Clinical Decision Support System with Renal Dose Adjustment Did Not Improve Subsequent Renal and Hepatic Function among Inpatients: The Japan Adverse Drug Event Study

Ryuhei Wada[1]   Jiro Takeuchi[1]   Tsukasa Nakamura[2]   Tomohiro Sonoyama[3]   Shinji Kosaka[4]
Chisa Matsumoto[5]   Mio Sakuma[1]   Yoshinori Ohta[6]   Takeshi Morimoto[1]

[1] Department of Clinical Epidemiology, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan
[2] Department of Infectious Diseases, Shimane Prefectural Central Hospital, Izumo, Shimane, Japan
[3] Department of Pharmacy, Shimane Prefectural Central Hospital, Izumo, Shimane, Japan
[4] Shimane Prefectural Central Hospital, Izumo, Shimane, Japan
[5] Center for Health Surveillance & Preventive Medicine, Tokyo Medical University, Tokyo, Japan
[6] Education and Training Center for Students and Professionals in Healthcare, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan

Address for correspondence Takeshi Morimoto, MD, PhD, MPH, Department of Clinical Epidemiology, Hyogo College of Medicine, Nishinomiya, Hyogo 663-8501, Japan (e-mail: morimoto@kuhp.kyoto-u.ac.jp).

Abstract

Background Medication dose adjustment is crucial for patients with renal dysfunction (RD). The assessment of renal function is generally mandatory; however, the renal function may change during the hospital stay and the manual assessment is sometimes challenging.

Objective We developed the clinical decision support system (CDSS) that provided a recommended dose based on automated calculated renal function.

Methods We conducted a prospective cohort study in a single teaching hospital in Japan. All hospitalized patients were included except for obstetrics/gynecology and pediatric wards between September 2013 and February 2015. The CDSS was implemented on December 2013. Renal and hepatic dysfunction (HD) were defined as changes in the estimated glomerular filtration rate (eGFR) and alanine aminotransferase or alkaline phosphatase levels based on these measurements during hospital stay. These measurements were obtained before (phase I), after (phase II), and 1 year after (phase III) the CDSS implementation.

Results We included 6,767 patients (phase I: 2,205; phase II: 2,279; phase III: 2,283). The patients' characteristics were similar among phases. Changes in eGFR were similar among phases, but the incidence of RD increased in phase III (phase I: 228 [10.3%]; phase II: 260 [11.4%]; phase III: 296 [13.0%], $p = 0.02$). However, the differences in

Keywords
► clinical decision support system
► adverse drug event
► renal dysfunction
► hepatic dysfunction
► renal dose adjustment

incidences of RD were not statistically significant after adjusting for eGFR at baseline and age. The incidences of HD were also similar among phases (phase I: 175 [13.2%]; phase II: 171 [12.9%]; phase III: 167 [12.2%], $p = 0.72$).

Conclusion   The CDSS implementation did not affect the incidence of renal and HD and changes in renal and hepatic function among hospitalized patients. The effectiveness of the CDSS with renal-guided doses should be investigated with respect to other endpoints.

Background and Significance

Renal dysfunction (RD) and hepatic dysfunction (HD) are common adverse drug events (ADEs) due to medication use among hospitalized patients.[1,2] Drug-induced RD accounts for approximately 1% of all hospitalizations.[3] Patients with preexisting RD are at a much higher risk of developing ADEs as renal excretion of drugs leads to elevated blood concentration.[4] Approximately 12% of adult inpatients in a teaching hospital were reported to have RD during their hospital stay.[5] In addition, a high incidence of ADEs has been associated with old age,[6] which is considered a risk factor for ADEs. Therefore, appropriate prescription in consideration of the patient's renal function is crucial in the future super-aging society.[7]

Similarly, the liver is also an organ that metabolizes and excretes drugs. Although primarily evoked by the hepatic excretion of drugs, HDs may occur as a result of elevated drug concentration caused by RD.[8] The RD and HD seem to have different adverse events due to medication use, but both are the most common toxicities, and have an increased incidence with regard to age, and are related to each other.[9] Thus, appropriate renal excretion of drugs may improve the incidence of HD due to medication use as well as RD.

