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Comparison and analysis of 4 drug interaction databases in nephrology patients using clinical pharmacy approaches: A cross-sectional study

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Abstract

Background and Aims: Potential drug-drug interactions (pDDIs) might change treatment outcome. pDDIs are frequently encountered in patients with renal dysfunction. Our aim is to analyse the compatibility of drug interaction databases and investigate drug interactions in nephrology patients.

Methods: In our study, the treatment orders of patients and a comparison of four databases (Uptodate®, Micromedex®, RxMediaPharma®, Drugs.com) were analysed retrospectively. 152 patients who were treated in a University Nephrology inpatient service between January 2018 and 2020 were included.

Results: At least one pDDI was detected in 129 (84.9%) patients. The median age of patients was 62, and the interquartile range was 50-72. A total of 1088 pDDIs belonging to 616 different drug pairs were detected. The age values of patients with at least one pDDI were found to be higher than the group without interaction (p=0.005). The total number of interactions in 4 different databases was significantly higher among patients with polypharmacy and comorbidity (p<0.001).

There was an agreement rate of 22% in terms of detecting drug interactions in 4 databases. There was an insignificant level of agreement at the rate of 5.2% in terms of similarity in severity levels. In the pairwise comparison of databases, the highest agreement for identifying interactions (65.3%) and severity levels (21.4%) was between Uptodate® and RxMediaPharma®.

Conclusion: The frequency of interaction is high in nephrology. More than one database should be checked due to the low compliance rates between databases by the clinical pharmacist.

Keywords Clinical pharmacy · Concordance · Drug-drug interactions · Nephrology · Interaction databases

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INTRODUCTION

The treatment of complex diseases requires several medications. While drug combinations can be very effective, they can also result in drug-drug interactions (DDIs). Potential drug-drug interactions (pDDIs) can lead to treatment failure and adverse drug reactions (ADRs). The resulting ADRs are highly associated with increased morbidity and mortality (Kheshti et al., 2016). Drug interactions are responsible for more than 30% of all ADRs and are associated with 44% of drug-related deaths (Abbas et al., 2022). Studies conducted in different patient groups and settings show that the prevalence of DDIs ranges from 16% to 96% (Özdamar & Özdamar, 2021).

The number of drugs is related to drug interactions. In one study, the incidence of drug interactions in a patient using two different drugs was estimated to be 5.6%. When the number of drugs used was five, this rate increased to 56%, and when it was seven, it increased to 100% (Karas, 1981).

Chronic kidney disease (CKD) is often accompanied by comorbidities such as diabetes, hypertension, cardiovascular events and thus, multiple drugs are required to treat these comorbidities. Some studies have found that CKD patients on dialysis use an average of 10-12 different medications simultaneously. Drug interactions exacerbate health problems of patients with CKD and so, can increase health care costs and hospital stay duration (Fasipe et al., 2018).

Due to impaired renal excretion of drugs, individuals with CKD constitute a high-risk population for potentially severe DDIs (Marquito et al., 2014). CKD patients are also at high risk for DDIs due to changes in the pharmacodynamics and pharmacokinetics of pharmaceutical agents. Not all pDDIs may be clinically apparent, but when they occur, they can lead to adverse outcomes such as treatment failure or drug-induced toxicity, resulting in increased costs, morbidity, and even mortality (Okoro & Farate, 2019).

The characteristics of CKD include changes in drug pharmacokinetics due to the disease itself and the use of multiple drug therapies and reactive immunosuppressive drugs. Therefore, drug-related problems are very common in CKD patients, and specialised personnel are needed to monitor medications. Additionally, the therapeutic range of immunosuppressive drugs is narrow. Such drugs include tacrolimus and cyclosporine. Both require serum concentration monitoring (Liu et al., 2021). Careful dose adjustments based on expert knowledge of the patient's creatinine clearance, drug pharmacology, and interactions are required to manage treatment (Mason & Bakus, 2010).

