	16(13.68)	26(22.22)	112(95.73)
Non-quantitative safety problem (adverse drug reactions)	1.07(1,28)	125 (5.13)	37(31.62)	13(11.11)	13(11.11)	63(53.85)
Quantitative safety problem	0	0	0	0	0	0

[a] Unless otherwise indicated: Numbers present n (%); Negative outcomes associated with medications (NOM), Standard deviation (SD), hemodialysis (HD), peritoneal dialysis (PD), kidney transplant (KT).

Table 3. Types of DRPs identified as potential causes of ineffectiveness or unsafety in the treatment of uncontrolled health problems among KRT patients.

Types of DRPs	**N=3,303[a] DRPs**		**N=117[a] patients**			
	mean (SD)	N	HD	PD	KT	Total
Wrong administration	0.09(0.28)	10(0.30)	8(6.84)	0	2(1.71)	10(8.55)
Individual characteristics	0.21(0.66)	24(0.73)	8(6.84)	3(2.56)	4(3.42)	15(12.82)
Not necessary drug	0.07(0.08)	130(3.94)	27(55.10)	11 (9.40)	11 (9.40)	49(41.88)

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 16 January 2024 doi:10.20944/preprints202401.1186.v1

Improper medication storage	0.01(0.09)	1(0.03)	0	0	1 (0.85)	1(0.85)
Contraindication	0.03(0.16)	3(0.09)	0	1(0.85)	2 (1.71)	3(2.56)
Wrong dose/ posology/ length	0.55(0.36)	1,090 (33.00)	71 (60.68)	16 (13.67)	26 (22.22)	113(96.58)
Duplicity	0.02(0.13)	2(0.06)	0	0	2 (1.71)	2(1.71)
Wrong Dispensing	0	0	0	0	0	0
Wrong Prescription	0	0	0	0	0	0
Precautions	0.02(0.13)	2(0.06)	2 (1.71)	0	0	2(1.71)
Non-adherence	1.94(3.16)	227(6.87)	43 (36.75)	9 (7.69)	13 (11.11)	65(55.56)
Lack of knowledge of medicines	0.01(0.09)	1(0.03)	0	0	1 (0.85)	1(0.85)
Medicines Interactions	0.01(0.09)	1(0.03)	1 (0.85)	0	0	1(0.85)
Other conditions affecting the treatment	0.09(0.36)	10(0.30)	3 (2.56)	0	4 (3.42)	7(5.98)
Risk of adverse effects (adverse drugs reactions)	4.56(3.95)	533(16.14)	65 (55.55)	14 (11.97)	26 (22.22)	105(89.74)
Undertreated condition	10.62(6.51)	1,243 (37.63)	71 (60.68)	16 (13.68)	27 (23.07)	114(97.44)
Other DRPs	0.21(0.74)	24 (0.73)	10 (8.55)	0	4 (3.42)	14(11.97)

[a] Unless otherwise indicated: Numbers present n (%); Drug-related problems (DRP), Standard deviation (SD), hemodialysis (HD), peritoneal dialysis (PD), kidney transplant (KT).

3.3. Medications

At the baseline, patients used a total of 1,398 medications, out of which 1,222 were administered at home. By the end of the study period, the overall medication count increased to 1,460, with 1,279 medications administered at home (Table 4). No statistically significant differences were found between the medians of total medications, administered at home and during the dialysis process at baseline and at the end of the study.

Table 4. Overview of the types of medications used in the treatment of patients with KRT[a].

ATC code	Medication	N=117[b]
H05	Anti-parathyroid agents	
H05BX01	Cinacalcet	40(34.19)
H05BX02	Paricalcitol	64(54.70)
H05BX04	Etelcalcetide	18(15.38)
H05BX05	Calcifediol	97(82.91)
H03AA01	Levothyroxine sodium	21(17.95)
A11CC	Vitamin D and analogues	
A11CC03	Alfacalcidol	3(2.53)
V03AE	Drugs for treatment of hyperkalemia and hyperphosphatemia	
V03AE01	Polystyrene sulfonate	39(34.21)
V03AE02	Sevelamer	73(62.39)
V03AE03	Lanthanum carbonate	14(11.97)
V03AE04	Calcium acetate and magnesium carbonate	18(15.38)
V03AE05	Sucroferric oxyhydroxide	17(14.53)