The appropriate doses of renally excreted drugs are sometimes difficult to determine because some elderly patients with normal creatinine (Cr) levels may have RD. Therefore, physicians should prescribe these drugs based on the calculated renal function, such as Cr clearance or estimated glomerular filtration rate (eGFR).[10,11] However, such calculations are bothersome, and it remains difficult to distinguish between drugs requiring renal adjustment and drugs not requiring such adjustment in daily clinical practice. This could be resolved by a clinical decision support system (CDSS) available in developed countries.[12–14] The CDSS is equipped with a list of recommended and appropriate drug doses that could be adjusted for patients with RD at each drug ordering step.[15,16] We have developed our own CDSS, which promotes appropriate prescriptions for patients with RD.[17]

Objectives

Implementation of CDSS has improved the appropriate prescription rates, but its effectiveness on patient outcomes, such as occurrence of ADEs, is not well studied.[18–22] Therefore, we conducted this prospective cohort study at a tertiary care teaching hospital to investigate the effectiveness of CDSS with renal adjustment capability on subsequent changes in renal and hepatic functions of hospitalized patients. We hypothesized that the CDSS with renal adjustment would prevent the deterioration of renal or hepatic function, which were common toxicities of medication use.

Methods

Study Design and Patient Population

The Japan Adverse Drug Event (JADE) study was a series of cohort studies that evaluated the epidemiology of ADEs and medication errors in the real-world settings.[6,23–25] Using the JADE study series, we analyzed data from a prospective cohort study conducted from September 2013 to February 2015 at a tertiary care teaching hospital where the CDSS with renal adjustment was implemented during the study period. The hospital had a total of 634 beds with 13 medical and 11 surgical divisions and an intensive care unit. We included all patients with and without RD to show the impact of CDSS on the hospital as whole. The obstetrics/gynecology and pediatric wards were excluded because they had a low prevalence of patients with RD and low rates of medication use. We collected data for a 3-month period for each phase: phase I was from September to November 2013 before the CDSS implementation; phase II was from December 2013 to February 2014 just after the CDSS implementation on December 1, 2013; and phase III was from December 2014 to February 2015. The 3-month study period was set because the mean length hospital stay was 14 days in Japan and 3 months were considered long enough to include 3,000 patients and follow-up with most of them at each phase.

Patients aged ≥15 years admitted to the hospital for three study periods were included (►Figure 1). We excluded patients with an eGFR value of 15 mL/min/1.73 m^2 or lower on admission and those without eGFR values on admission or during the follow-up period.

The study was approved by the institutional review board of the hospital (approval number: Chu-Rin R 12055), and the board waived the requirement of written informed consent because all data were obtained as part of daily routine practice and the opt-out method was used as the consent.

Clinical Decision Support System Implementation

The master list of drugs necessitating renal adjustment was developed based on the package inserts, the practice guideline for chronic kidney disease (CKD) published in 2012,[26] and the guidelines for antimicrobial use.[27] We then implemented the drug master list in the computerized ordering
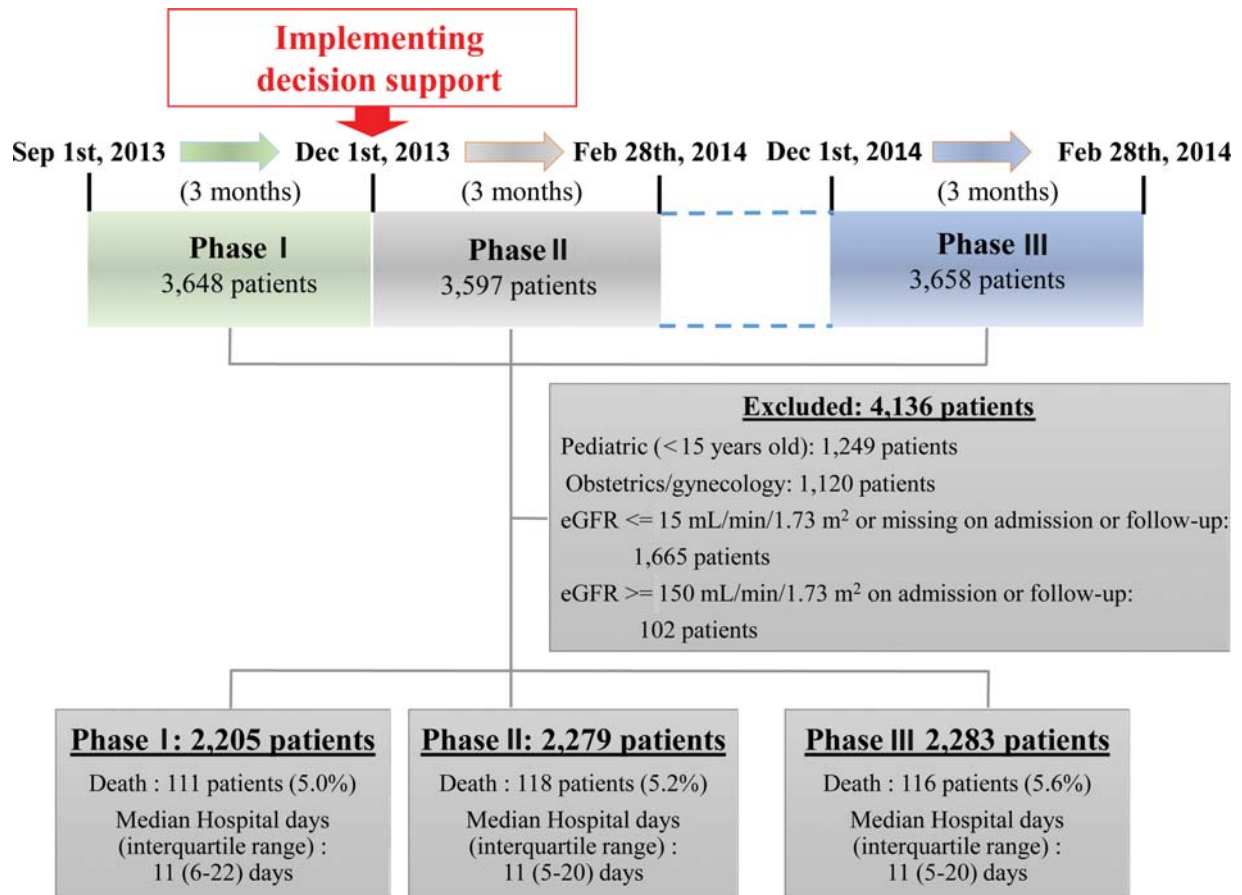
Fig. 1 Study flow chart.

