10.5152/turkjnephrol.2024.24764

Original Article

Turkish Journal of Nephrology

Medication Prescribing Patterns for Chronic Kidney Diseases: Analysis of Drug-Dose Adjustments, Polypharmacy, and Drug Interactions

Ainur Assan[1], Zakira Kerimbayeva[2], Ikilas Moldaliyev[1], Dmitriy Syssoyev[3], Ali Issayev[4], Aizat Seidakhmetova[5], Rita Assabayeva[6], Meruyert Madikenova[3], Dmitriy Sychev[7], Abduzhappar Gaipov[3]

[1]Department of Medicine, Khoja Akhmet Yassawi International Kazakh-Turkish University, Turkestan, Kazakhstan
[2]Department of Public Health and Management, Astana Medical University, Astana, Kazakhstan
[3]Department of Medicine, Nazarbayev University School of Medicine, Astana, Kazakhstan
[4]Department of Ophthalmology, Kazakh National Research Institute of Eye Disease, Astana, Kazakhstan
[5]Department of Emergency Medical Care and Nursing, South Kazakhstan Medical Academy, Shymkent, Kazakhstan
[6]Department of Oncology, City Multidisciplinary Hospital with Oncology Center, Shymkent, Kazakhstan
[7]Department of Clinical Pharmacology and Therapy, Russian Medical Academy of Continuous Professional Education, Moscow, Russian Federation

ABSTRACT

Background: Multiple drug prescriptions in chronic kidney disease (CKD) escalate metabolic buildup, nephrotoxicity, and end stage kidney disease progression. We aimed to study polypharmacy and harmful multi-drug interactions at the nephrology department of South-Kazakhstan Regional hospital.

Methods: We analyzed electronic medical records of 485 patients with glomerular diseases (ICD-10 codes: N00-N08) admitted to the nephrology department from January 2018 to December 2021. We evaluated polypharmacy risk, dividing patients into low-risk, moderate-risk, and severe-risk groups based on the number of prescribed medications: 2-5, 6-9, and 10 or more, respectively. Additionally, we examined the occurrence and combinations of unsafe multi-drug interactions.

Results: The study group included 45% CKD stage-1, 29% CKD stage-2, and 26% CKD stage-3 and above patients, with a median medication count of 9.5. Low-risk, moderate-risk, and severe-risk polypharmacy affected 12.2%, 48.2%, and 39.6% of patients, respectively. Inappropriate multi-drug combinations were particularly prevalent in early CKD stages. Notably, among commonly prescribed drugs, 19 out of 23 lacked dose adjustments according to the CKD stage.

Conclusion: This pioneering study investigates polypharmacy and multi-drug interactions in CKD patients in Kazakhstan, revealing significant risks.

Keywords: Chronic kidney disease, dose adjustment, polypharmacy, drug interactions, nephrotoxicity.

Corresponding author: Ainur Assan ainur.assan@ayu.edu.kz

Received: March 23, 2024 **Revision Requested:** May 8, 2024
Last Revision Received: July 1, 2024 **Accepted:** July 8, 2024 **Publication Date:** September 12, 2024

Cite this article as: Assan A, Kerimbayeva Z, Moldaliyev I, et al. Medication prescribing patterns for chronic kidney diseases: Analysis of drug-dose adjustments, polypharmacy, and drug interactions. *Turk J Nephrol.* 2024;33(4):324-332.

INTRODUCTION

Multiple drug prescriptions and inappropriate dose adjustments in different stages of chronic kidney disease (CKD) remain one of the main factors leading to adverse drug interactions, accumulation of end metabolites, nephrotoxicity, and progression to end-stage kidney disease (ESKD).[1] One of the critical conditions for providing quality medical care is the rational use of pharmacotherapy. The World Health Organization (WHO) defines rational pharmacotherapy as the administration of drugs to patients that are appropriate for the clinical situation, at doses that meet individual needs, for an adequate period of time, and at the lowest cost to patients and society.[2] However, the quality of medical care today requires a comprehensive approach to prescribing drugs.[3] Drug adverse reactions in some cases can cause serious harm to the health of patients and even cause death.[4]