 doi:10.20944/preprints202401.1186.v1

V03AE07	Calcium acetate	24(20.51)
V03AE09	Patiromer calcium	2(1.71)
V03AE10	Sodium zirconium cyclosilicate	16(13.68)
B03XA	Other antianemic preparations	
B03XA02	Darbepoetin alfa	96(82.05)
B03	Iron preparations	84(73.68)
A02	Drugs for acid related disorders	102(87.18)
A10A	Insulins and analogues	28(23.93)
A10B	Blood glucose lowering drugs, excl insulins	26(22.22)
A10BA02	Metformin	1(0.85)
A10BX02	Repaglinide	6(5.13)
A10BH01	Sitagliptin	2(1.71)
A10BH02	Vildagliptin	3(2.56)
A10BH05	Linagliptin	12(10.26)
B01	Antithrombotic agents	110(94.02)
C01	Cardiac therapy	18(15.38)
C03	Diuretic	72(61.54)
C02	Antihypertensives	97(82.91)
C02CA04	Doxazosin	48(41.03)
C08CA11	Manidipine	49(41.88)
C07AB03	Atenolol	27(23.08)
C07AB07	Bisoprolol	24(20.51)
C09CA01	Losartan	11(9.40)
C10	Lipid modifying agents	70(59.83)
C10AA05	Atorvastatin	39(33.33)
C10AA01	Simvastatin	25(21.37)
C10AX09	Ezetimibe	16(13.68)
C10AX06	Omega-3-triglycerides incl. other esters and acids	18(15.38)
D	Dermatologicals	5(4.27)
M04A	Antigout preparations	55(47.01)
N02	Analgesics	19(16.24)
N03	Antiepileptics	11(9.40)
N05	Psycholeptics	13(11.11)
N06	Psychoanaleptics	14(11.97)
R	Respiratory system	28(23.93)
L04	Immunosuppressants	37(31.62)
J07BN	Covid-19 vaccines	115(98.29)

[a] The list of medications is exhaustive for our cohort and was identified as documented in the medical records. [b] Unless otherwise indicated: Numbers present n (%).

The predominant instance of quantitative ineffectiveness, characterized by insufficient prescribed quantity or dosage of medication, was observed with darbepoetin alfa, accounting for 94 cases (97.9%). To examine the potential association between quantitative ineffectiveness in NOM and darbepoetin alfa, a chi-square test of independence was performed ($X^2(1, N = 117) = 6.27$, $p < 0.05$) (OR=7.62, 95% CI= 0.814-97.38).

In total, 64.4% (47 cases) demonstrated non-compliance with sevelamer, while 66.7% (22 cases) exhibited non-adherence to calcium polystyrene sulfonate. A chi-square test of independence was performed to investigate the statistically significant relationship between non-adherence and sevelamer ($X^2(1, N = 117) = 6.12$, $p < 0.05$) (OR=2.589, 95% CI= 1.131-6.057). Additionally, a chi-square test of independence was executed to explore the association between non-adherence and calcium polystyrene sulfonate ($X^2(1, N = 117) = 2.30$, $p = 0.13$) (OR=1.897, 95% CI= 0.767-4.911).

 doi:10.20944/preprints202401.1186.v1

3.4. Factors Influencing NOMs/DRPs

The total of the DRPs, specifically the risk of adverse effects (adverse drug reactions, ADR) (r_s= 0.314; p<0.001), wrong dose/ posology/ length (r_s=0.344; p<0.001), non-adherence to medication (r_s= 0.244; p=0.008), undertreated conditions (r_s=0.912; p <0.001), and the total number of comorbidities (r_s=0.395; p <0.001), exhibited significant associations with NOMs, specifically the number of untreated health problems.

The number of the following DRPs: risk of adverse effects (r_s=0.389; p<0.001), individual characteristics (r_s=0.311; p<0.001), wrong dose/ posology/ length (r_s= 0.730; p<0.001), and undertreated conditions (r_s = 0.299; p<0.05), demonstrated significant associations with the number of NOMs, specifically quantitative ineffectiveness. Conversely, urea (r_s = 0.322; p<0.001), creatinine (r_s = 0.231; p<0.05), calcium (r_s = -0.196; p<0.05), phosphorus (r_s = 0.401; p<0.001), parathyrin (r_s = 0.413; p<0.001), ferritin (r_s = 0.254; p<0.01), erythrocytes (r_s = -0.198; p<0.05), hemoglobin (r_s = -0.250; p<0.01), hematocrit (r_s = -0.250; p<0.01), and platelets (r_s = -0.211; p<0.05) were significantly associated with the number of NOMs, specifically quantitative ineffectiveness.

