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RESEARCH ARTICLE

Impact of pharmacists' interventions on physicians' decision of a knowledge-based renal dosage adjustment system

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Abstract

Background Early interventions with clinical decision support system (CDSS) guidance have ensured appropriate drug dosing for patients with renal impairment. However, the low rates of physician compliance with CDSS alerts have been reported. *Objective* We investigated whether designated pharmacist interventions were associated with physician' acceptance of the knowledge-based renal dosage adjustment system (K-RDS) for patients with reduced renal function. *Setting* A retrospective, single-center study was conducted using a healthcare information system at a tertiary teaching hospital. *Methods* This study compared physicians' acceptance of the K-RDS with and without designated pharmacists. The severity of prescription errors and the impact of service provided by the pharmacist were evaluated using the validated method developed by Overhage and Lukes. From April to June 2017, we enrolled patients who were ≥ 20 years of age and admitted with an estimated glomerular filtration rate under 50 ml/min on medications that required dose adjustments. *Main outcomes measure* The number of dosing alerts of the K-RDS and physicians' acceptance rates were compared between a control group guided by the central pharmacy only and a group with assigned designated pharmacists. The factors associated with the physicians' acceptance rate were also analyzed using a multivariate logistic regression method. The impact of service provided by the pharmacist were considered as 'highly significant' (categories: 1–2). Severity of prescription errors were defined as 'serious' if they corresponded to categories 1–2 of the Overhage and Lukes scale for severity, and interventions were relevant if they corresponded to categories 1–3 in the impact of service provided by the pharmacist scale. *Results* Among 1363 prescription interventions, 491 (36.0%) were performed by designated pharmacists. The K-RDS alert acceptance rate by the physicians was 54.4% in the designated pharmacist group and 47.0% in the control group ($p = 0.0233$). The statistically significant association was found in the designated pharmacists group in 'highly significant' service provided by the pharmacist ($p < 0.001$, OR 1.772; 95% CI 1.362–2.305) and 'serious' severity of prescription errors ($p = 0.012$, OR 1.657; 95% CI 1.116–2.460). The presence of designated pharmacists (OR 1.353, $p = 0.0272$), patient's gender (OR 0.758, $p = 0.0016$), department specialty (OR 0.659, $p < 0.0001$), eGFR (OR 1.538 if < 10 ml/min; OR 1.519 if 10–40 ml/min, $p < 0.0001$), and medications (OR 6.058–43.992 depending on the medication category, $p < 0.0001$) were significant factors affecting physicians' acceptance. *Conclusion* Pharmacists' interventions effectively improved physicians' acceptance of the K-RDS alerts.

Keywords Dose adjustment · Korea · Pharmacist intervention · Physicians' acceptance · Renal function

Impacts on practice

- Pharmacist interventions have a positive effect on improving physicians' acceptance of a knowledge-based renal dosage adjustment system (K-RDS).
- Physicians acceptance of pharmacists intervention suggestions vary by medication category, department type, and the patient's renal function.

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- Active pharmacist interventions in conjunction with the K-RDS can effectively promote appropriate drug use and prevent drug-related problems in patients with reduced renal function.

Introduction

A real-time clinical decision support system (CDSS) integrated into physicians' workflow has been shown to profoundly affect the cost, quality, and safety of healthcare delivery [1]. When embedded with computerized physician order entry (CPOE), CDSS guidance has also been shown to reduce the rate of adverse drug events (ADEs) [2].

Hospitalized patients with renal impairment are anticipated to benefit from CDSS due to their particularly high susceptibility to dosing errors related to parent compounds and metabolites being cleared by the kidneys [2, 3]. A previous study on dosing guideline compliance suggested that, for inpatients with renal impairment, about 15% to 74% of the drugs were administered with the inappropriate dosage or drug selection and that prescribed drugs were commonly contraindicated for patients with renal insufficiency [4]. Several studies have revealed the predictors of inappropriate administration of renal drugs to be patient age, number of prescribed drugs, and comorbidities, including hypertension, diabetes, hypercholesterolemia, and obesity [5].