It was found that undesirable drug interactions develop in 5%-10% of patients in outpatient settings, whereas the probability of adverse reactions among inpatients

was 10%-20% of cases.[5] In 5% of cases, medicine side effects were the main reason for hospitalization. These adverse events lead to increased hospital stays and the cost of therapy.[6] The rational choice of a drug in the treatment of kidney disease is one of the key factors influencing the course of the disease, including the patient's health indicators. The main criteria that determine the choice of a drug are its efficacy and safety. The safety of the drug is a vital factor that determines the rationality of the drug therapy prescribed by the doctor, especially if long-term use is required. In real clinical practice, the most common errors are irrational drug selection, dosing, management regimens, excessive use, and excessive duration.[7]

Chronic diseases are the leading causes of morbidity, disability, and mortality on a global scale (60% of all deaths). Chronic kidney disease is a progressive disease with a high morbidity and mortality rate that affects the general adult population and is common in people with diabetes and hypertension. Pharmacological interventions seek to preserve kidney function while also improving outcomes.[8] Pharmacotherapy complications are common in patients with CKD.

Polypharmacy has emerged as a public health issue,[9] as multidrug use or "polypharmacy," occurs in many conditions that can result in adverse events/effects such as adverse drug reactions.[10] Polypharmacy, which is commonly defined as the concurrent use of 5 drugs, has been identified as a major global public health threat. Aging and multimorbidity are major contributors to polypharmacy and are linked to a variety of negative health outcomes and mortality. Given the numerous risk factors and complications associated with CKD, these patients are especially vulnerable to polypharmacy and the use of potentially inappropriate medications.[11]

According to WHO, mortality from chronic diseases can be reduced by 3 times through rational drug therapy.[12] To date, the problem of rational, effective, and safe use of medicines in the Republic of Kazakhstan is still relevant.

An analysis of the literature showed low alertness among various specialties regarding the rational therapy of adequate doses of drugs, considering CKD and the possibility of adverse drug interactions.[13] A previous study on patients with CKD regarding the rational use of drugs showed low adherence to the rational use of drugs among non-surgical and non-nephrological specialties.[14] However, in Kazakhstan, the level of rational prescribing of drugs for patients with CKD by nephrologists remains insufficiently studied, not to mention other specialties. Our goal was to study the rationality of pharmacotherapy for chronic kidney failure in a specialized hospital, considering GFR and drug interactions for the presence of dangerous combinations.

MAIN POINTS

- Undesirable drug interactions develop in 5%-10% of outpatients and 10%-20% of inpatients, with medicine side effects being a significant cause of hospitalization in 5% of cases. These events lead to increased hospital stays and therapy costs.
- There is a need for further research into the rational prescribing of drugs for chronic kidney disease patients, particularly among nephrologists, to improve patient outcomes and minimize adverse drug events.
- In this study, polypharmacy is categorized into 3 groups based on the number of simultaneously prescribed medications: (i) low-risk, where 2 to 5 medications are prescribed; (ii) moderate-risk, 6-9 medications; and (iii) severe-risk, where 10 or more medications are prescribed simultaneously.
- Patients with moderate-risk polypharmacy were the most common across all chronic kidney disease stages.
- Severe-risk polypharmacy prescriptions included pentoxifyl line/spironolactone and ketoprofen/pentoxifylline combinations the most, whereas among moderate-risk prescriptions, the ketoprofen/pentoxifylline combination was more prevalent.
- Inappropriate combinations of medicines, such as pento xifylline/spironolactone and ketoprofen/pentoxifylline, were frequently prescribed to stage I CKD patients and those with Stage three or higher CKD.

MATERIAL AND METHODS

Study Design and Population

This is a retrospective study that includes adult patients admitted to the nephrology department at a regional hospital between January 2018 and December 2021 with a diagnosis of glomerular diseases according to the International Code of Diseases (ICD-10). Medical records, including patient demographics, clinical laboratory data, and prescribed drugs, were reviewed. Inclusion criteria were ICD-10 codes N00-N08, age between 18 and 70 years, and both genders. Exclusion criteria were the following: patients with other than N00-N08 ICD-10 codes, patients who underwent dialysis therapy, and those who were in the intensive care unit. Initially, 4585 medical records were downloaded for review. Of these, 4075 were excluded because of different ICD-10 codes, and 25 records were removed due to lack of information. The final cohort consists of 485 individual medical records. This study was approved by the Ethics Committee of Ahmet Yassawi University (Date: 03.01.2024, Number: 24). All participants provided informed consent before their involvement in the study.