Moreover, the number of the following DRPs: risk of adverse effects (r_s =0.451; p<0.001), wrong dose/ posology/ length (r_s = 0.215; p<0.05), and undertreated conditions (r_s = 0.184; p<0.05), were significantly associated with the number of NOMs, specifically non-quantitative safety. On the contrary, albumin (r_s = -0.186; p<0.05) and magnesium (r_s = -0.194; p<0.05) were significantly associated with the number of non-quantitative safety.

A chi-square test of independence was conducted to explore the significant relationship between undertreated condition in NOM and the following variables: the presence of wrong dose/ posology/ length ($X^2(1, N = 117) = 28.49$, $p < 0.05$) and the presence of undertreated conditions ($X^2(1, N = 117) = 38.33$, $p < 0.05$).

Similarly, a chi-square test of independence was used to investigate the significant association between non-Quantitative Ineffectiveness in NOM and hyperphosphatemia ($X^2(1, N = 117) = 7.68$, $p < 0.05$).

Furthermore, chi-square tests of independence were conducted to assess the significant relationships between quantitative ineffectiveness in NOM and the following variables: the presence of wrong dose/ posology/ length ($X^2(1, N = 117) = 92.77$, $p < 0.01$), the presence of undertreated conditions ($X^2(1, N = 117) = 29.29$, $p < 0.05$), and anemia ($X2(1, N = 117) = 14.04$, $p < 0.05$).

Additionally, a chi-square test of independence was performed to investigate the significant relationship between non-Quantitative Safety in NOM and the following variables: the presence of wrong dose/ posology/ length ($X^2(1, N = 117) = 4.83$, $p < 0.05$), the presence of risk of adverse effects ($X^2(1, N = 117) = 11.15$, $p < 0.05$), and vitamin D deficiency/insufficiency ($X^2(1, N = 117) = 4.68$, $p < 0.05$).

We examined the relationship between independent variables and dependent variables (non-Quantitative ineffectiveness, Quantitative ineffectiveness, and non-Quantitative safety) through the application of both univariate and multivariate logistic regression methods.

In the univariate logistic regression analysis, hyperphosphatemia was found to be associated with non-Quantitative ineffectiveness. Additionally, the risk of adverse effects, undertreated conditions, and anemia showed associations with Quantitative ineffectiveness. Moreover, the risk of adverse effects and vitamin D deficiency/insufficiency were linked to non-Quantitative safety.

Variables with a p-value < 0.05 in bivariate analysis were subsequently included in the multiple logistic regression. The results of the multivariate analysis revealed that participants with hyperphosphatemia were 0.08 times more likely to experience non-Quantitative ineffectiveness compared to those without hyperphosphatemia (OR = 0.0845, 95% CI: 0.0044-0.5192, p = 0.02).

Moreover, participants with a risk of adverse effects were 1.802 times more likely to have NOM compared to those without a risk of adverse effects (OR = 1.802, 95% CI: 0.076-18.631). Participants with undertreated conditions were 23.883 times more likely to have NOM compared to those without undertreated conditions (OR = 23.883, 95% CI: 1.265-1062.966). Participants with anemia were 8.836 times more likely to experience NOM compared to those without anemia (OR = 8.836, 95% CI: 0.851-90.667) (Table 5).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 16 January 2024 doi:10.20944/preprints202401.1186.v1

Table 5. Factors influencing Quantitative Ineffectiveness in KRT Patients.

Factors	Category	Quantitative ineffectiveness (prescribed quantity or dosage of a medication is insufficient)		OR	95% CI	P-value
		No	Yes			
Risk of adverse effects	No	2 (16.7%)	10 (83.3%)	1		
	Yes	3 (2.9%)	102 (97.1%)	1.802	0.076-18.631	0.6481
Undertreated conditions	No	2 (66.7%)	1 (33.3%)	1		
	Yes	3 (2.6%)	111 (97.4%)	23.883	1.265-1,062.966	0.0445
Anemia	No	3 (25,0%)	9 (75.0%)	1		
	Yes	2 (1.9%)	103 (98.1%)	8.836	0.851-90.667	0.0524

Participants with a risk of side effects were 14.625 times more prone to have NOM of non-Quantitative safety compared to those without the risk of side effects (OR = 14.625, 95% CI: 2.646-273.914, p = 0.012). Moreover, participants with vitamin D deficiency/insufficiency were 2.177 times more likely to encounter NOM of non-Quantitative safety compared to those without vitamin D deficiency/insufficiency (AOR = 2.177, 95% CI: 0.954-5.058, p = 0.06).