To overcome the potential undesired safety issues in renally impaired patients, a computerized renal dosing adjustment system (RDS) has been widely implemented to guide prescribing practices and to prevent drug-related problems. Early CDSS-guided interventions that ensure appropriate drug dosing in patients with renal impairment have shown encouraging results. However, a recent study reported surprisingly low acceptance rates for the RDS alerts, often reflected by physicians' overrides of the alerts because of poor specificity or too many alerts.

CDSS adoption resolves the problems associated with incorrect dosing in renal impairment that arise when physicians prescribe large volumes of medication orders [6]. However, the rate-limiting step of the process is when physicians must decide whether or not to accept system alerts. Paradoxically, investigators observed multiple factors associated with the acceptance of alerts. Alert acceptance has been shown to be influenced by independent factors, such as the frequency of the alert, quality of display, alert level, admission status, and drugs with dose-dependent toxicity, besides knowledge levels or human factors, such as display characteristics, textual information, and prioritization [6]. Another study found the following potential determinants influenced the acceptance of dosing guidelines: reporting eGFR in addition to serum creatinine, renal function, changes in renal function during hospital admission, and admitting medical specialty, such as surgical versus non-surgical [7].

Pharmacist involvement effected an improvement of compliance by physicians to the CDSS for patients with reduced renal functions. Pharmacist-based CDSSs became a potent intervention by adding a cognitive "human factor" operating by clinical pharmacists [8]. However, there are no studies on the relationship between physicians' acceptance of knowledge-based renal dosage adjustment system (K-RDS) alerts and pharmacist involvement in healthcare institutions in Korea.

Aim of the study

We aimed to investigate whether designated pharmacist interventions improved physicians' acceptance of the K-RDS usage for inpatients with reduced renal function. We also investigated the predictive factors influencing prescribers' acceptance of the alerts.

Ethics approval

This study was approved by the Seoul National University Bundang Hospital Institutional Review Board (IRB No. B-1711-432-112). All procedures were performed in accordance with the ethical standards of the national research committee and with the Declaration of Helsinki and its later amendments or comparable ethical standards. The requirement of formal consent was waived owing to the study's retrospective nature.

Methods

Knowledge-based renal dosage system

Two hundred twenty-five medications from the hospital formulary were managed by the K-RDS. The medications were selected via a literature review and consultations with clinical pharmacists, nephrologists, and infectious disease specialists. The final protocol was embedded into the hospital's electronic medical record system in August 2006. Creatinine clearance in the protocol was calculated according to the Cockcroft-Gault equation, and renal insufficiency was classified into 3 categories: mild (eGFR 50–80 ml/min), moderate (eGFR 10–50 ml/min) and advanced (eGFR < 10 ml/min) [9]. The K-RDS informed physicians of decreases of a patient's renal function and recommended adjusting drug doses according to renal function. However, physicians could choose to adjust, discontinue, or override the drug doses recommended by the K-RDS system.

Study design

This was a retrospective study to assess physicians' acceptance of dosing changes recommended by K-RDS alerts. We compared a designated pharmacist group to a control group guided only by pharmacists working in the inpatient central pharmacy. In the study hospital, the role of a designated pharmacist was to review prescriptions doses, formulations, frequencies, routes, adverse drug reactions, alternative medications choices, therapeutic drug monitoring, nutritional services, and documentation of the interventions in the pharmacist records. They participated in interdisciplinary collaborative team rounds in the geriatric ward, surgical intensive care unit, neurologic intensive care unit, and emergency intensive care unit. Designated pharmacists were eligible if they had at least 3 years of clinical experience and a minimum of 1 year of residency. Although pharmacy interventions were also performed in the control group, the major difference between the designated pharmacist group and the control group was that the designated pharmacist was responsible for the specific units and participated in the interdisciplinary collaborative team resulting in more opportunities for communication between physicians and pharmacists. Through this, the designated pharmacist was able to perform face-to-face interventions at the bedside with more clinical time, while physicians in the control group performed interventions guided by phone conversations with pharmacists in the pharmacy. The severity of prescription errors and the clinical relevance of the designated pharmacist interventions were evaluated using the validated method proposed by Overhage and Lukes [24]. The clinical relevance of pharmacist intervention was determined based on the likely consequences in patient care: (1) extremely significant, (2) highly significant, (3) significant, (4) little significant, (5) insignificant and (6) injurious intervention, and the severity of prescription errors was determined five severity categories: (1) potentially lethal, (2) serious, (3) significant, (4) least and (5) no error ("Appendix"). The assessment of the severity of the errors and the clinical relevance were independently performed by two independent reviewers (KS and MS), and disagreements were resolved by consensus or by a third reviewer. The impact of service provided by the pharmacist were considered as 'highly significant' (categories: 1–2). Severity of prescription errors were defined as 'serious' if they corresponded to categories 1–2 of the Overhage and Lukes scale for severity, and interventions were relevant if they corresponded to categories 1–3 in the impact of service provided by the pharmacist scale [24].