Outcome of Interests

The primary outcome of interest was the number of prescribed drugs, their dosage, frequency, and duration of administration, as well as the interaction of drug safety if many medications were inappropriately prescribed in combination. The dose

adjustment based on glomerular filtration rate (GFR) and the number of incorrectly prescribed drugs were assessed.

We used the fifth edition of "The Renal Drug Handbook" and other available databases for proper drug adjustments.[15,16] Drug combination safety interactions were studied using the online Drug Interactions Checker.[17] The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI calculator.[18]

Polypharmacy is defined based on reference and categorized into 3 groups based on the number of simultaneously prescribed medications: (i) low-risk, where 2-5 medications are prescribed; (ii) moderate-risk, 6-9 medications are prescribed; and (iii) severe-risk, where 10 or more medications are prescribed simultaneously.[19] Patients were also divided into CKD groups based on their eGFR levels at admission.

The secondary outcome of interest was the development of acute kidney injury (AKI) during the hospital stay, which was identified using KDIGO AKI criteria.[20]

Dangerous drug combinations were identified among the cohort of patients with incorrectly prescribed drug dosages. We identified the 6 most dangerous combinations and studied the number of patients who were prescribed these combinations. They are as follows:

1. Pentoxifylline/enoxaparin.
2. Nitrofurantoin/simvastatin.
3. Pentoxifylline/spironolactone.
4. Ketoprofen/spironolactone.
5. Ketoprofen/pentoxifylline.
6. Ketoprofen/enoxaparin.

These combinations are considered dangerous for patients with CKD. The first combination, pentoxifylline and enoxaparin, increases the risk of bleeding due to their synergistic effect on blood thinning and reducing clot formation.[21] The second combination was chosen because nitrofurantoin can cause pulmonary toxicity and has been associated with liver toxicity. When combined with simvastatin, which can also cause liver damage and muscle toxicity (rhabdomyolysis), the risk of severe liver injury and rhabdomyolysis increases.[22,23] Both pentoxifylline and spironolactone, the third combination, can affect blood pressure and electrolyte balance. Spironolactone can cause hyperkalemia (high potassium levels), and pentoxifylline can enhance the effect of diuretics, potentially leading to significant electrolyte disturbances and hypotension.[24,25] Nonsteroidal anti-inflammatory drugs (NSAIDs) like ketoprofen can reduce kidney function and decrease the effectiveness of diuretics like spironolactone. This combination (fourth combination) increases the risk of hyperkalemia and kidney impairment, which are particularly concerning in CKD patients. The combination of ketoprofen and pentoxifylline heightens the risk of gastrointestinal and kidney complications, especially in CKD patients who are already at risk for these issues.[26] Lastly, the combination of an NSAID (ketoprofen) with an anticoagulant (enoxaparin) significantly increases the risk of serious bleeding events, including gastrointestinal bleeding and intracranial hemorrhage.[27]

Statistical Analysis

Statistical analysis was carried out using STATA. Numbers and percentages were presented, disaggregated by sex, degree of polypharmacy, etc. Other variables for which the median and quartile range were calculated included age, duration of hospitalization, number of drugs prescribed, and levels of proteinuria, hemoglobin, alanine, and aspartic acid. The statistical significance of these values between severity groups was assessed by the analysis of variance test for continuous variables and the Chi-square test for categorical variables.

Drugs requiring dose adjustment depending on the stage of CKD were analyzed, and recommended doses were derived for this group. The recommended dosages were compared with the actual prescribed dosages. In addition, the percentage and absolute number of patients with incorrect doses were analyzed. Graphs showing the degree of polypharmacy were constructed according to the stage of CKD and the degree of polypharmacy.

RESULTS

Demographic Data

The general characteristics of the study population are presented in Table 1. Overall, there were 510 patients; however, data for 25 patients were lost due to data entry errors, resulting in a total of 485 patients in the study. Stages of CKD in patients were categorized into 3 groups: CKD 1 – 218 patients, CKD 2 – 142 patients, and CKD 3+ – 125 patients. Among all hospitalized patients, there were 269 (52.7%) males and 241 (47.3%) females, with a median age of 33 years. Age differences between patients, independent of their gender, across different CKD groups were significant (*P*-value < .001). The median number of medications was 8. Median hemoglobin levels, alanine transaminase, and aspartate transaminase levels at admission were measured to be 130 g/L, 18.2 IU/L, and 19.6 IU/L respectively. The difference in these descriptives between each CKD category was not statistically significant. Also, there is a lack of data for these measurements at discharge. The duration of patients' hospital stay, depending on their CKD levels, was 10 days based on their median. Unfortunately, the hospital stay was not categorized or measured based on the number of drugs patients received. The total number of in-hospital episodes of acute kidney injuries (AKI) was 16. These episodes were distributed as follows: 4 for CKD 1, 3 for CKD 2, and 9 for CKD 3+. There are no data available to determine whether these AKI episodes were potentially drug-related.

