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Unlocking therapeutic symphonies: Innovations in clinical decision support for drug-disease interactions in kidney transplantation

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A B S T R A C T

Introduction: Drug-disease interactions (DDSIs) are associated with increasing morbidity, mortality, and healthcare costs. These interactions are preventable if recognized and managed properly. Medication safety is critical in kidney transplant patients due to polypharmacy, co-morbidities, and susceptibility to adverse events. Clinical decision support systems (CDSSs) can play a key role therein. Therefore, this study aims to report on the process of developing an innovative, patient-centered, context-aware CDSS for managing DDSIs in kidney recipients.

Material and Methods: Clinically important DDSIs were identified in the medications of patients at a kidney transplant outpatient clinic. Subsequently, rules for their detection and management were extracted based on pharmacology references and clinical expertise. A CDSS was developed and piloted following recommendations on medication CDSS design principles.

Results: The knowledge base for this CDSS was developed with clinical context sensitivity. We defined priority levels for alerts, established associated display rules, and determined necessary actions based on the transplantation clinical workflow. The DDSI-CDSS correctly detected 37 DDSIs and displayed nine warnings and 28 cautionary alerts for the medications of 113 study patients (32.7% DDSI rate). The system fired three warnings for diltiazem in bradyarrhythmia, and two for each of the following medications and underlying diseases: aspirin in asthma, erythropoietin alfa in hypertension, and gemfibrozil in gall bladder disease. The potential consequences of the identified DDSIs were GI complications (17%), deterioration of the existing disease/condition (6.1%), and an increased risk of arrhythmias (2.6%), thrombosis (2.6%), and hypertension (1.7%). Complying with system alerts and recommendations would potentially prevent all these DDSIs.

Conclusion: This study delineates the process of developing an evidence-based DDSI-CDSS for kidney transplantation, laying the groundwork for future advancements. Our results underscore the clinical significance of these interactions and emphasize the imperative for their accurate and timely detection, particularly in these vulnerable patients.

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INTRODUCTION

Medication therapy is essential to treat diseases and improve patient quality of life [1]. However, this therapy is not entirely safe and is associated with drug-related problems (DRP) [2]. In recent decades, improving the quality of medication therapy and preserving patient safety has taken center stage. Clinicians use clinical references such as Lexi-drug interaction and Stockley's drug interaction references to resolve some DRPs, such as drug-drug interactions (DDIs) [3]. However, one of the DRPs for

which information is not easily and widely available is drug-disease interactions (DDSIs). In this interaction category, a medication used to treat one disease worsens the other co-existing diseases or conditions of a patient [1].

Studies have shown that DDSIs are not rare [4, 5]. A study reported that 13.9% of all prescriptions in community pharmacies had a drug warning related to DDSIs [6]. The most common DDSIs have been reported following the use of non-dihydropyridine calcium channel blockers in heart failure (EF<40%); non-steroidal anti-inflammatory drugs (NSAID) in peptic ulcers, kidney failure, high blood pressure, and other cardiovascular diseases; loop diuretics in renal disorders and urinary incontinence; beta-blockers in exacerbate chronic obstructive pulmonary disease; anti-cholinergic agents in dementia; and antipsychotics, tricyclic antidepressants, and benzodiazepines in patients prone to falls [1, 6]. Similar to other drug interactions, DDSIs are also associated with the risk of adverse drug events (ADEs), increasing morbidity, mortality, and healthcare services costs [5].

It is noteworthy that DDSIs are mostly preventable if recognized and managed properly. Attempts have been made to develop tools to address DDSIs such as clinical guidelines, Beers and McLeod criteria, the screening tool of older persons' prescriptions (STOPP), and the screening tool to alert to right treatment (START) [7, 8]. However, these tools contain information on selective DDSIs (e.g., in porphyria, QT syndrome, renal failure and liver cirrhosis) and those that cover a wide range of comorbidities are limited [9-11]. Although the official drug label (Summary of Product Characteristics (SmPC)) is an important source of information about DDSIs, they do not always provide information about the effects and risks in specific patient groups, and their recommendations are often insufficient, vague, and unhelpful in practice. For example, one study highlighted challenges with SmPC recommendations for drug use in cirrhotic patients, particularly concerning their lack of clarity [12]. Moreover, due to the rapid growth in the number of patients with multi-morbidity and their polypharmacy situation, as well as the ever-increasing number of new drugs on the market, the optimization of drug therapies has increasingly become too complex to be managed by clinicians alone even with availability of such tools [13]. Studies suggest that Clinical Decision Support Systems (CDSSs) can provide more advanced support for clinicians in drug therapy optimization than their mere access to references and clinical guidelines [14]. They can combine data on patients' individual conditions with pharmacological knowledge about DDSIs to enable timely monitoring and management of DDSIs [15]. It was shown that the implementation of the DDSIs considerations in CDSSs used in Dutch pharmacies helped physicians and pharmacists to detect potential DDSIs when prescribing and dispensing drugs [9]. Another study also showed that using a CDSS at the point of care reduced the prescription of QT prolonging drugs by 54.6% in patients who were at high risk of Torsade's de pointes [16]. They can also support the safer prescription of drugs that interfere with impaired kidney function in kidney diseases [17].