Study population

Inclusion criteria were hospitalized patients who were 20 years of age or older with an eGFR under 50 ml/min, based on the latest measured serum creatinine level, and who were prescribed medications that required renal dose adjustments. We excluded patients with missing or incorrect data in their hospital records as well as those who received discharge orders within the study period. For study purposes, we divided eGFR differently from the K-RDS protocol of the hospital system. The study renal insufficiency categories for the study were, mild (eGFR 40≤–<50 ml/min), moderate (eGFR 10≤–<40 ml/min), and advanced (eGFR < 10 ml/min). The departments were divided into three groups, medical, surgical, and intensive care unit, and divided medication category using the Anatomical Therapeutic Chemical (ATC) classification system.

Data collection

Alert data were collected electronically from April to June 2017. Patient age, patient gender, weight, height, serum creatinine, medications, and reasons for alerts being overridden were recorded. We only included new prescription orders.

Definitions

We defined an inappropriate dose as any dose that was greater than the recommended dose for a given indication. Alert acceptance by a physician was defined as when the orders were discontinued or modified according to the recommendations of the alerts. Alert override was defined as when the orders were continued despite contrary recommendations by the alerts. The acceptance rate was the ratio of the number of prescriptions alerts modified or discontinued divided by the total number of prescription alerts.

Statistical analysis

We used descriptive statistics to analyze the alerts, with the Chi-square test used to compare categorical variables and *t* tests used to compare continuous variables if the distribution was normal. Multivariate logistic regression analysis identified independent factors associated with an alert's acceptance. Any variable whose univariable test had a *p* value < 0.25 was a candidate for the multivariable model along with all variables of known clinical importance. Following the fit of the multivariable model, the importance of each variable included in the model was verified. Variables that did not contribute to the model were eliminated, and a new model was fitted (backward elimination). This process of deleting, refitting, and verifying continued until it appeared that all of the important variables were included in the model, and those excluded were clinically or statistically unimportant. Statistical analyses were done with SAS version 9.4.

Results

Among a total of 668,414 prescriptions, 9168 prescription alerts (1.4%) were generated. After considering the exclusion criteria, 2341 prescription alerts were evaluated. The demographic characteristics of the study sample are shown in Table 1. The acceptance rate was 54.4% in the designated pharmacist group and 47.0% in the control group ($p=0.023$). Ranitidine and famotidine were the medications that generated the most alerts. The medication categories that most frequently generated alerts were H2 antagonists (57.5% in the designated pharmacist group and 44.1% in the control group) and antimicrobials (27.8% in the designated pharmacist group and 35.0% in the control group). The between-group differences in alert frequency by department type ($p<0.001$) and medication category ($p=0.004$) were also statistically significant.