Table 1. General Characteristics of the Study Population.

	Total	CKD 1	CKD 2	CKD 3+	*P*
Number of patients (%)	485	218 (45%)	142 (29%)	125 (26%)	
Age, median (IQR)	33.4 (24.7-43.5)	29.4 (22.7-40.0)	35.8 (28.0-47.0)	35.0 (28.7-49.8)	<.001
Male ender, n (%)	253 (52.2)	117 (53.7)	72 (50.7)	64 (51.2)	.833
Hemoglobin at admission (g/L), median (IQR)	130 (112-146)	134 (114-147)	128 (115-149)	123 (109-141)	.019
Alanine transaminase at admission (IU/L), median (IQR)	18.2 (11.1-29.7)	16.4 (10.2-23.0)	20.2 (12.0-33.0)	19.0 (12.5-35.6)	.015
Aspartate transaminase at admission (IU/L), median (IQR)	19.6 (15.0-28.1)	19.0 (15.0-25.0)	21.3 (15.8-31.7)	19.8 (14.0-31.0)	.824
Proteinuria (g/L), median (IQR)	0.5 (0.1-1.4)	0.5 (0.1-1.3)	0.5 (0.1-1.3)	0.7 (0.2-1.5)	.551
Number of prescribed drugs, median (IQR)	8 (6-12)	8 (6-12)	8 (7-11)	9 (7-13)	.077
Duration of hospital stay, median (IQR)	10 (9-12)	11 (9-13)	10 (9-12)	10 (9-12)	.669
In-hospital episodes of Acute Kidney Injury, n (%)	16 (2.9)	4 (1.8)	3 (2.1)	9 (5.6)	.13

The table presents the general characteristics of the study population across various stages of CKD, nncompassing stages 1, 2, and 3 and above. It illustrates key demographic and clinical factors, including the number of patients in each CKD stage, median age with interquartile range, gender distribution, and laboratory parameters such as hemoglobin levels and liver enzyme activities. It also highlights medication usage, duration of hospital stays, and incidences of in-hospital AKI.

Frequency of Polypharmacy

Low-risk polypharmacy, moderate-risk, and severe-risk polypharmacy were observed in 12.2%, 48.2%, and 39.6% of patients, respectively (Figure 1). We observed inappropriate multiple-drug combination prescriptions in the early stages of CKD especially (218). Among all CKD categories, moderate-risk and severe-risk polypharmacy were more common than low-risk. Among drugs commonly prescribed, 19 of 23 drugs have not undergone dose correction based on the CKD stage.

Dangerous Combinations of Prescriptions Based on the Level of CKD

Among the prescribed medicines in total, 6 combinations of prescriptions are considered dangerous. They were pentoxifyl line/enoxaparin, nitrofurantoin/simvastatin, pentoxifylline/spironolactone, ketoprofen/spironolactone, ketoprofen/pentoxifylline, and ketoprofen/enoxaparin (Figure 2). The most prescribed combinations for patients in with CKD1 and CKD3+ categories were pentoxifylline/spironolactone (14 patients with CKD3+ and CKD1) and ketoprofen/pentoxifylline (13 patients with CKD3+, 12 patients with CKD1) (Figure 2).

Dangerous Combinations of Prescriptions Based on the Level of Polypharmacy

The pentoxifylline/spironolactone combination was the most common in severe-risk polypharmacy, which is a prescription of 10 or more medications, being prescribed more than 30 times (Figure 3). The ketoprofen/pentoxifylline combination was prescribed more than 20 times with severe-risk polypharmacy. Other dangerous combinations of drugs were prescribed up to 10 times with moderate-risk polypharmacy, which is 6-9 medications.