Clinical pharmacists are specialists who routinely provide patient care and interact with patients and other health care professionals to optimise pharmacotherapy. Integrated professional communication among nephrologists, clinical pharmacists, and nurses should be encouraged to optimise the care of patients (Fasipe et al., 2018).

Studies have shown that pharmacists and physicians can reduce serious interactions by using drug interaction databases (Halkin et al., 2001). The most appropriate database should balance low and high risk alerts. Excessive alerts can lead to fatigue and suppression of clinically significant interactions, whereas a lack of alerts increases the risk of ignoring potential harm and reduces the user's perception of the system's reliability and usefulness (Biase et al., 2022).

This research aims to retrospectively determine the frequency of pDDIs in patients in Erciyes University Hospital Nephrology Department and evaluate the concordance between four drug databases: Uptodate®, Micromedex®, Drugs.com, which are international databases, and a region-specific local software RxMediaPharma®, which has a drug interaction checker module. Limited studies are performed in nephrology in terms of drug interactions and compatibility between different databases. This is the first study that analysed local drug software Rxmediapharma while using nephrology prescriptions.

MATERIALS AND METHODS

Ethics Approval

Approval was obtained from the Ethics Committee for Non-Interventional Clinical Research at Erciyes University with Decision No. 2022/408. The study was conducted retrospectively using records from the outpatient clinic and inpatient service of the Nephrology Department of the Faculty of Medicine.

Study Design

The sample size was determined with the hypothesis that the kappa statistic for agreement between the two devices would be 40%. The minimum acceptable kappa rate was taken as 15%, and the interaction rate was assumed to be 50%. These values were determined based on similar studies in the literature (Sancar et al., 2019; Hegde et al., 2015; Al-Ramahi et al., 2016; Khamas et al., 2021; Günayet al., 2022). It was determined that at least 123 participants were needed for the study, with 80% power and a 5% margin of error. The calculation was based on a related study in the literature (Donner & Eliasziw, 1992). A total of 152 patients in Erciyes University Hospital nephrology inpatient service were included in the study.

Table 1. Categorisation of drug databases by severity levels

Severity Category	Uptodate®	Drugs.com	RxMediaPharma®	Micromedex®
Severe (3)	Avoid (X)	Major-contraindicated (drugs3)	Level 3-contraindicated and level 3	Contraindicated
Major (2)	Major (D)	Major and moderate-avoid/major and moderate-adjust dose/moderate-adjust dosing range (drugs2)	Level 2	Major
Moderate (1)	Moderate (C)	Major close monitoring Moderate monitoring (drugs1)	Level 1	Moderate

Source: Uptodate® Drug Interactions 2022; Drugs.com Drug Interactions Checker 2022; RxMediaPharma® Interactive Drug Information Source 2022; Micromedex® Drug Interactions 2022.

Evaluation of the Databases

In our study, four different databases with the highest sensitivity (ability of the software correctly identifying clinically significant drug pairs) and specificity (ability of the software ignoring clinically insignificant interaction pairs) were used to determine pDDIs. These databases were Uptodate® and Micromedex®, which have the highest sensitivity and specificity in the literature, Drugs.com, which provides free access, and RxMediaPharma®, a Turkish national database (RxMediaPharma®, 2020). If any drug interaction was found by at least one (≥ 1) database, it was included as a pDDI in our analysis.

Statistical Analysis

For descriptive statistics, numerical variables are presented as mean, median, standard deviation, and 25th and 75th percentiles, while categorical variables are given as count and percentage values. The Shapiro-Wilk test and graphics (box-and-whisker plots and histograms) were used to assess the normality assumption. Since the normality assumption was not met for variables between the two independent groups, the Mann–Whitney U test was used to examine differences between the groups. The Kappa Statistic was used to assess the agreement between the two methods. The Fleiss Kappa statistic was used to assess the agreement between four methods when the data structure was in two categories, while the Krippendorff's alpha coefficient was used when the data structure was ordinal. Agreement rates were calculated by dividing the number of same pDDI severity levels in two databases by the total number of detected pDDIs. Data analysis was performed using Turcosa Analytics Ltd Co Turkey statistical software. The "irr" package in R 4.0.5 was used for the concordance analyses. The significance level was taken as $p<0.05$.