Pharmacist interventions

During the study period, 1363 interventions were performed in 715 patients. Medication errors were considered serious in 7.9% of cases, and 86.9% of pharmacist interventions were considered relevant. The impact of service provided by the pharmacist and severity of prescription errors are shown in Table 2. The statistically significant association was found in the designated pharmacists group in 'highly significant' service provided by the pharmacist ($p<0.001$, OR 1.772; 95% CI 1.362–2.305) and 'serious' severity of prescription errors

Table 1 Population demographics

Characteristics	Designated pharmacist group (259 alerts)	Control group (2082 alerts)	*p* value
Age, mean ± SD (years)	73.4 ± 11.5	73.4 ± 11.0	0.969
Age group, n (%)			0.099
20–64 years	50 (19.3%)	364 (17.5%)	
65–74 years	57 (22.0%)	590 (28.3%)	
≥ 75 years	152 (58.7%)	1128 (54.2%)	
Gender, n (%)			0.542
Male	120 (46.3%)	923 (44.3%)	
Female	139 (53.7%)	1159 (55.7%)	
Department type, n (%)			< 0.0001
Medical	91 (35.1%)	815 (39.1%)	
Surgical	140 (54.1%)	1123 (53.9%)	
Intensive care unit	28 (10.8%)	144 (6.9%)	
Range of eGFR, n (%)			0.563
< 10 ml/min	113 (43.6%)	951 (45.7%)	
10≤–< 40 ml/min	111 (42.9%)	822 (39.5%)	
40≤–< 50 ml/min	35 (13.5%)	309 (14.8%)	
Medication category, n (%)			0.004*
Analgesics	4 (1.5%)	71 (3.4%)	
Anticonvulsant	0 (0.0%)	21 (1.0%)	
Antihistamine	1 (0.4%)	9 (0.4%)	
Antihypertensive	1 (0.4%)	37 (1.8%)	
Antimicrobial[a]	72 (27.8%)	728 (35.0%)	
Arthritis and gout	1 (0.4%)	22 (1.1%)	
Cardiovascular	7 (2.7%)	56 (2.7%)	
H2 antagonist	149 (57.5%)	918 (44.1%)	
Hypoglycemic	24 (9.3%)	183 (8.8%)	
Neuromuscular	0 (0.0%)	31 (1.5%)	
Pentoxiphylline	0 (0.0%)	6 (0.3%)	

t test, Chi-square test

SD standard deviation

**p* value of the all medication category

[a]The antimicrobials that require therapeutic drug monitoring have been excluded from the K-RDS such as aminoglycosides and vancomycin. Cephalosporins was the most common antibiotic, followed by penicillins and metronidazole

Table 2 The impact of service provided by the pharmacist and severity of prescription error

	Designated pharmacist group (491 cases) N (%)	Control group (872 cases) N (%)	p value OR (95% CI)
Gender			0.033*
Male	275 (56.0)	540 (61.9)	1.278 (1.021–1.599)
Category of impact of service provided by the pharmacist			
1. Extremely significant	0 (0.0)	0 (0.0)	
2. Highly significant	136 (27.7)	155 (17.8)	
3. Significant	291 (59.3)	602 (69.0)	
4. Little significant	49 (10.0)	58 (6.7)	
5. Insignificant	15 (3.1)	57 (6.5)	
Highly significant service			
Highly significant	136 (27.7%)	155 (17.8%)	< 0.001** 1.772 (1.362–2.305)
Category of severity of prescription error			
1. Potentially lethal	0 (0.0)	0 (0.0)	
2. Serious	51 (10.4)	57 (6.5)	
3. Significant	286 (58.2)	512 (58.7)	
4. Least	111 (22.6)	212 (24.3)	
5. No error	43 (8.8)	91 (10.4)	
Serious prescription error			
Serious	51 (10.4%)	57 (6.5%)	0.012*** 1.657 (1.116–2.460)

CI confidence interval

*Chi-square test

**Chi-square test between 'highly significant' versus 'non-highly significant' (the impact of service provided by the pharmacist were considered as 'highly significant' categories 1–2 and non-highly significant if they corresponded to categories 3–5)

***Chi-square test between 'serious group' versus 'non-serious group' (severity of prescription errors were defined as 'serious' if they corresponded to categories 1–2 and non-serious if they corresponded to categories 3–5)

($p=0.012$, OR 1.657; 95% CI 1.116–2.460) (categories 1–2 of the Overhage and Lukes scale for severity) (Table 2). The designated pharmacists performed 491 (36.0%) interventions among 1363 interventions. Most of the pharmacists' interventions consisted of providing drug information (19.3% in the designated pharmacist group and 14.9% in the control group) followed by renal dose adjustment (12.6% in the designated pharmacist group and 13.5% in the control group), therapeutic drug monitoring (8.8% in the designated pharmacist group and 4.0% in the control group), and dosing interval (8.6% in the designated pharmacist group and 10.8% in the control group). (Table 3).