3.5. Types of Interventions for Preventing or Resolving NOMs/DRPs among KRT Patients

Throughout the 29-month study period, healthcare providers conducted a total of 3,355 interventions aimed at addressing issues associated with medication usag[e. On average, there were 1.4 interventions per NOM and 1.0 intervention per DRP. The most prevalent interventions included dose modification (997 interventions; 29.72%), addition of a new medication (830 interventions; 24.74%), patient health education (580 interventions; 17.29%), medication withdrawal (318 interventions; 9.48%), dosage modification (178 interventions; 5.31%), and schedule modification (26 interventions; 0.77%). Among patient health education interventions, the most frequent were related to non-pharmacological advice (376 interventions; 11.21%), medication adherence (130 interventions; 3.87%) and the use and administration of medicines (74 interventions; 2.20%).

Pharmacists provided health education interventions to the 117 patients, constituting 3.49% of the interventions. On average, there were 1.0 pharmacist intervention per patient. These interventions were accepted in 85.5% of cases, totaling 100 accepted interventions.

4. Discussion

Individuals with KRT face an elevated risk of developing DRPs/NOMs. This increased risk can be attributed to the presence of comorbidities, complications, and the intricate nature of their medication regimen [1,4]

In this study, we found a mean of 12.14 medications and 18.64 comorbidities per patient. However, our findings were inconsistent with those reported in studies conducted in Ethiopia [4], India [12] and USA [1].

The present study found that the most prescribed class of drugs were antithrombotic agents (94.02%) and Covid-19 vaccines (98.07%), and the most common comorbidities were mineral and bone disorder (91.45%) and anemia (89.74%).

A total of 2,436 NOMs and 3,303 DPR were identified in the 117 patients reviewed. The most common NOMs were untreated health problem (58.95%) and quantitative ineffectiveness (35.43%). The most common DRPs were undertreated condition (37.63%) and wrong dose/ posology/ length (33.00%). The rate of NOMs was 20.82% and the rate of DRPs was 28.23%. Other studies identified DRPs [4,12] and only one identified NOMs [1,7].

 doi:10.20944/preprints202401.1186.v1

Our analysis of NOMs showed a need for additional drug therapy (58.94%), which is significantly different from the rates in Ethiopia (31%), France (30%), India (40.6%), Canada (51.3%), and the USA (61.5%) [8].

The most common NOM found in the current study was an untreated health problem (99.15%), while the most prevalent DRP was a poorly treated health problem (97.44%).

Ineffective drug therapy contributed for 35.92% of all NOMs identified in the present study, which contrasts with studies conducted in Ethiopia (10%), India (40.6%), Canada (51.3%), Beirut (28%), and the USA (14.9%) [8].

In the present study, the DRPs nonadherence to medicines were identified in 65 patients (55.55%) and ADR in 63 patients (53.85%). In comparison, other studies have identified nonadherence to medicines in 25% patients with ESRD undergoing hemodialysis in Nepal [13] and 19% patients in Palestine [14]. A study conducted in Greece has found that 60 patients reported at least one or more ADR [15], another study conducted in Germany identified high rates of severe drugs events (QTc prolongation, hyperkalemia and hemorrhage) in 8.5% of 67 patients undergoing dialysis [16], and a study conducted in United Arab Emirates found 14 ADR in 130 CKD patients (105 patients stage 5) (10).

Heath care professionals, including pharmacists and nephrologists resolve NOMs/DRPs by pharmacological and non-pharmacological interventions (i.e., addition of a new medication, patient health education, medication withdrawal, dosage modification, and schedule modification). In comparison, other studies identify interventions for the management of CKD [1,17,18].

In this study, the total number for various DRPs, including ADR, wrong dose/ posology/ length, non-adherence, and undertreated health problems, exhibited a statistically significant correlation with the total number of NOMs related to untreated health problems.

Similarly, the total number of DRPs, including ADR, individual characteristics, inappropriate dose, wrong dose/ posology/ length, and undertreated conditions, demonstrated a significant association with the total number of NOMs related to quantitative ineffectiveness. Additionally, the values of various parameters such as urea, creatinine, potassium, calcium, phosphorus, parathyroid hormone, ferritin, erythrocytes, hemoglobin, and hematocrit were significantly correlated with the total number of NOMs related to quantitative ineffectiveness.

Furthermore, the total number of DRPs involving the ADR, wrong dose/ posology/ length, and other health problems impacting treatment showed a significant association with the total number of NOMs related to non-quantitative safety problems.