The degree of agreement was defined using the kappa coefficient as follows: <0.00: "No agreement"; 0.00-0.20: "Slight agreement"; 0.21-0.40: "Fair agreement"; 0.41-0.60: "Moderate agreement"; 0.61-0.80: "Substantial agreement"; 0.81-1.00: "Almost perfect agreement". This classification is based on the kappa coefficient rating by Landis and Koch (Landis, & Koch, 1977).

RESULTS

It was determined that out of the 152 patients included in the study, 90 (59.2%) were male and 62 (40.8%) were female. The median age of all patients was 62 years, with an interquartile range (IQR) of 50-72.

At least one pDDI was detected in 129 (84.9%) patients. The median age of patients without any potential DDIs was 52 (IQR: 46-63), while the median age of patients with interactions was 66 (IQR: 52-73.5) (p=0.005). There was a statistically significant difference in the age distribution between the groups. Age values were found to be higher in the group with interactions than in the group without interactions. There was no statistically significant relationship between gender and pDDI status.

Taking five or more medications simultaneously is evaluated as polypharmacy. Among all patients, polypharmacy was observed in 81.6% (n=124). Polypharmacy was observed in 94.6% (n=122) of patients with interactions and in 8.7% (n=2) of patients without interactions (p <0.001). There was a statistically significant difference in polypharmacy between the group categories. Polypharmacy was observed in more patients in the group with interactions compared with the group without interactions.

When all patients were examined, it was determined that 78.9% (n = 120) had another concomitant disease. The most common comorbidities were hypertension (66.4%), diabetes (41.4%) and coronary artery disease (29%).

Number of Drug Interactions Categorically

In our study, 148 different drugs were identified in the drug interaction list for patients. The drugs are listed according to the Anatomical Therapeutic Chemical Classification System (ATC). Data are in Table 2.

Drugs used for the digestive system and metabolism are mostly involved in DDIs, followed by immunosuppressants,

Table 2. Distribution of drug groups in the DDI list according to the ATC classification system