Factors influencing physicians' acceptance

Guidance from a designated pharmacist, patient gender, medication category, eGFR, and department specialty were significant factors affecting physicians' acceptance. Patient age did not significantly affect the physicians' acceptance of the K-RDS alerts (Table 4).

Discussion

Computerized CDSS guidance has been found to be beneficial in improving the quality of clinicians' prescribing patterns, reducing medication errors, and ultimately preventing ADEs. Despite these known positive impacts, the CDSS implementation remains difficult. CDSS alerts do not take into account the collective aspects of healthcare work situations, and the alerts often disrupt the cognitive processes inherent to decision making due to poor timing, wrong display mode, and incorrect or weak content of the information delivered [10].

In this study, the acceptance rate was 54.4% in the designated pharmacist group compared with 47.0% in the control group. Our results seem slightly lower than what was reported in a previous study on a CDSS for medication dosing in renal insufficiency in which physicians in the intervention group followed the decision support recommendations in 57% of prescriptions [11]. This result may mean that the threshold of the K-RDS is lower than other CDSS. Initially, one of the purposes of the K-RDS was to educate residents and to provide appropriate pharmacotherapy to patients with reduced renal function by informing physicians of changes in renal function. The acceptance rate of a CDSS may vary depending on the alert types and the intent of the CDSS alert system. For example, in one inpatient study, investigators found an 88% override rate for drug interaction alerts and a 69% override rate for drug allergy alerts [12]. Similarly, it was found that ambulatory physicians overrode 91% of the drug allergy alerts and 89% of the high-severity drug–drug interaction alerts [13]. Furthermore, few studies have evaluated the appropriateness of alert overrides, and little prior data exist about the appropriateness of overrides by alert type.

The Agency for Healthcare Research and Quality (AHRQ) suggested the following methods for solving alert fatigue: increase the alert specificity by reducing or eliminating clinically inconsequential alerts and tier alerts according to severity (https://psnet.ahrq.gov/). With regard to improving the K-RDS acceptance rate, a detailed analysis of the physicians' override reasons needs to be done, and then the

Table 3 Pharmacist interventions during the study periods

Types of interventions	Designated Pharmacist group (491 cases) N (%)	Control group (872 cases) N (%)
Drug information*	95 (19.3)	130 (14.9)
Renal dose adjustment**	62 (12.6)	118 (13.5)
Therapeutic drug monitoring	43 (8.8)	35 (4.0)
Dosing interval	42 (8.6)	94 (10.8)
Dosage formulation	39 (7.9)	63 (7.2)
Off-label	39 (7.9)	25 (2.9)
Subtherapeutic dose	30 (6.1)	80 (9.2)
Therapeutic parenteral nutrition	26 (5.3)	92 (10.6)
Drug interaction	25 (5.1)	38 (4.4)
Administration route	19 (3.9)	26 (3.0)
Omission	19 (3.9)	17 (1.9)
Administration schedule	13 (2.6)	36 (4.1)
Adverse drug reaction	12 (2.4)	25 (2.9)
Contraindications	12 (2.4)	9 (1.0)
IV Compatibility	6 (1.2)	8 (0.9)
Insurance coverage	3 (0.6)	7 (0.8)
Therapeutic duplication	2 (0.4)	24 (2.8)
Lack of lab data	2 (0.4)	14 (1.6)
Chemotherapy regimen verification	1 (0.2)	11 (1.3)
Dosing unit	1 (0.2)	3 (0.3)
Potentially inappropriate medications for age	0 (0.0)	14 (1.6)
Patient counselling	0 (0.0)	3 (0.3)