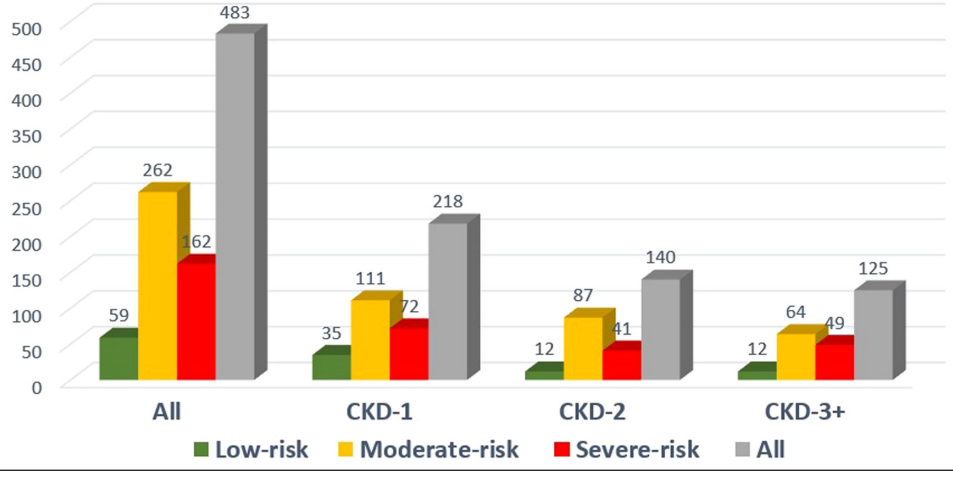

Figure 1. Frequency of polypharmacy.

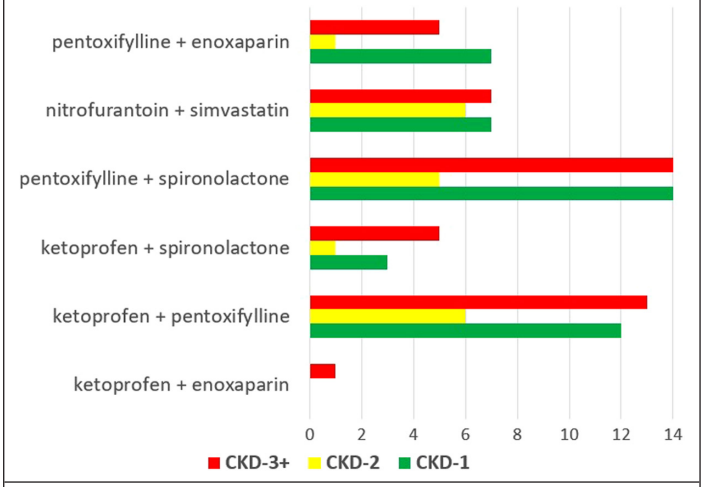

Figure 2. The number of inappropriate combinations of prescriptions with CKD category.

DISCUSSION

In this study, patients were categorized by CKD stages and levels of polypharmacy. Patients in stage 1 CKD were predominantly subjected to moderate-risk polypharmacy, followed by severe-risk polypharmacy, and subsequently, low-risk polypharmacy. This pattern was similarly observed in stage 2 CKD patients and those with stage 3 or higher CKD (Figure 1). Polypharmacy was also evaluated based on inappropriate combinations of medicines. Stage 1 CKD patients, as well as those in stage 3 and higher CKD patients, were frequently prescribed medications containing combinations of pentoxifylline/spironolactone and ketoprofen/pentoxifylline (Figure 2). Moreover, severe-risk polypharmacy prescriptions included these 2 combinations most frequently, whereas among moderate-risk prescriptions, the ketoprofen/pentoxifylline combination was more prevalent (Figure 3).

Elaborating on the pattern of moderate-risk polypharmacy being the most common prescription among all CKD patients, a prescription of 6-9 medicines at a time can be explained as a way of trying to prevent comorbidities that come with each level of CKD. Unfortunately, such multiple drug prescriptions pose a controversial concern regarding their real impact on patient's health and their efficiency in the prevention of comorbidities. If polypharmacy is not considered in the context of kidney failure, it is directly associated with increased mortality, particularly in the elderly population. A systematic study and meta-analysis of 47 studies demonstrated a significant association between polypharmacy and mortality, employing both discrete and categorical definitions.[28] Another study aimed to determine the link between an elevated risk of fractures in patients with chronic kidney failure. Polypharmacy was found to be associated with fractures, irrespective of the stage of CKD.[29] All these adverse effects resulting from incorrectly selected doses ultimately lead to poor clinical outcomes and a decline in patients' quality of life. In 2007, a study was conducted by Sweileh et al investigated the prevalence of inappropriate medication prescribing, serious adverse reactions associated with nephrotoxic drugs, and dosing errors in individuals with CKD. The study found that histamine receptor blockers, antibiotics, and cardiac medications were the most frequently prescribed inappropriate drugs. Remarkably, approximately 77.5% of the prescribed medications during hospitalization were not adjusted based on the GFR. This study underscores the urgent need to address dosing errors, particularly during hospitalization, to ensure optimal medication management in patients with kidney insufficiency.[30] Furthermore, economic costs are rising. The consumption and purchase of incorrect drug dosages are increasing, along with the number of hospital bed days and resuscitations. Hassan et al (2009) conducted a comprehensive assessment to examine the incidence of dosing errors among patients with CKD in the nephrology department. Additionally, they investigated the