Drug Classification and Drug Names	Number of potential drug interactions
A Digestive system and metabolism: Lansoprazole, pantoprazole, omeprazole, esomeprazole, sodium bicarbonate, calcium carbonate, famotidine, magnesium carbonate, magnesium oxide, sucralfate	117
L04 Immunosuppressants: Tacrolimus, everolimus, cyclosporine, azathioprine, mycophenolic acid, mycophenolate mofetil, and leflunomide	114
C07 Beta-blocking agents: Metoprolol, carvedilol, propranolol, bisoprolol, nebivolol	89
B01 Antithrombotic agents: Aspirin, clopidogrel, enoxaparin, warfarin, dipyridamole, tinzaparin, edoxaban, ticagrelor	85
J01 Systemic antibacterials: Clarithromycin, ceftriaxone, piperacillin-tazobactam, trimethoprim-sulfamethoxazole, metronidazole, ciprofloxacin, ampicillin, meropenem, cefuroxime, vancomycin, levofloxacin, ertapenem, moxifloxacin	81
N06 Psychoanaleptics: Sertraline, paroxetine, duloxetine, trazodone, mirtazapine, venlafaxine, memantine, citalopram	78
C03 Diuretics: Furosemide, hydrochlorothiazide, spironolactone, indapamide, tolvaptan	75
C08 Calcium channel blockers: Nifedipine, amlodipine, diltiazem	62
N05 Psycholeptics: Hydroxyzine, pramipexole, quetiapine, haloperidol, olanzapine, alprazolam, risperidone, lorazepam	61
H02 Systemic corticosteroids: Prednisolone, methylprednisolone, and dexamethasone	60
R03 Drugs for obstructive airway diseases: Budesonide, salbutamol, ipratropium, salmeterol, indacaterol, and formoterol	48
C01 Cardiac therapy: Amiodarone, isosorbide monohydrate, digoxin, ranolazine	41
C09 Agents acting on the renin-angiotensin system: Perindopril, candesartan, losartan, ramipril, olmesartan, valsartan, fosinopril	31
A10 Drugs used in diabetes: Insulin aspart, insulin lispro, insulin glargine, metformin, linagliptin	25
N02 Analgesics: Tramadol, fentanyl, oxycodone	24
N03 Antiepileptics: Pregabalin, gabapentin, lamotrigine, levetiracetam, carbamazepine	23
V Drugs used in hyperkalemia and hyperphosphatemia: Sodium polystyrene , calcium acetate, lanthanum	22
J02 Systemic antifungals: Fluconazole and voriconazole	20
C10 Lipid-modifying agents: Atorvastatin, rosuvastatin, fenofibrate	19
C02 Antihypertensives: Doxazosin	19
G04 Urologicals: Silodosin, tamsulosin, solifenacin	17
B03 Antianemic preparations: Iron sucrose, folic acid, iron (3) hydroxide sucrose, ferric hydroxide polymaltose, iron (2) fumarate, iron sulphate	16
H03 Thyroid therapy: Levothyroxine	15
J05 Systemic antivirals: Valganciclovir, acyclovir, tenofovir, entecavir, oseltamivir, ganciclovir	15
A06 Drugs used in constipation: Lactulose	11
M04 Drugs for gout: Allopurinol-colchicine	10
R06 Systemic antihistamines: Cetirizine, cyproheptadine, fexofenadine	9
L01 Antineoplastic agents: Anagrelide, bortezomib, cyclophosphamide	9
A11 Vitamins: Calcitriol, cholecalciferol	7
A04 Antiemetics: Granisetron and scopolamine	7
P01 Antiprotozoal agents: Hydroxychloroquine	6
A03 Other drugs for functional gastrointestinal disorders: Metoclopramide	5
C04 Peripheral vasodilators: Pentoxifylline	3
A07 Antidiarrheals, intestinal anti-inflammatory/anti-infective agents: Loperamide	3
H05 Calcium homeostasis: Cinacalcet	2
M01 Anti-inflammatory and antirheumatic products: Meloxicam	2
A12 Mineral supplements: Calcium gluconate	2
R05 Cough and cold preparations: Codeine	1
L03 Immunostimulants: Filgrastim	1

Source: (World Health Organisation (WHO) ATC/DDD Index 2023)

with tacrolimus being the most interactive substance in this group.

Among all patients, the median number of drugs used was 7 (IQR: 5-9). For those without detected interactions, this value was 2 (IQR: 2-3), while for those with interactions, it was 8 (IQR: 6-9). The number of drugs on prescription was higher in the group with interactions than in the group without interactions ($p<0.001$).

pDDIs were examined using the Uptodate®, Micromedex®, RxMediaPharma®, and Drugs.com drug databases. Across all patients, a total of 1,088 potential drug-drug interactions (pDDIs) involving 616 unique drug pair combinations were identified. In our study, 7.2 pDDIs per patient were identified among the 152 patients evaluated. Among the interaction pairs, 335 (54.4%) were classified as pharmacodynamic, 200 (32.5%) as pharmacokinetic, and 81 (13.1%) as unknown mechanisms.

The Most Common Interactions in the Study

Within the scope of the study, the severity and mechanisms of the most frequently encountered interactions are in Table 3.

Severity of Interactions According to the Databases

According to the Uptodate®, at least one pDDI was identified in 78.9% (n=120) of the patients. When potential DDIs were examined, a total of 521 pDDIs were identified, with 419 (80.4%) interactions at severity level C, 74 (14.2%) interactions at severity level D, and 28 (5.4%) interactions at severity level X. According to the Uptodate®, there were 3.4 pDDIs per patient.