A study conducted in Ethiopia [8] highlighted additional elements, such as marital status, polypharmacy, and the number of comorbidities, associated with DRPs/NOMs. Similarly, a study conducted in the United Arab Emirates [10] reported factors including comorbid conditions, length of hospital stay, and polypharmacy as significant contributors to these issues.

Study Limitation: The identification of NOMs lacked the establishment of causal relationships; instead, it relied on information retrieved from medical records and patient interviews.

5. Conclusions

The present study determined that the average rates of NOM and DRP per KRT patient admitted to the nephrology department were 20.82 and 28.23, respectively.

Overall, it became clear that the intricacy of the medication regimen, coupled with the patients' disease status, contributes to a higher incidence of NOMs. This specific patient population requires a thorough medication review, ongoing follow-up, and comprehensive healthcare from all relevant medical professionals to prevent complications arising from the administered therapies and healthcare interventions.

Author Contributions: Conceptualization, A.P.-C, F.-M.-M., M.Á.C.-H. and A.J.-M.; Methodology, A.P.-C., F.-M.-M., M.Á.C.-H., A.J.-M., M.P.-B. and A.P.-M.; Software, A.P.-C; Validation, A.P.-C.; Formal Analysis A.P.-C., F.-M.-M., M.Á.C.-H., A.J.-M., M.P.-B. and A.P.-M.; Investigation, A.P.-C., F.-M.-M., M.Á.C.-H., A.J.-M., M.P.-B. and A.P.-M.; Resources, A.P.-C., F.-M.-M., M.Á.C.-H., A.J.-M., M.P.-B. and A.P.-M.; Data Collection, A.P.-C; Writing – Original Draft Preparation, A.P.-C., F.-M.-M., M.Á.C.-H., A.J.-M., M.P.-B. and A.P.-M.; Writing –

Review & Editing, A.P.-C., F.-M.-M., M.Á.C.-H., A.J.-M., M.P.-B. and A.P.-M.; Visualization, A.P.-C., F.-M.-M., M.Á.C.-H., A.J.-M., M.P.-B. and A.P.-M.; Supervision, F.-M.-M., M.Á.C.-H., A.J.-M., M.P.-B. and A.P.-M.; Project Administration, A.P.-C., F.-M.-M., M.Á.C.-H., A.J.-M.; Funding Acquisition, A.P.-C., F.-M.-M., M.Á.C.-H., A.J.-M., M.P.-B. and A.P.-M. All authors have read and agreed to the published version of the manuscript.

Funding: Financial support received as a Doctoral Grant [reference number OAICE-143-2020] from the Office of International Affairs and External Cooperation, University of Costa Rica and The APC was funded by Fundación para la Investigación Biosantitaria de Andalucía Oriental-Alejandro Otero (Granada, Spain).

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board Andalusian Biomedical Research Ethics Committee (Protocol code FIS-IRB-2020-01 and date of approval July 28, 2020). Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: For Data supporting reported results contact corresponding author.

Acknowledgments: This publication is part of the results derived from the doctoral thesis titled "Seguimiento farmacoterapéutico de personas con enfermedad renal crónica estadio 5 en tratamiento renal sustitutivo: impacto clínico y humanístico" [Ph.D. in Pharmacy Program, University of Granada].

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analysis, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