*Drug information is the service providing any medication-related information as followings; providing information on therapeutic alternatives due to drug shortage, new drugs approval, Formulary addition or changes by the Pharmacy and Therapeutics Committee, safety alerts, patient's self-medication and administration of loading dose such as clopidogrel or antimicrobials

**Renal dose adjustment is the service to intervene a reduction of dosage considering the patient's degree of renal function such as to recommend dose reduction of ciprofloxacin when patient's renal function decreased

Table 4 Factors influencing physicians' acceptances

Characteristics		OR (95% CI)	*p* value
Patient's age group	20–64 years versus ≥ 75 years	0.949 (0.748–1.204)	0.555
	65–74 years versus ≥ 75 years	0.931 (0.763–1.136)	
Designated pharmacist	versus control	1.353 (1.035–1.768)	0.027
Female	versus male	0.758 (0.638–0.900)	0.002
Medication category	Analgesics versus neuromuscular	6.058 (1.648–22.270)	< 0.0001
	Anticonvulsant versus neuromuscular	43.992 (9.001–215.008)	
	Antihistamine versus neuromuscular	9.260 (1.602–53.543)	
	Antihypertensive versus neuromuscular	7.212 (1.773–29.345)	
	Antimicrobial versus neuromuscular	18.543 (5.444–63.155)	
	Cardiovascular versus neuromuscular	9.862 (2.648–36.727)	
	H2 antagonist versus neuromuscular	9.549 (2.801–32.555)	
	Hypoglycemic versus neuromuscular	8.439 (2.392–29.774)	
	Miscellaneous versus neuromuscular	26.524 (3.266–215.418)	
eGFR	< 10 ml/min versus 40≤–< 50 ml/min	1.538 (1.176–2.013)	< 0.0001
	10≤–<40 ml/min versus 40≤–< 50 ml/min	1.519 (1.262–1.829)	
Department	Medical versus intensive care unit	0.659 (0.469–0.926)	< 0.0001

CI confidence interval

threshold can be adjusted according to the analysis result. Alternatively, a future study could evaluate the appropriateness of alert overrides. This may help identify a number of ways that alerts can be improved and it can also help characterize the variation in the appropriateness of alert overrides.

This study has significant implications for suggesting factors that affect renal dosage acceptance. In particular, we found that interventions by pharmacists positively influenced physicians' acceptance, and patient gender, medication category, department type, and patient renal function were also influencing factors. In terms of medication categories, the most frequently generated alert was from H2 antagonists such as ranitidine and famotidine followed by antimicrobials and hypoglycemic agents. With the K-RDS, the antimicrobial drugs are classified as antimicrobial agents only in the decision making process, and the antimicrobials that require therapeutic drug monitoring services, such as aminoglycosides and vancomycin, have been excluded from the K-RDS. Thus, cephalosporins were the most common antibiotics, followed by penicillins and metronidazole. In the antimicrobial category, the most frequently generated alert medication was cefazolin, followed by piperacillin/tazobactam. Most cefazolin prescriptions were for surgical prophylaxis. These findings were similar to previous studies on prescriptions for patients with reduced renal function, which found that the most frequently inappropriately used drugs were metformin and glyburide along with ranitidine, allopurinol, ramipril, and perindopril [4]. One study performed regression model analysis to assess the predictors of inappropriate drug administration for patients with reduced renal function. The most frequently considered predictors were age and the number of prescribed drugs [4]. Another study reported that user acceptance was positively correlated with alert frequency (OR 1.30, 95% CI 1.23 to 1.38), quality of display (OR 4.75, 95% CI 3.87 to 5.84), and alert level (OR 1.74, 95% CI 1.63 to 1.86). Moreover, alert acceptance was higher for hospitalized patients (OR 2.63, 95% CI 2.32 to 2.97) and drugs with dose-dependent toxicity (OR 1.13, 95% CI 1.07 to 1.21) [6]. Another study reported that physicians were more likely to accept alerts for elderly patients (> 65 years old), and 38% were more likely to accept alerts for patients with more than five current medications or five chronic clinical conditions [1].