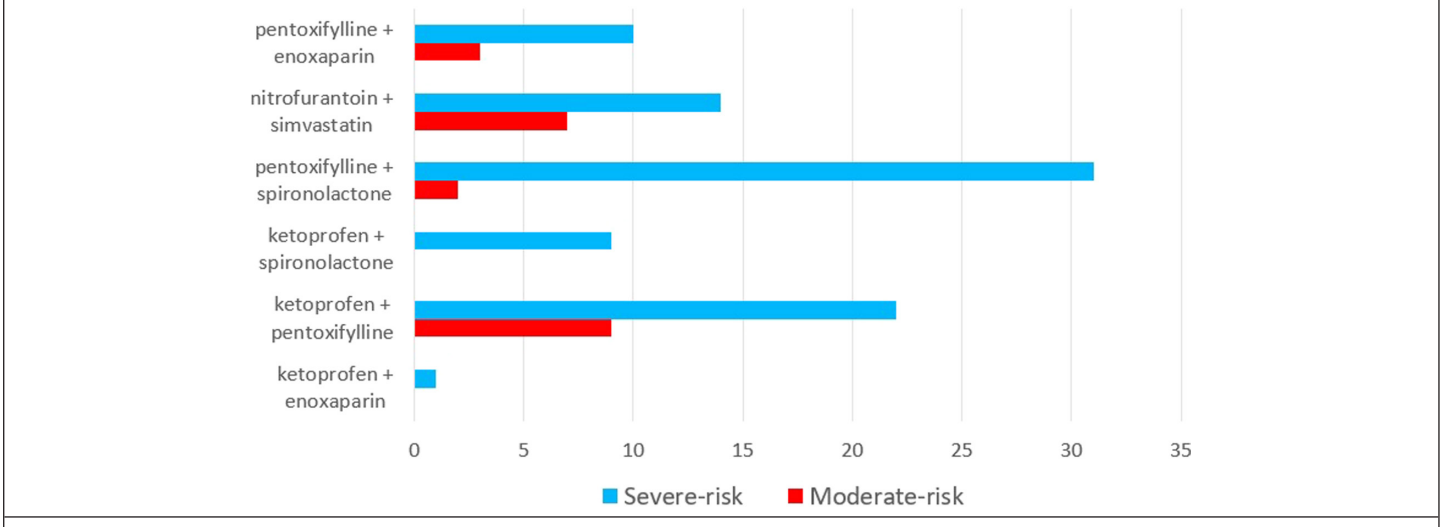

Figure 3. Number of dangerous combinations of prescriptions based on the level of polypharmacy.

role of pharmacists in adjusting medication doses and preventing drug-related adverse events. The study specifically focused on drug dosing practices in CKD patients. Prior to implementing any interventions, it was observed that among the 2814 prescriptions analyzed, 607 (21.6%) necessitated dose adjustment or discontinuation based on kidney function, while 322 prescriptions (53.0%) deviated from the recommended guidelines. Based on these findings, the researchers concluded that the implementation of a specialized renal dosing service within the hospital setting could significantly enhance the proportion of drug dosages tailored to kidney function. Such an approach not only holds promise for optimizing drug therapy but also offers potential cost savings and improved patient safety by mitigating the occurrence of adverse events.[31] As a result, properly modifying dosages of drugs in patients with CKD causes fewer adverse drug effects, lowers therapeutic expenses, reduces bed days and death rates, and preserves the efficacy of treatment. Consequently, clinicians must frequently build individualized treatment plans to accomplish the expected results while reducing adverse events. A study conducted at the University of North Carolina Hospitals examined markers of readmission within 30 days in maintenance hemodialysis patients and found that patients with severe-risk polypharmacy had a 1.7 times higher likelihood of readmission. Furthermore, reducing the number of outpatient medications decreased the probability of readmission within 30 days by 70%-80%.[32]