Medication safety and optimization are critical in kidney transplant patients, primarily due to polypharmacy, the narrow therapeutic window of transplant medications, and multi-morbidity of patients, leading to susceptibility to adverse events such as graft dysfunction. Previous studies on DDSIs have focused on general patient population and elderly patients while taking into account interactions in limited number of co-diseases (or conditions) [15, 18]. Similarly, studies of CDSSs have been in other medical domains or covering other types of drug interactions [3, 19]. However, to our knowledge, the literature lacks studies of DDSIs and DDSI-CDSSs in the transplantation fields. As part of our initiative to address patient safety in kidney transplantation, we examined the prevalence of DDSIs in the context of transplantation care and developed an innovative context-aware and patient-centered computerized CDSS to support clinicians. This study briefly reports on the process of designing this CDSS based on evidence extracted from the clinical context and its pilot implementation to manage DDSIs in kidney recipients.

MATERIAL AND METHODS

Study setting

This study was conducted in an outpatient kidney transplant clinic at Urmia University of Medical Sciences, Urmia, Iran, in spring 2023. A renal transplant management system (RTMS) is available in this clinic, equipped with a computerized provider order entry (CPOE) and CDSSs for DDIs and drug-lab interactions [3, 20]. The study was reviewed and approved by the institutional research ethics committee of the university.

Identification of DDSIs

In the first step, a list of DDSIs and measures for their proper management were extracted from pharmacology references for the medications used by kidney transplant patients. These DDSIs pertained to the most commonly prescribed drugs, identified during a two-month prospective study in the study setting [3]. The primary pharmacology textbooks and references used for DDSI detection included "UpToDate," "Prescriber's Digital Reference," "Medscape Interaction Checker," "Drugs.com," the Beers and McLeod criteria, the STOPP/START, and some relevant literature [15, 21-25]. The identified

DDSIs were then reviewed and modified by an expert panel consisting of nephrologists and pharmacotherapists to align with the top priorities in the transplant context from a clinical standpoint. Accordingly, we excluded DDSIs that were considered trivial and would likely have caused alert override later if they were used in the system development.

Development of the knowledge base for the DDSI-CDSS module

The resulting information in the previous phase was then presented as IF-THEN rules (e.g., IF Psoriasis exists, THEN use Atenolol with caution) and compiled into a knowledgebase. Our decision support rules were categorized for major and moderate DDSIs based on the seriousness of their patient outcomes and the required responses, such as 'complete avoidance' or 'prescription with caution needing close symptom monitoring.' In line with the previous CDSS modules in the RTMS, the alert display was considered interruptive and non-interruptive, respectively [3, 20]. To create workflow diagrams, Unified Modeling Language (UML) was used, and the CDSS system was programmed using the C#.Net programming language and Structured Query Language (SQL) Server databases.

Pilot of the CDSS

The proper functioning of the CDSS to detect DDSIs was primarily evaluated using fictitious patient data. We defined 109 fictitious patients to test various algorithms associated with individual drugs and their interacting underlying diseases. After resolving the bugs, the system was employed to detect DDSIs in the medication prescriptions of 113 real consecutive patients who were visited by nephrologists during a one-week period in the study setting in the spring of 2023. The aim of these tests was to achieve optimal sensitivity, specificity, and accuracy in detecting interactions by this DDSI-CDSS compared to our extracted DDSI rules. This verification was manually conducted by comparing patients' medical data and DDSIs and assessing the system's performance in correctly detecting them.

RESULTS

Selected medications for the knowledge base

For 595 kidney recipients, 115 types of immunosuppressive and non-immunosuppressive medications were prescribed. Twenty-one drugs did not have any DDSIs, and for the remaining 94 drugs, we extracted 350 DDSIs, their potential patient outcomes, and measures for management. These DDSIs included 72 major, 260 moderate, and 18 minor interactions in the original list. Based on our expert opinion and after checking for double alerts due to overlaps with DLI-CDSS alerts for hepatic and renal diseases, we selected 51 drugs with 100 high-priority DDSI alerts. This selection comprised 31 alerts for warnings and 69 alerts for taking caution to manage DDSIs, and they were chosen to be embedded in the system.

Table 1 presents the list of selected medications and the alert categories for high-priority DDSIs. Fig 1 depicts the process flow in our study.