According to the Drugs.com, at least one pDDI was found in 82.3% (n=125) of the patients. When the patient's pDDIs were examined, an average of 5.7 interactions per patient was found. These interactions are classified into three categories based on the severity level. A total of 864 pDDIs were identified, with 2 (0.2%) under "major contraindicated" (drugs 3), 159 (18.4%) under "major-moderate (adjust dose-avoid generally)" (drugs 2), and 703 (81.4%) under "moderate-major close monitoring" (drugs 1).

According to the RxMediaPharma®, at least one pDDI was found in 77.6% (n=118) of the patients. pDDIs are classified into three severity levels according to RxMediaPharma®. There were a total of 548 pDDIs in the patients, with 77 (14%) contraindicated and level 3, 132 (24.1%) level 2, and 339 (61.9%) level 1. There were 3.6 interactions per patient.

Table 3. Characteristics of the DDIs

DDI	Uptodate	Drugs.com	RxMediaPharma	Micromedex	Mechanism	Potential outcome
Tacrolimus-prednisolone (n=23)	C	-	Level 3	-	PK	Tacrolimus serum concentration decreases
Furosemide-lansoprazole (n=11)	-	Moderate/ monitor	-	-	PD	Risk of hypomagnesemia
Tacrolimus-pantoprazole (n=10)	-	Moderate/ monitor	Level 2	-	unknown	Risk of hypomagnesemia and increased tacrolimus serum concentration
Aspirin-metoprolol (n=10)	-	-	-	Moderate	PD	Blood pressure may increase
Aspirin-clopidogrel (n=8)	C	Moderate/ monitor	Level 1	Major	PD	Increased risk of bleeding
Levothroxin-lansoprazole (n=7)	-	Moderate/ monitor	-	Moderate	PK	Levothroxin bioavailability is reduced
Atorvastatin-clopidogrel (n=7)	-	Moderate/ monitor	-	Moderate	PK	Decreased effect of clopidogrel
Furosemide-aspirin (n=7)	C	-	Level 1	Major	PD	Decreased diuretic effect and risk of nephrotoxicity
Tacrolimus-diltiazem (n=6)	C	Moderate/ monitor	Level 1	Major	PK	Increased tacrolimus toxicity
Moxifloxacin-methyl prednisolone (n=5)	C	Major/Close monitoring	Level 1	Major	PD	Increased risk of tendinitis and tendon rupture
Amlodipine-calcium carbonate (n=5)	C	Moderate/ monitor	-	-	PD	The effectiveness of amlodipine may be reduced

PK: Pharmacokinetics, PD: Pharmacodynamics

According to the Micromedex®, at least one pDDI was found in 72.4% (n=110) of the patients. According to the Micromedex® drug database, there were a total of 424 pDDIs in the patients, with 10 (2.1%) contraindicated, 230 (54.2%) major, and 184 (43.4%) moderate interactions. There were 2.8 interactions per patient. Figure 1 shows the number and percentage of pDDIs and their severity levels after removing duplicate interactions in each database.

Comparison of the Compatibility of the Databases

The databases showed variations in identifying DDIs. All databases can determine the severity of interactions but found different severity levels for the interactions.

When evaluating the agreement between pairs of drug databases, the highest overall agreement rate was 82.6%, found between Uptodate® and RxMediaPharma® according to the Kappa formula. Data are in Table 4.

Considering the compatibility rates of the databases in determining DDIs, the Kappa analysis revealed a weak level of agreement of 22% among the four databases.

Agreement of Severity Levels Between Databases

When evaluating the compatibility of drug databases in determining the severity of DDIs, the highest overall agreement rate of 77.7% was found between Uptodate® and RxMediaPharma®. The compatibility rates in determining the severity of pDDIs are shown in Table 5.

When looking at the compatibility rates of drug databases in determining the severity of DDIs, the Kappa analysis revealed a slight level of agreement of 5.2% among the four databases.