References

1. Pereira-Céspedes A, Jiménez-Morales A, Palomares-Bayo M, Martínez-Martínez F, Calleja-Hernández MÁ. Medication review with follow-up for end-stage renal disease: Drug-related problems and negative outcomes associated with medication-A systematic review. *J Clin Med* [Internet]. 2023 -08-02 [cited Oct 17, 2023];12(15):5080.
2. Susilawati NM, Halimah E, Saidah S. Pharmacists' strategies to detect, resolve, and prevent DRPs in CKD patients. *Pharmacia* [Internet]. 2021;68(3):619-26.
3. Kim AJ, Lee H, Shin E, Cho E, Cho YS, Lee H, Lee J. Pharmacist-led collaborative medication management for the elderly with chronic kidney disease and polypharmacy. *Int J Environ Res Public Health* [Internet]. 2021 APR;18(8):4370.
4. Legesse ES, Muhammed OS, Hamza L, Nasir BB, Nedi T. Medication related problems among ambulatory patients with chronic kidney disease at st. paul's hospital millennium medical college, addis ababa, ethiopia. *PLOS ONE* [Internet]. 2022 1 dic. [cited Oct 18, 2023];17(12):e0278563. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0278563
5. Alshamrani M, Almalki A, Qureshi M, Yusuf O, Ismail S. Polypharmacy and medication-related problems in hemodialysis patients: A call for deprescribing. *Pharmacy (Basel)* [Internet]. 2018 -07-25 [cited Oct 18, 2023];6(3):76.
6. Cavallari G, Mancini E. The nephrologist's role in the collaborative multi-specialist network taking care of patients with diabetes on maintenance hemodialysis: An overview. *J Clin Med* [Internet]. 2022 -03-10 [cited Oct 31, 2023];11(6):1521.
7. Chemello C, Aguilera M, Calleja-Hernández MA, Faus MJ. Efecto del seguimiento farmacoterapéutico en pacientes con hiperparatiroidismo secundario tratados con cinacalcet. *Farmacia Hospitalaria* [Internet]. 2012 September 1, [cited May 17, 2022];36(5):321-7. Available from: https://www.sciencedirect.com/science/article/pii/S1130634311002108
8. Garedow AW, Mulisa Bobasa E, Desalegn Wolide A, Kerga Dibaba F, Gashe Fufa F, Idilu Tufa B, Debalke S, Kumela Goro K. Drug-related problems and associated factors among patients admitted with chronic kidney disease at jimma university medical center, jimma zone, jimma, southwest ethiopia: A hospital-based prospective observational study. *Int J Nephrol* [Internet]. 2019 [cited Oct 17, 2023];2019:1504371.
9. Daifi C, Feldpausch B, Roa P-, Yee J. Implementation of a clinical pharmacist in a hemodialysis facility: A quality improvement report. *Kidney Med* [Internet]. 2021 [cited 15 June 2022];3(2):241,247.e1. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.085102074184&doi=10.1016%2fj.xkme.2020.11.015&partnerID=40&md5=86b9d9ceed4378caf3227d4ad582c0ab

10. Shouqair TM, Rabbani SA, Sridhar SB, Kurian MT. Evaluation of drug-related problems in chronic kidney disease patients. *Cureus* [Internet] [cited Nov 13, 2023];14(4):e24019. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9091809/
11. Faus-Dáder, MJ, Amariles-Muñoz, P, Martínez-Martínez, F. Atención Farmacéutica. Servicios farmacéuticos orientados al paciente. 2nd ed. Granada: Técnica Avicam; 2022.
12. Castelino RL, Sathvik BS, Parthasarathi G, Gurudev KC, Shetty MS, Narahari MG. Prevalence of medication-related problems among patients with renal compromise in an indian hospital. *J Clin Pharm Ther* [Internet]. 2011 -08 [cited Nov 10, 2023];36(4):481-7.
13. Sapkota A, Sedhain A, Kc T, Sigdel S, Subedi S. Adherence to treatment among patients with end-stage renal disease undergoing hemodialysis in selected centers in nepal. *J Nepal Health Res Counc* [Internet]. 2022 -06-02 [cited Nov 13, 2023];20(1):72-8.
14. Naalweh KS, Barakat MA, Sweileh MW, Al-Jabi SW, Sweileh WM, Zyoud SH. Treatment adherence and perception in patients on maintenance hemodialysis: A cross - sectional study from palestine. *BMC Nephrol* [Internet]. 2017 -05-30 [cited Nov 13, 2023];18(1):178.
15. Spanakis M, Roubedaki M, Tzanakis I, Zografakis-Sfakianakis M, Patelarou E, Patelarou A. Impact of adverse drug reactions in patients with end stage renal disease in greece. *Int J Environ Res Public Health* [Internet]. 2020 December 1, [cited Nov 10, 2023];17(23):9101. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7730015/
16. Sommer J, Seeling A, Rupprecht H. Adverse drug events in patients with chronic kidney disease associated with multiple drug interactions and polypharmacy. *Drugs Aging* [Internet]. 2020 -05 [cited Nov 13, 2023];37(5):359-72.
17. Galbraith L, Jacobs C, Hemmelgarn BR, Donald M, Manns BJ, Jun M. Chronic disease management interventions for people with chronic kidney disease in primary care: A systematic review and meta-analysis. *Nephrol Dial Transplant* [Internet]. 2018 -01-01 [cited Nov 13, 2023];33(1):112-21.
18. Parker JR. Use of an educational intervention to improve fluid restriction adherence in patients on hemodialysis. *Nephrol Nurs J* [Internet]. 2019 [cited Nov 13, 2023];46(1):43-7.