Table 1: The final list of drugs and their alert categories for high-priority drug-disease interactions

The name of prescribed drug	The interacting co-existing disease or condition	Alert category
Amitriptyline	Heart failure or ischemic heart disease	Caution
	Paralytic ileus or decrease GI motility	Caution
	Seizure	Caution
	Ophthalmic condition (increase intraocular pressure, narrow angle glaucoma)	Caution
	Myasthenia gravis	Caution
Aspirin	Asthma	Warning
Atenolol	Psoriasis	Caution
	Bradyarrhythmia or AV block	Warning
	Pheochromocytoma	Caution
	Chronic obstructive pulmonary disease (COPD)	Caution
	Myasthenia gravis	Caution
	Vasospastic angina	Caution
Atorvastatin	Myasthenia gravis	Caution
Captopril	Angioedema	Warning
	Psoriasis	Caution
Carbamazepine	Arrhythmia	Caution
Carvedilol	Heart block or sinus node dysfunction	Warning
	Myasthenia gravis	Caution
	Pheochromocytoma	Caution
	Psoriasis	Caution
	Prinzmetal's variant angina	Caution
Chlordiazepoxide	Porphyria	Caution
Ciprofloxacin	Seizure	Caution
	Myasthenia gravis	Warning
Clomipramine	Arrhythmia	Caution
Clonazepam	Porphyria	Caution
Co-amoxiclav	Cholestatic jaundice	Warning

The name of prescribed drug	The interacting co-existing disease or condition	Alert category
	Mononucleosis	Warning
Contraceptive LD	Angioedema	Caution
	Migraine	Warning
	Systemic lupus erythematosus	Warning
Cotrimoxazole	Porphyria	Warning
Digoxin	Bradyarrhythmia	Caution
	Myocarditis	Warning
Diltiazem	Bradyarrhythmia	Warning
Enalapril	Angioedema	Caution
Erythropoietin alfa	Thrombotic disorder	Caution
	Hypertension	Warning
Ferrous sulfate	Gastrointestinal (GI) disease	Caution
Flecainide	Congestive heart failure (CHF)	Caution
	Hypokalemia or hypomagnesemia	Caution
Fluoxetine	Mania	Caution
Gabapentin	Myasthenia gravis	Caution
	Drug dependence	Caution
Gemfibrozil	Gallbladder disease	Warning
Glibenclamide (Glyburide)	Type I diabetes or diabetic ketoacidosis	Warning
	Glucose-6-phosphate dehydrogenase (G6PD) deficiency	Caution
Haloperidol	Myocardial infarction	Caution
	Dementia	Caution
	Glaucoma	Caution
	Parkinson's disease	Warning
	Myasthenia gravis	Caution
Hydrochlorothiazide	Adrenal insufficiency	Warning
Lorazepam	Myasthenia gravis	Caution
Metformin	Type I diabetes	Warning
	Diabetic ketoacidosis	Warning
Metoprolol	Myasthenia gravis	Caution
	Pheochromocytoma	Caution
	Psoriasis	Caution
	Prinzmetal variant angina	Warning
Metronidazole	Cockayne syndrome	Caution
Mycophenolate	Gastrointestinal (GI) disease	Caution
Nifedipine	Hypertrophic cardiomyopathy (HCM) with outflow tract obstruction	Caution
	Congestive heart failure (CHF)	Warning
Nitrofurantoin	Glucose-6-phosphate dehydrogenase (G6PD) deficiency	Caution
Nitroglycerin	Hypertrophic cardiomyopathy (HCM)	Warning
Nortriptyline	Myocardial infarction	Caution
	Glaucoma	Caution
Sodium valproate	Mitochondrial disease	Warning
	Urea cycle disorders	Warning
Alendronate	Esophageal and gastrointestinal (GI) disease	Caution
Pentoxifylline	Cerebral or retinal hemorrhage	Warning
Phenytoin	Sinus bradycardia or sinoatrial block or second- and third-degree A-V block	Warning
	Porphyria	Caution
Pioglitazone	Congestive heart failure (CHF)	Warning
	Bladder cancer	Warning
Prazosin	Heart failure	Caution
Prednisolone or Prednisone	Myasthenia gravis	Caution
	Osteoporosis	Caution
Propranolol	Chronic obstructive pulmonary disease (COPD)	Caution
	Myasthenia gravis	Caution
	Pheochromocytoma	Caution
	Psoriasis	Caution
	Prinzmetal variant angina	Warning
Sildenafil	Myocardial infarction	Caution
	Seizure	Caution
Tacrolimus	QTC prolongation	Caution
Tamsulosin	Heart failure	Caution
Levofloxacin	Myasthenia gravis	Warning
	QTC prolongation	Caution
Terazosin	Heart failure	Caution
Quetiapine	Dementia	Caution
	Seizure	Caution
	QTC prolongation	Caution
Trifluoperazine	Glaucoma	Caution
	Arrhythmia	Caution
	Dementia	Caution
	Parkinson's disease	Caution
	Seizure	Caution
Warfarin	Pericardial effusion	Warning