Stage 1 CKD patients, as well as stage 3 and higher CKD patients, were frequently prescribed medications containing combinations of pentoxifylline/spironolactone and ketoprofen/pentoxifylline (Figure 2). Patients with chronic kidney failure necessitate dose adjustments based on their GFR and stage of CKD.[31] Administering drugs without proper dose adjustment poses an increased risk of adverse drug reactions.[33] Adverse drug reactions can manifest as mild-to-severe symptoms, including direct toxic effects of drugs and their metabolites, reduced drug efficacy, or accumulation of metabolites that the kidneys are unable to eliminate. These reactions can have profound consequences, impacting multiple organs and systems within the body.[34] Furthermore, inadequate or absent dose adjustment, along with polypharmacy, can directly inhibit kidney function. While individuals with a healthy kidneys may experience AKI due to drugs with inherent nephrotoxicity, patients with preexisting chronic kidney damage may experience progression to the next stage of CKD.[35] Clinically, this can result in sustained hypertension, severe anemia and bleeding, polyneuropathy, osteoporosis, and overall increased body toxicity.[36] In the study conducted by Vincenzo Arcoraci (2021), the prescription of contraindicated medications in older individuals with CKD was examined. Low doses of acetylsalicylic acid were identified as contraindicated drugs that were predominantly prescribed upon admission, with a decrease of 1.2% at discharge. There was an overall increase in therapeutic appropriateness in hospitalized elderly patients with CKD, despite a small percentage of therapeutic inadequacy at discharge, highlighting the need for closer collaboration with pharmacologists to improve medication management. The researchers also identified factors associated with the prescription of contraindicated drugs in elderly individuals with CKD in a hospital setting. A descriptive analysis was conducted to compare demographic and clinical characteristics, and logistic regression models were used to assess factors related to inappropriate drug use and the percentage change in drug utilization during hospitalization. At the time of admission, 21.9% of patients received at least one inappropriate medication, which decreased by 3.0% at discharge (P = .010). The authors found that the likelihood of using at least 1 contraindicated medication was significantly higher in patients receiving multiple drugs (OR 1.21, 95% CI 1.16-1.25, P < .001) and in those with end-stage CKD (G4: 16.90, 11.38-25.12, P < .001; G5: 19.38, 11.51-32.64, P < .001).[37]

Polypharmacy was also evaluated based on inappropriate combinations of medicines. Severe-risk polypharmacy prescriptions included 2 combinations, pentoxifylline/spironolactone and ketoprofen/pentoxifylline, the most, whereas among moderate-risk prescriptions, the ketoprofen/pentoxifylline combination was more prevalent (Figure 3). Research by Solak et al has demonstrated limited practice of dose adjustments by physicians in non-internal medicine clinics for dialysis patients, even when nephrologist consultations are sought.[14] Interestingly, our investigation revealed that dose adjustments and the avoidance of potentially dangerous drug combinations are not consistently implemented, even in specialized hospital settings. Various factors contribute to the disregard of dose adjustments. Notably, physicians face significant challenges due to heavy workloads resulting from inadequate staffing and a large number of patients. This restricts the time available to specialists for formulating individualized treatment plans that encompass appropriate dose adjustments for all prescribed medications. Additionally, physicians may be reluctant to deviate from the clinical protocols established by the Kazakhstan's Ministry of Health. Any departure from these standard treatment protocols necessitates thorough justification for each modification made to the therapeutic regimen. Furthermore, there may be legal implications if circumstances are not favorable. Adhering strictly to the clinical protocol algorithm provides doctors with a sense of legal protection. Conversely, a study conducted by Egyptian researchers has reported that severe-risk polypharmacy among renal patients with comorbidities is inevitable.[38]