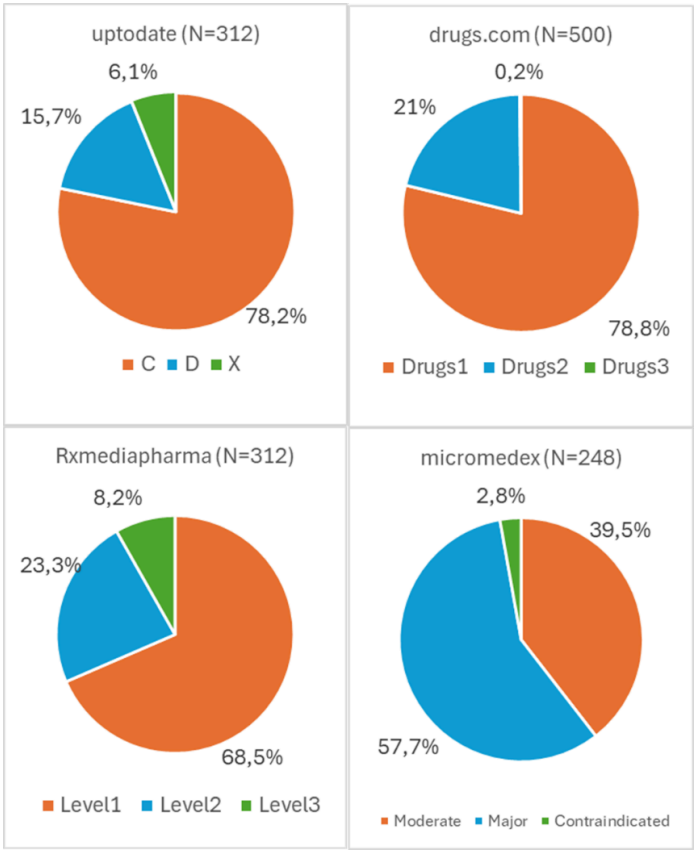

Figure 1. Numbers and percentages of pDDIs

DISCUSSION

CKD patients are at risk of adverse drug outcomes. Considering the high prevalence of comorbidities, these patients use multiple medications. As the number of prescribed drugs

Table 4. Compatibility rates of drug databases for identifying pDDIs

Drug Databases	Overall Agreement	Kappa coefficient	Standart error	*p-value*
Uptodate®- Micromedex®	%62.2	0.245 (Fair agreement)	0.03	<0.001
Uptodate®- Drugs.com	%46.4	0.08 (Slight agreement)	0.03	0.01
Uptodate®- Rx MediaPharma®	%82.6	0.653 (Substantial agreement)	0.03	<0.001
Micromedex®- Rx MediaPharma®	%61	0.219 (Fair agreement)	0.04	<0.001
Micromedex®- Drugs.com	%47.9	0.072 (Slight agreement)	0.03	0.006
Rx MediaPharma®- Drugs.com	%43.1	0.133 (Slight agreement)	0.03	<0.001

Table 5. Compatibility rates of drug databases in determining the severity of pDDIs

Drug Databases	Overall agreement	Kappa coefficient	Standard error	*p-value*
Uptodate® - Micromedex®	% 46.1	0.052 (Slight agreement)	0.017	0.003
Uptodate® - Drugs.com	% 37	0.017 (Slight agreement)	0.022	0.447
Uptodate® - Rx mediapharma®	% 77.7	0.214 (Fair agreement)	0.017	<0.001
Micromedex® - Rx mediapharma®	% 46.9	0.08 (Slight agreement)	0.025	0.002
Micromedex® - Drugs.com	% 29.4	0.025 (Slight agreement)	0.021	0.230
Rx mediapharma® - Drugs.com	% 33.7	0.212 (Fair agreement)	0.0309	<0.001

increases, so does the number of pDDIs, which can lead to serious side effects (Sommer et al., 2020).

The frequency of significant drug interactions was high in our study; at least one pDDI was detected in 84.9% of patients and was similar to the literature. A study on end-stage kidney disease found a pDDI frequency of 89.1% (Al-Ramahi et al., 2016). This indicates that the risk of drug interaction-related problems might be increased in nephrology patients.