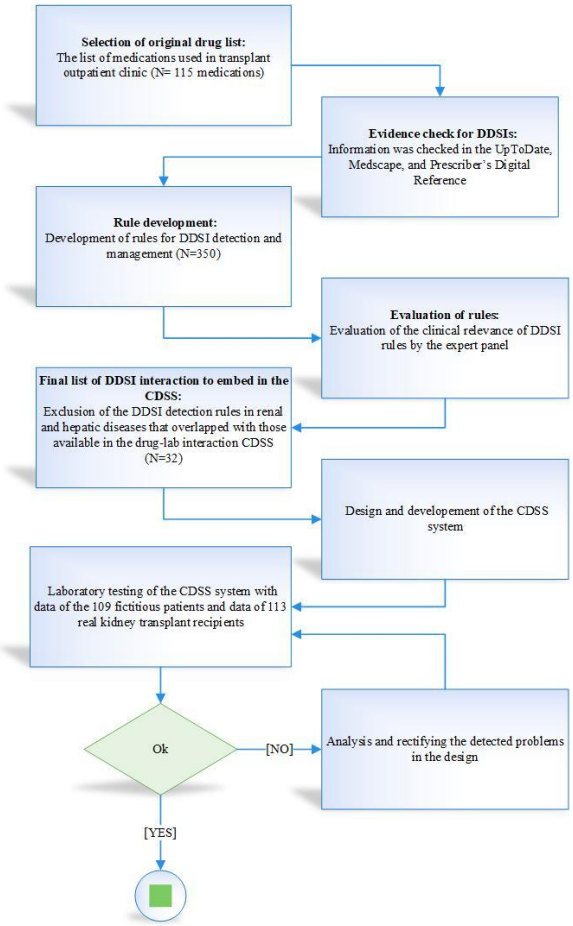


Fig 1: The process flow in this study

Knowledgebase for the DDSI-CDSS

For 51 selected medications, there were 100 high-priority DDSIs. The most common interacting co-existing diseases for these medications were cardiovascular diseases (e.g., heart failure, ischemic heart disease, and sinus node dysfunction), neurological/psychological disorders (e.g., seizure, myasthenia gravis, Parkinson disease, and mania), endocrine interactions (e.g., adrenal insufficiency and diabetes), gastrointestinal (GI) diseases/conditions (e.g., decreased GI motility and cholestatic jaundice), autoimmune diseases (e.g., systemic lupus erythematosus), and genetic diseases (e.g., Glucose-6-phosphate dehydrogenase deficiency) (Fig 2). The most common potential adverse outcomes for DDSIs included an increased risk of underlying disease deterioration, congestive heart failure, cardiac arrhythmias, increased or decreased blood pressure, bronchial obstruction, hemorrhagic or thrombotic consequences, and GI complications.

Among these 51 drugs, atenolol had the highest number of interactions with different underlying diseases. For example, it interacted with psoriasis, bradyarrhythmia or AV block, pheochromocytoma, chronic obstructive pulmonary disease (COPD), myasthenia gravis, and vasospastic angina. Among the diseases, myasthenia gravis had the highest number of interactions with different drugs, interacting with 12 medications: amitriptyline, atenolol, atorvastatin, carvedilol, ciprofloxacin, gabapentin, haloperidol, lorazepam, metoprolol, prednisolone/prednisone, propranolol, and levofloxacin.

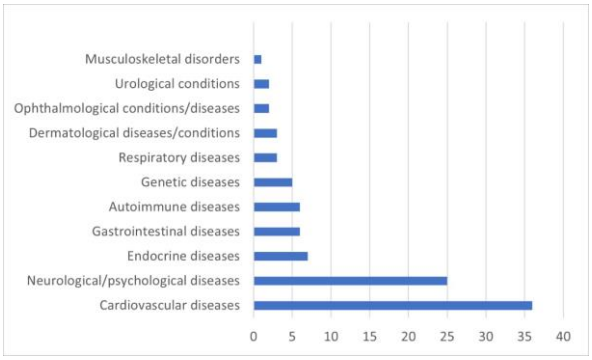


Fig 2: The most common co-existing diseases interacting with 51 medications in the CDSS knowledge base (the X axis represents the number of medications out of 51 interacting with specific co-existing disease categories)