Similar to our study, which showed a positive effect of pharmacist interventions on alert acceptance rates among prescribing physicians, pharmacy-managed dosing services and computerized dosing programs have been proven to be successful in assisting practitioners in monitoring and adjusting drug therapy in patients with CKD in a cost-effective way that prevents drug-related problems [14–19]. In an observational prospective follow-up study, a clinical pharmacist identified drug-related problems, such as indication, dosage, monitoring, drug–drug interactions, and therapeutic duplications in a setting that routinely used CPOE and a CDSS. Given the type of drug-related problems identified by clinical pharmacists when compared to those identified by physicians solely guided by a CDSS, the role of clinical pharmacists is to provide additional value in settings using an advanced CDSS [14, 20].

The pharmacists' interventions were considered highly relevant (86.9% of cases), and the statistically significant association was found in the designated pharmacists group in 'highly significant' service provided by the pharmacist ($p < 0.001$, OR 1.772; 95% CI 1.362–2.305) and 'serious' severity of prescription errors ($p = 0.012$, OR 1.657; 95% CI 1.116–2.460) (categories 1–2 of the Overhage and Lukes scale for severity.) [25]. The most frequent pharmacist intervention was providing drug information, followed by overdose and therapeutic drug monitoring, and dosing intervals. Providing drug information includes the provision of any medication-related information, such as providing information on therapeutic alternatives due to drug shortages, new drug approvals, formulary additions or changes by the Pharmacy and Therapeutics Committee, safety alerts, patient self-medication, administration of loading doses for drugs such as clopidogrel or antimicrobials. Renal dose adjustment intervention refers to recommendations by a pharmacist to reduce a drug dosage with consideration of the patient's degree of renal impairment, such as dose reduction of ciprofloxacin when patient's renal function decreased. The intervention performed a medication profile review to address potential drug-related problems. In the designated pharmacist group, the most frequent intervention was providing drug information, which accounted for 19.3% of all interventions. This included responding promptly to a doctor or nurse's question and giving recommendations to physicians regarding medication changes during multidisciplinary medical rounds.

Additionally, in the designated pharmacist group, the number and rate of interventions for therapeutic drug monitoring and off-label were higher than those in the control group. This seems to be because the designated pharmacist reviews the medical records and checks the nutritional status of the patients and monitors for adverse events before participating in multidisciplinary rounds. With good communication between the designated pharmacist and physicians, the benefits of the K-RDS could be improved.

In one study, pharmacists performed or conducted clinical interventions (for example, pharmacokinetic consultations, dose adjustments based on patient-specific evaluations of clearance and renal or hepatic function, general medication reconciliations, therapeutic interchanges, drug order clarifications, and chemotherapy order reviews) through the use of a CDSS. As a result, the pharmacy intervention increased with an average of a 105% increase in the number of interventions per month. The annual estimated cost savings increased to 96% per year [21].

Improving medication safety is a traditional area of the pharmacy field. Finding drug-related safety problems and resolving unwanted consequences should be effectively achieved [22]. Thus, the developments of pharmacy-based CDSSs that considers the human factors of professionals and the technical factors of the information technology (IT)-based K-RDS should enhance the benefits to patient care. For example, pharmacists not only modify and adjust the CDSS alert threshold and its information, but they also can communicate with physicians and other end users to ultimately contribute to safer prescriptions by providing proper drug information and performing medication reconciliation.

The study hospital opened as a fully digitized hospital in May 2003, free of any paper-based medical records. It was accredited as a healthcare information and management systems society (HIMSS) analytics electronic medical record (EMR) adoption model stage 7 hospital in October 2010. The hospital aims to maximize this health IT and its benefits to provide patient care in a more comprehensive manner [23]. Furthermore, it is expected that pharmacists will monitor the status of real-time alerts of the K-RDS and update the dosing guidelines of the K-RDS when the medication guidelines or hospital policies change. In this way, pharmacists can improve the effectiveness of the K-RDS by monitoring its operation status in real time. The role of hospital pharmacists when the CDSS is used in all hospitals is to reconfigure the knowledge base of the CDSS and to adjust the CDSS's alert thresholds to prevent inappropriate alerts and to perform CDSS-based interventions to improve physicians' acceptance.