The analysis of dangerous combinations of drugs allowed us to identify new risks for patients with CKD. Prescribing a combination of anticoagulant drugs and NSAIDs has many risks. One of them is anesthesia for kidney transplants or other abdominal operations. Combined spinal-epidural anesthesia may be an option for patients scheduled for kidney transplantation. This option of anesthesia in these patients has its advantages, such as minimal toxicity, the absence of the need for mechanical ventilation in the postoperative period, the low likelihood of iatrogenic lung infection, and other risks associated with

the side effects of general anesthesia.[39] The combination of low molecular weight heparin and NSAIDs increases the risk of epidural or spinal hematoma, which can result in paralysis.[40] The most common combination in our case was pentoxifylline and spironolactone. Furthermore, NSAIDs enhance the anticoagulant effect of heparinoid therapy, which may increase the risk of bleeding. This is primarily reflected in a longer bleeding time and an increased likelihood of gastrointestinal bleeding.[41] Another common doctor-prescribed combination of pentoxifylline and ketoprofen causes an increase in prothrombin time and thus negatively affects hemostasis.[43] The combination of NSAIDs and diuretics, such as spironolactone and ketoprofen, inhibits the synthesis of prostaglandins in the kidneys which are normally responsible for blood flow to the kidneys during dehydration.[43] In addition, inhibition of prostaglandin activity leads to hyperactivation of vasopressors, resulting in increased blood pressure and a decrease in the hypotensive effect of diuretics.[44] The reduced diuretic effect of this combination may also increase the risk of congestive heart failure. Non steroidal anti inflammatory drugs also enhance diuretics' potassium-sparing effect, which can result in hyperkalemia. Low molecular weight heparins in combination with diuretics (spironolactone + enoxaparin) have the same effect.[45] Parallel use of nitrofurantoin and simvastatin could raise the risk of peripheral neuropathy. They both have this side effect, and combining them only increases the risks. Diabetes and being over the age of 60 are risk factors for patients. Despite treatment removal, neuropathy can worsen or become permanent in some cases.[46]

This study possesses a few limitations. First of all, there is a relatively small number of observations, as evidenced by the study of a statistically significant difference in polypharmacy among 3 groups of patients, divided by stages of CKD. This value turned out to be extremely close to the statistically significant number *P* (n = 0.059n = 0.059). Second, due to the study's retrospective nature, some data and patient studies may not have been entered into the database or simply not performed, such as measurements of median hemoglobin levels, alanine transaminase, and aspartate transaminase levels. Third, our study was conducted in a single medical institution, indicating that the study was not multicenter.

This is the first study investigating polypharmacy and multidrug interactions in CKD patients in Kazakhstan. It provides valuable insights into the relationship between CKD stages and the prevalence of polypharmacy, as well as the occurrence of inappropriate medication combinations among CKD patients. Our findings reveal a distinct pattern where all patients across different CKD stages are predominantly subjected to moderate-risk polypharmacy, followed by severe-risk polypharmacy, and subsequently low-risk polypharmacy. Moreover, our analysis of inappropriate medication combinations highlights the frequent prescription of medications containing pentoxifyl line/spironolactone and ketoprofen/pentoxifylline to Stage 1 CKD patients and those with stage 3 or higher CKD. Notably, severe-risk polypharmacy prescriptions are more likely to include these combinations, while the ketoprofen/pentoxify lline combination is more prevalent among moderate-risk prescriptions. This pattern of polypharmacy potentially impedes the treatment trajectory of CKD patients. Despite the limitations of the study, these findings demonstrate the importance of vigilant medication management in CKD patients, particularly in assessing the appropriateness of polypharmacy and monitoring for potential adverse drug interactions. Healthcare providers should consider the unique pharmacokinetic and pharmacodynamic characteristics of medications in the context of CKD to optimize therapeutic outcomes and minimize the risk of medication-related complications. Future research should focus on developing targeted interventions and guidelines to support evidence-based prescribing practices tailored to the specific needs of CKD patients, ultimately improving the quality of care and patient outcomes in this population, while also assessing the degree of polypharmacy in other internal medicine departments and suggesting possible strategies to reduce this burden.

Data Availibility Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Ahmet Yassawi University (Date: 03.01.2024, Number: 24).

Informed Consent: Informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.A., A.G.; Design – A.G., A.A.; Supervision – A.G., Z.K., I.M., D.S.; Resource – A.A., R.A., A.S.; Materials – A.A.; Data Collection and/or Processing –D.S., A.I., M.M., A.G.; Analysis and/or Interpretation – A.A., A.G., D.S.; Literature Search – A.A., M.M.; Writing – A.A., A.G., D.S.; Critical Review – A.A., Z.K., I.M., D.S., A.I., A.S., R.A., M.M., D.S., A.G.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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