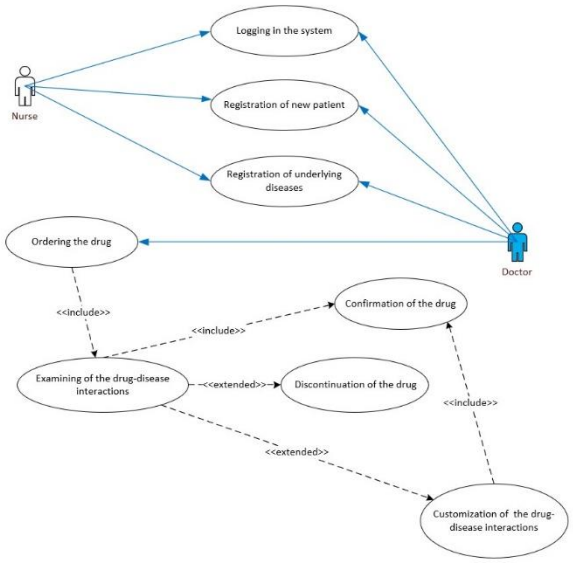


Fig 3: Use cases in the DDSI-CDSS

Fig 3 displays the use cases employed in this CDSS. A general algorithm for the decision workflow in this CDSS is presented in Fig 4. Sample diagrams for individual drugs are provided (Fig 5). The knowledge base includes the IF-THEN rules and the contents for the alerts.

Priority levels of alerts, associated display rules, and actions needed

After a closer examination of 100 DDISs and their severity levels, two types of alerts and alert display workflows/processes were considered for proper management in the system. Thirty-one out of the one hundred were major interactions with high priority

and rather severe consequences for patients. For these, the alert display was decided to be interruptive during the prescription workflow (delivered through a pop-up). The remaining 69 interactions, which had a moderate severity level with undesirable potential outcomes, were provided as non-interruptive DDSIs alerts to physicians but with visual cues. This allowed physicians to decide whether to check them immediately or later.

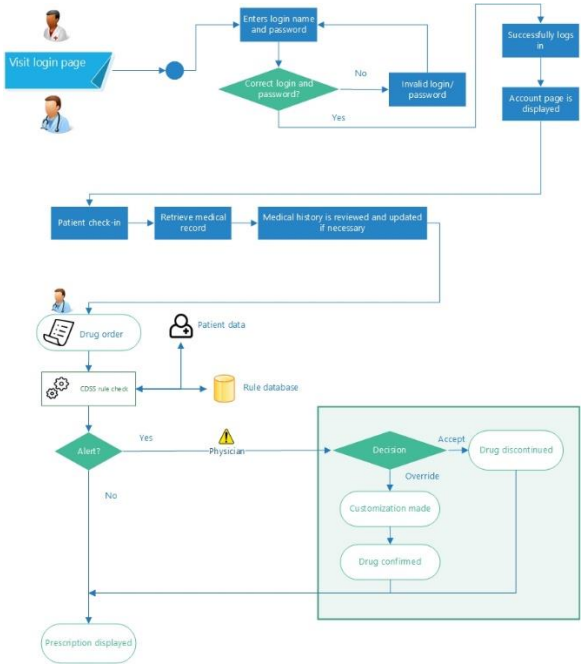
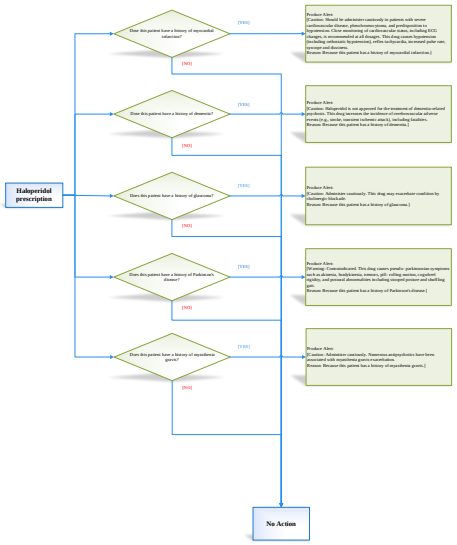
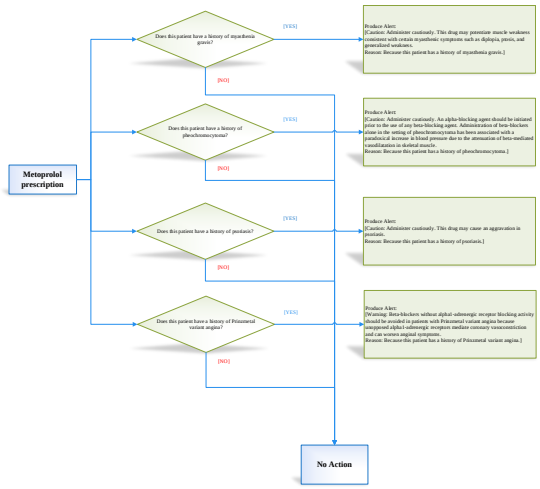


Fig 4: Decision workflow embedded in the DDSI-CDSS



a



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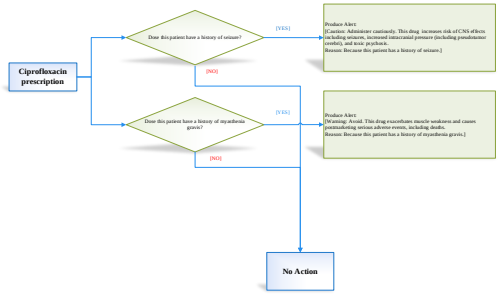