This study had some limitations. It was conducted at a study at a single institution with a retrospective medical record study design. Pharmacist interventions were obtained using consultation notes. The disease severity of the patients was not taken into account in the analysis of the physicians' acceptance of the K-RDS system. Patients with an eGFR < 10 ml/min were mostly undergoing hemodialysis or peritoneal dialysis according to renal function. However, the number of dialysis patients was low; thus, dialysis patients were not analyzed. Our result may be overestimates due to the low adjustment of the K-RDS threshold for physician education purposes. This study was designed to compare physician responses to K-RDS prescription alerts according to the degree of pharmacist involvement (designated pharmacist vs. control group with central pharmacy guidance only). Since the number of pharmacists and the number of wards assigned to the designated pharmacist group were fewer than those associated with the control group, the number of prescription alerts (259) in the wards with the designated pharmacists were far fewer than the number of prescription alerts (2082) assigned to the control group.

A concern that fast-advancing intelligence technology associated with the fourth Industrial Revolution might take over human labor activity compels us to find the new roles for pharmacists. Our study demonstrated the pharmacists' roles and responsibilities within the realm of IT-based healthcare systems to improve the quality of patient care and pharmacy services.

Conclusion

Our study suggests that pharmacist interventions have a positive effect on improving physicians' acceptance of the K-RDS, which benefits patient care. We also found that physician acceptance varies by medication category, department specialty, and the degree of a patient's renal function. The K-RDS with active pharmacist involvement can promote appropriate drug administration and prevent drug-related problems in patients with reduced renal function.

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Conflicts of interest The authors have no conflicts of interest to disclose.

Appendix

See Table 5.

Table 5 Classification of the different categories of the validated method proposed by Overhage and Lukes regarding 'severity of prescription error' and 'impact of service provided by the pharmacist'

	Severity of prescription error
1.	Potentially lethal
	High potential to compromise the life of patients
	Potentially life-saving drug prescribed at a dose too low for the condition for which it is being used
	High dose (> normal dose × 10) of a drug with a narrow therapeutic range
2.	Serious
	Route of administration can lead to severe toxicity
	Dose of a medication too low for a serious disease in a patient with distress acute
	High dose (normal dose × 4–10) of a drug with a narrow therapeutic range
	The dose may result in potentially toxic concentrations
	The drug may exacerbate the condition of the patient (side effects or contraindications)
	Spelling or interpretation errors of medications that could lead to dispensing the wrong drug
	Documented allergy to a drug
	High dose (> normal dose × 10) of a drug with normal therapeutic range
	Omission of a pretest for a drug that could cause hypersensitivity
3.	Significant
	High dose (normal dose × 1.5–4) of drugs with narrow therapeutic range
	Dose of a medication too low for the condition of the patient
	High dose (normal dose × 1–1.5) of a drug with normal therapeutic range
	Therapeutic duplications
	Inappropriate dosage interval
	Omission of a drug in the medical prescription
4.	Least
	Incomplete information in the medical prescription
	Inappropriate or unavailable pharmaceutical form
	Prescription of drugs not included in the pharmacotherapeutic guide of the hospital
	Illegible, ambiguous or non-standard abbreviations
5.	No error
	Medical prescription required additional information or clarification
	Cost savings
	Impact of service provided by the pharmacist
1.	Extremely significant
	The recommendation avoids a situation that endangers the life of patients
2.	Highly significant
	The recommendation prevents damage for a vital organ
	Recommendation prevents serious adverse reactions resulting from a drug interaction or a contraindication for use
3.	Significant
	Recommendation improves the quality of life of the patient (standard practices described in the hospital)
4.	Little significant
	The benefit of the recommendation is neutral depending on the interpretation of the professional
5.	Insignificant
	Only information
	Generalised recommendations not specific of a patient
6.	Injurious intervention
	Inappropriate recommendations that can lead to a worsening of the condition patient

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