In a study on critical patients with CKD, the mean age of patients was found to be 60.2 ± 12.1 (Aghili & Kasturirangan, 2021). In a Nigerian study on adult CKD patients, the mean age of those with pDDIs was 48.9 ± 14.0, while those without pDDIs had a mean age of 52.1 ± 16.8 (Okoro & Farate, 2019). These two studies showed no statistically significant difference in age between patients with and without pDDIs ($p>0.05$). However, our study found a statistically significant difference in age distribution among the group categories. Variations may be due to different databases used for evaluating drug interactions, study design (e.g., retrospective and prospective), differences in prescription habits, and the clinical settings (e.g., inpatient or outpatient).

A study in CKD patients determined an average of 6.3 ± 3.1 (1-17) drugs per patient and observed polypharmacy in 87.7% of patients (Sgnaolin et al., 2014). Similar rates were found in our study.

In a study on DDIs in critical patients with CKD, the most common comorbidities were diabetes (68.1%), hypertension (63.7%), and electrolyte imbalance (53.8%) (Aghili et al., 2021). When comparing our study with the literature, the most common comorbidities were found similar such as hypertension (66.4%), diabetes mellitus (41.4%), coronary artery disease (29%), and chronic obstructive pulmonary disease (11.8%).Drug interaction agreement rates might be affected by prescription habits. In our study, CKD was the most common diagnosis as expected in a nephrology inpatient service.

In nephrology clinic patients, sodium bicarbonate and calcium carbonate are commonly used to treat acidosis and phosphatemia due to kidney dysfunction (Cheng et al., 2021). Similarly, the use of the acid-suppressing drug group was quite high in our study and indeed, it was the most frequent one. The second most frequently interacting group was immunosuppressants, with tacrolimus being the most commonly interacting drug in our study. The safe and effective use of tacrolimus requires careful dose titration and patient monitoring (Habet, 2021). Patients who have undergone organ transplantation have a huge risk of tacrolimus-related problems such as organ rejection or supratherapeutic tacrolimus toxicities such as infections. These problems might be triggered by drug interactions.

The number of prescription drugs was statistically higher in the interaction group than in the non-interaction group in our study ($p<0.001$). Similarly, a study examining adult nephrology patients found that the number of drugs used by the patients with interactions was statistically significantly higher than those without interactions (Okoro & Farate, 2019). As a nature of having multiple comorbidities, the drug interaction potential increases for the number of drug increases.

In an Indian study evaluating DDIs in kidney failure patients using the Micromedex® database, it was reported that 50.6% of interactions were pharmacodynamic, 46.8% were pharmacokinetic, and 2.6% had an unknown mechanism which is similar to our study results. Pharmacokinetic drug interactions might be monitored with strict therapeutic drug monitoring methods, and both pharmacokinetic and pharmacodynamic drug interaction problems should be monitored by checking adverse drug reactions.

In our study, the most frequently detected interaction pair was tacrolimus and prednisolone. In a study on DDIs in critical patients with CKD, using only the Lexicomp® database, the most common interaction pair was found to be furosemide-insulin, followed by amlodipine-calcium carbonate (Aghili et al., 2021). Moreover, in a study on DDIs in patients with CKD in India, using only the Medscape database, the most common interaction pairs were sodium bicarbonate-iron sulphate and calcium carbonate-iron sulphate (Hegde et al., 2015).

In our the present study, statistical significance was found between the presence of comorbidities and the number of interactions in all databases examined, except for Drugs.com level 3, RxMediPharma® level 3, and contraindicated levels in Micromedex® ($p<0.05$). Likewise, in a study conducted in Palestine on haemodialysis patients using the Lexicomp® database to examine DDIs, a similar relationship was found between the presence of comorbidities and the number of interactions ($p<0.05$) (Al-Ramahi et al., 2016).

In our study, statistical significance was found between the presence of polypharmacy and the number of interactions in all databases examined, except for Drugs.com level 3 and contraindicated levels in Micromedex® ($p<0.05$).