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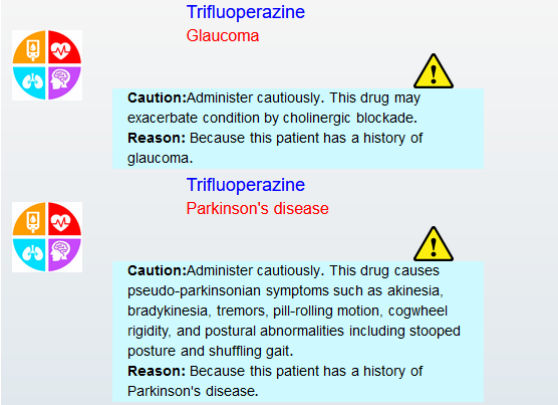
Fig 5: Sample diagrams for individual drugs

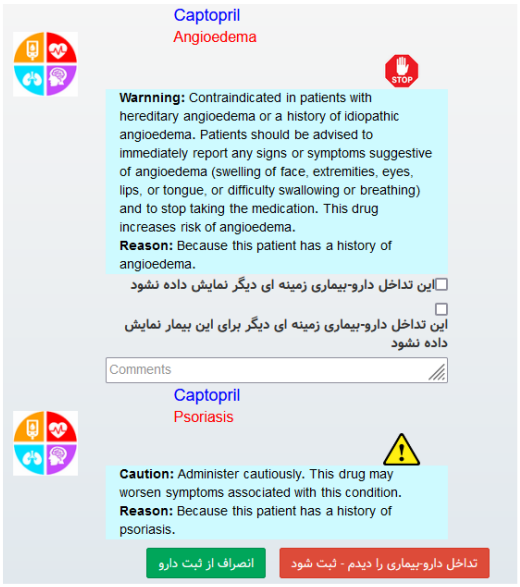
For easier visual comprehension of the alert's contents, they were displayed using color codes: a red stop hand sign for major interactions and a yellow cautious sign for moderate interactions. It is noteworthy that in either case, physicians were free to continue with their prescription plan or change the prescribed drug.

Multiple alerting contents for a single medication in the presence of multiple underlying conditions were displayed on a single alert. Three screenshots illustrating alert displays are provided in Fig 6. Alerts required physicians to either stop the ongoing prescriptions or override them.

a. A warning alert



b. A cautionary alert



c. Multiple alerts for one single medication (displayed in one window)

Fig 6: Illustrative screenshots of CDSS alerts in the DDSI-CDSS

Piloting of the system

After the initial development of the system, we iteratively tested the logic embedded in the system using data from 109 fictitious patients to detect DDSIs. This process identified several bugs, which we promptly addressed until no further technical problems were detected.

Subsequently, we conducted a pilot test of the system with data from 113 patients collected from our clinic. Among these patients, 54% were female, with a mean age of 46 years (ranging from 9 to 74) (Table 2). The most common medications included mycophenolate, corticosteroids, and cyclosporine (as immunosuppressive), along with diltiazem, cotrimoxazole, and calcium-D (as non-immunosuppressive). The prevalent underlying diseases and conditions were hypertension, GI disorders, and diabetes.

The system successfully detected 37 DDSIs, displaying nine warning and 28 cautionary alerts for the medications of these 113 patients (32.7%). Specifically, the system issued three warnings for diltiazem due to bradyarrhythmias and two warnings for each of the following medications based on underlying diseases: aspirin (asthma), Erythropoietin alfa (hypertension), and gemfibrozil (gall bladder disease). The potential consequences of these detected DDSIs included GI complications (17%), deterioration of existing diseases/conditions (6.1%), an increased risk of arrhythmias (2.6%), thrombosis (2.6%), and hypertension (1.7%). For instance, the prescription of mycophenolate in 20 patients triggered alerts cautioning against its use due to patients' GI tract disorders (Table 3).

Table 2: Characteristics of real patients whose data were used to validate the CDSS system

Characteristics		No. of patients (From 113)
Gender	Female	54
Age (years)	Mean	46
	Range	9 to 74
Immunosuppressive medications	Mycophenolate	95
	Prednisolone or Prednisone	82
	Cyclosporin	79
Non-immunosuppressive medications	Diltiazem	75
	Trimethoprim/sulfamethoxazole	73
	Calcium-vitamin D	57
	Omeprazole	52
	Ciprofloxacin	46
	Losartan	40
Underlying diseases	Hypertension (HTN)	42
	Gastrointestinal (GI) disease	28
	Diabetes	24
	Hepatic impairment	17
	Chronic obstructive pulmonary disease (COPD)	14
	Fatty liver	11
	Thrombotic disorder	11

Table 3: The alerts of the DDSI-CDSS for 113 patients in the pilot phase

The type of alerts	Drug name	Underlying disease	Number
Warning	Diltiazem	Bradyarrhythmia	3
	Aspirin	Asthma	2
	Gemfibrozil	Gallbladder disease (cholelithiasis)	2
	Erythropoietin alfa	Hypertension	2
Caution	Mycophenolate	Gastrointestinal diseases	20
	Erythropoietin alfa	Thrombotic disorders	3
	Carbamazepine	Arrhythmia	2
	Ciprofloxacin	Seizures	2
	Levofloxacin	QTC prolongation	1

DISCUSSION

Our study aimed to evaluate DDSIs in the outpatient setting within the kidney transplantation field. Based on the resulting evidence, we developed a tailor-

made CDSS to facilitate the management of these interactions in a highly fragile patient population. Almost one-third of the patients in our study had DDSIs in their prescriptions with potential serious outcomes, attributable to underlying diseases and conditions such as arrhythmias, hypertension, asthma, and seizures. These findings underscore the significance of safety measures in addressing DDSI risks within a vulnerable patient population characterized by polypharmacy and multiple co-existing diseases/conditions. The identification of numerous potential DDSI interactions, along with their context-sensitive priority levels and potential serious outcomes, emphasizes the critical need for effective solutions. The CDSS from our study serves as a valuable tool for detecting and managing these interactions, thereby enhancing patient safety efficiently.

While CDSSs have been recognized for addressing various facets of complex organ transplant care [26], there has been limited reporting on systems specifically designed to target different types of medication interactions [27]. In order to effectively manage DDSIs, both pharmacological knowledge about the drug effects on the disease and clinical knowledge about the specific conditions of each patient should be considered simultaneously [28]. In practice, due to the wide range of information about drug interactions, it is challenging for doctors and pharmacists to remember them all and flawlessly detect these interactions in patients' drug therapy. Most physicians are typically more familiar with drugs used in their specialty than drugs used in other specialties [29]. In one study, it was shown that physicians can usually only detect 44% of DDIs and 55% of DDSIs [30]. One effective approach to address drug safety issues is by strategically placing heightened value on interprofessional communication between clinicians from different specialties [28]. However, the lack of effective interprofessional communication and collaboration often limits the exchange of knowledge between these professionals and leads to potentially inappropriate medication and patient outcomes [31]. CDSSs, such as the one developed in this study, have the potential to support clinicians by aligning their clinical decisions based on targeted clinical knowledge, patient information, workflow context, and other health-related data [32, 33].

In CDSS designs, there are three layers: data management, processing or inference engines, and the user interface, working together to provide knowledge-based recommendations. The data management layer combines medical information and knowledge bases, patient information, and artificial intelligence algorithms. In the processing layer, rules or algorithms are applied to the knowledge base data and patient information. Finally, the results are displayed through the user interface layer, which can include mobile or web applications, EHR system dashboards, or mobile alerts and notifications [34]. The module developed in this study falls under the category of knowledge-based systems, where existing information and knowledge are stored in the knowledge base using IF-THEN rules. These rules aim to detect and prevent some of the serious consequences of DDSIs, such as hypertension, thrombosis, and arrhythmias. Consistent with our results, a study showed warnings for serious potential clinical consequences of 375 DDSIs, especially an increased risk of exacerbations of diseases/conditions, including bleeding, cardiac arrhythmia, hypotension, myocardial infarction, hyperkalemia, lactic acidosis, thrombosis, bowel dysfunction, hemolysis, and other adverse drug reactions [35]. Moreover, our study took into account context-sensitive considerations by considering the opinions and working methods of nephrologists and pharmacotherapists in their everyday practice in the design of the CDSS. Prior research has emphasized the importance of addressing such issues to enhance the satisfaction of the primary users of Health Information Technology (HIT) systems and their better integration into clinical workflow [3, 20].

Kidney transplant patients are susceptible to co-morbidities, complications related to immune system suppression, and chronic transplant rejection. Therefore, efforts to optimize their drug therapy are crucial. Previous studies have reported the design of CDSSs for DDIs and DLIs and have highlighted some challenges in automatically identifying interactions while also considering the clinical context and the complexities of designing CDSSs for such interaction [3, 19, 20, 36]. In addition to general challenges, one of the main hurdles in designing and evaluating DDSI-CDSSs is the lack of standards for the definitions of diseases and conditions [9]. For instance, in examining DDSIs in prior studies, no nomenclature and classification systems exist for diseases or patient conditions, such as benign prostatic hyperplasia, heart block, glaucoma, syncope, postural hypotension, and constipation [37]. To address this deficiency and because some conditions and diseases overlap in clinical manifestations but have different causes (such as delirium and psychosis), it is necessary to define patient conditions and diseases accurately according to international classification systems [9, 38]. Another challenge is the insufficient information and evidence about DDSIs [9, 37]. For example, in the SmPC, the use of sertraline in diabetic patients is cautioned because some studies describe effects of sertraline on glucose levels [39]. On the contrary, other studies do not consider these effects to be significant [40, 41]. Studies have shown that one of the best approaches to identify and extract the most important DDSIs is to consider the opinions of physicians and pharmacists and to review the main medical sources [9, 18, 37]. In line with