In a previous study where pDDIs in community pharmacy prescriptions were checked using the Medscape, Micromedex®, and Drugs.com drug databases, the agreement rate between Micromedex® and Drugs.com in identifying the number of patients with and without pDDIs was found to be 68.6% (Kappa value = 0.686) (Sancar et al., 2019). In a study evaluating pDDIs in a haematology ward using

three databases—Lexicomp®, Medscape, and Micromedex®—the agreement rate between Lexicomp® and Micromedex® in identifying the number of patients with and without pDDIs was found to be 40% (Kappa value = 0.4) (Bahçecioğlu, 2021). According to a recent study performed in nephrology patients, the Lexicomp and Medscape systems exhibited poor agreement (Bektay et al., 2024).

In a study evaluating pDDIs in a haematology ward using three databases—Lexicomp®, Medscape, and Micromedex®—the agreement rate between Lexicomp® and Micromedex® in determining the severity of pDDIs was found to be 9.9% (Kappa value = 0.099) (Bahçecioğlu, 2021). The findings of that study are consistent with those of our study. In our study, when evaluating the agreement of drug databases in identifying pDDIs, the Kappa analysis revealed a weak level of agreement of 22% among the four databases. Agreement rates were lower in our study in terms of nephrology prescriptions. In addition, due to this detected incompatibility, it is appropriate to use more than one database.

There is limited data in the literature on the agreement of known databases in identifying pDDIs. Additionally, to the best of our knowledge, there is no study that has examined the agreement using the RxMediaPharma® database for interaction determination. Therefore, it is not possible to make a literature comparison regarding the RxMediaPharma® database. It is a local software generally being used by community pharmacists for checking health regulations in prescriptions for outpatient treatment. It has many modules, such as the drug interaction checker, and drug identification modules but it does not show references in the drug interaction checker module (RxMediaPharma®, 2020) .

Based on the results of the current study and other studies in the literature, pDDI programs should be re-evaluated to improve their agreement by assessing evidence-based results and severity classifications. According to the report of a consensus panel evaluating the evidence for pDDIs in the clinical decision-making process, the following recommendations were made to obtain high-quality information from pDDI programs: establish consistent terminology and use the Drug Interaction Probability Scale (DIPS) to assess case reports of potential pDDIs (Scheife et al., 2015). Additionally, improving health policies and hospital systems, such as implementing alerts in electronic prescription systems when a patient's current medications interact with newly prescribed drugs, could be beneficial (Ergun et al., 2019). The optimal database should have a balance between low- and high-risk alerts. Excessive warnings can lead to fatigue and suppression of clinically important interactions, whereas a lack of warning can increase the risk of ignoring potential damage and reduce the user's perception of the reliability and usefulness of the system.

CONCLUSION

In this study, it is determined that there is inconsistency between databases in terms of determining the severity levels and interactions. The frequency of potential clinically significant drug-drug interactions (pDDIs) detected by drug databases in patients in the nephrology department was found to be high. Due to the frequency of interactions observed in nephrology patients, interactions in this patient group should be regularly examined using the information provided by databases and managed together with their clinical implications. In this context, the inclusion of a clinical pharmacist within the multidisciplinary health care team can contribute to the improvement of health care services. This study might give an idea to clinicians who work in the nephrology department to choose the right database or at least raise awareness about polypharmacy and its potential outcomes. A common language is needed in medical software.

Ethical Committee Approval	This study involved human participants. Ethics Committee Approval was obtained from Erciyes University Clinical Research Ethics Committee with Decision No. 2022/408
Informed Consent	This was a retrospectively designed study, and only patient files were used for data collection. No personal information is presented in the manuscript.
Peer Review	Externally peer-reviewed.
Author Contributions	ContributionsConception/Design of Study: N.G., E.D.; Data Acquisition: N.G.; Data Analysis/Interpretation: N.G.; Drafting Manuscript: E.D.; Critical Revision of Manuscript: E.D.; Final Approval and Accountability: N.G., E.D.
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