recommendations from prior studies, we adopted an approach to grasp the intricacies of clinical work [3, 20]. Our aim was to comprehend the types, severity, and frequency of interactions by incorporating clinicians' perspectives, thereby enhancing the effectiveness of alerts. Furthermore, we integrated a level of flexibility into the system, enabling clinicians to tailor the appearance of alerts according to their preferences. This customization feature ensures that alerts are aligned with clinicians' individual needs and ultimately serves the best interests of patients.

Returning to the individual patient level, the next challenge is to examine the priority and relevance of DDSIs according to the individual patient characteristics and conditions [42]. Patients can play a role in the identification and management of DDSIs by monitoring their symptoms after any changes in the medication regimen and also by requesting closer monitoring from their physicians (e.g., through further counseling or discussing the changes) [43]. By using tools such as electronic personal health records [44], patients can contribute by providing a detailed medical history of comorbidities and medications (including over-the-counter (OTC) drugs or herbal supplements) to their physicians. OTC drugs can potentially lead to DDSIs (e.g., some NSAIDs in patients with heart failure); therefore, an appropriate and comprehensive medical history is essential to check the possibility of DDSIs and their proper management [18, 37, 45].

Despite the importance of all the above-mentioned aspects, creating a balance between the comprehensiveness of warnings and their applicability in clinical practice is also necessary. In a study, it has been shown that most drug therapy warnings are concentrated in a minority of drug groups and patients [6]. For example, the most common diseases and conditions involved in DDSIs included benign prostatic hyperplasia, chronic kidney disease, heart failure, dementia, diabetes, heart block, glaucoma, Parkinson's, gastric ulcer, postural hypotension, seizures, constipation, and syncope [37]. It has been noted that cardiovascular diseases seem to have the largest share in the identified DDSIs [46]. Meanwhile, the most common drug groups that lead to medication errors and subsequent hospital admission included NSAIDs, beta-blockers, angiotensin-converting enzyme inhibitors, and opioids [6]. Therefore, to create such a balance and prevent alert fatigue, it is necessary to consider the consequences of DDSIs and prioritize special groups of diseases/conditions and drug groups covered in these CDSSs [6]. Among the proposed strategies to reduce alert fatigue are the consideration of patient conditions (e.g., age, prescribed drugs, and history of renal failure), monitoring of their laboratory test results [6, 47]. and categorization of alerts by type and clinical significance [48]. It is important that the benefits of warnings in terms of contributing to drug safety should be carefully weighed against the risk of alert fatigue, with the ultimate aim of avoiding alerts for situations with low risks or those with no need for action [49].

Following the successful design and application of these systems in practice, another important challenge is the rapid changes in medical science, clinical guidelines, and the introduction of new drugs into the market, which, in turn, seriously affects the maintenance and updating of a significant number of DDSIs [50]. Therefore, maintaining and updating the content of CDSSs' databases should be considered an important part of their life cycle. For this reason, periodic reviews by pharmacists and multidisciplinary expert panel meetings during the life of such systems are strongly recommended [51].

CONCLUSION

DDSIs are a common and serious problem in medication safety in kidney transplant recipients, mainly stemming from the high prevalence of co-morbidities and polypharmacy in this vulnerable patient population. The growth of these two conditions makes drug therapy optimization a serious challenge, sometimes inadvertently causing more harm than good. CDSSs can assist healthcare providers in various patient care decisions and tasks by helping them manage the complexities of clinical work through the automation of the detection process.

By incorporating reminder mechanisms and delivering high-priority warnings based on the clinical context, CDSSs can enhance prescribers' awareness more effectively, leading to a positive impact on their performance through the reduction of medication errors and associated side effects. In the present study, the processes of developing a CDSS for the management of DDSIs were reported in the kidney transplantation field. This CDSS supplements prior existing interaction CDSSs designed for kidney transplant medications. We hope that the design and application of such systems in the health care, especially in developing settings, will contribute to maintaining the drug safety, especially in kidney transplant patients, more effectively.

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AUTHOR'S CONTRIBUTION

All authors contributed to the literature review, design, data collection and analysis, drafting the

manuscript, read and approved the final manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding the publication of this study.

FINANCIAL DISCLOSURE

No financial interests related to the material of this manuscript have been declared.

ETHICS APPROVAL

This study was approved by the researcher's institute review board at Urmia University of Medical Sciences. The approval code number was IR.UMSU.REC.1401.088.

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