system on the electronic medical record and constructed the CDSS (Supplemental Table [available in the online version]). When physicians prescribed any drug on the master list, the prescription guide with the recommended dose for calculated Cr clearance was displayed at the time of drug selection. This function was available for all patients including those without RD or HD because physicians might select different doses under the special conditions. Physicians could not only select one order with the appropriate dose from the list of recommended doses but also overwrite it and select other doses due to clinical reasons, such as off-label use. The drugs were continued until the physician in charge decided to stop or discharge the patients. The CDSS was active from phase I to III and displayed the prescription guide during phase II to phase III. The CDSS did not display the prescription and it worked in the background, keeping the log during phase I.

Data Collection
All data pertaining to patients' characteristics, laboratory tests, and drug prescriptions were automatically stored in the electronic medical record. The actions of the CDSS were also recorded. The variables collected were patient's age, admission date, ordering physician, admitting diagnosis, height, weight, eGFR, Cr clearance level, serum Cr level, and hepatic function values such as alanine aminotransferase (ALT) and alkaline phosphatase (ALP) levels. In addition, the eGFR values in this

study were calculated using the formula recommended by the Japanese Nephrology Society as showed below[28]:

$$eGFR \ (mL/min/1.73 \ m^2) = 194 \times serum \ Cr^{-1.094} \times Age^{-0.287} \times 0.739 \ (in \ females)$$

In terms of medication use, the name, dose and frequency of the prescribed drug, and actions of ordering physicians against the prescription guides were recorded.

Outcomes
The outcomes were RD and HD (►Table 1). The RD was diagnosed based on the practice guideline for CKD published in 2012,[26] including renal impairment (RI), decrease in eGFR, and change in eGFR (mL/min/1.73 m²), while HD was diagnosed based on a manual for the diagnostic criteria for drug-induced liver injury,[29] and American Gastroenterology Society guidelines,[30] including HD in ALT (HD-ALT) and HD in ALP (HD-ALP).

Statistical Analyses
The incidences of RD and HD and the changes in measurements were compared among phases as a whole and stratified by the eGFR value (≥ 60 vs. < 60 mL/min/1.73 m²) and age (< 65 vs. ≥ 65 years) on admission. Because the baseline values of eGFR could be associated with the following changes in eGFR, we adjusted for eGFR as well as age at

Table 1 Definition of renal and hepatic dysfunction

Outcomes		Definitions	
Renal dysfunction			
Renal impairment		Baseline eGFR (mL/min/1.73 m^2)	Minimum eGFR during the follow-up period (mL/min/1.73 m^2)
		≥ 60	< 60
		45–59	< 45
		30–44	< 30
		< 30	< 15
Decrease in eGFR		Baseline eGFR Minimum eGFR during the follow-up period ≥ 15 mL/min/1.73 m^2	
Changes in eGFR (mL/min/1.73 m^2)		Baseline eGFR Minimum eGFR during the follow-up period	
Hepatic dysfunction			
Hepatic dysfunction in ALT		Baseline ALT (IU/L)	Maximum ALT during the follow-up period (IU/L)
	Male	< 33	> 66
		$\geq 33, < 165$	> 165
		$\geq 165, < 495$	> 495
		≥ 495	$> 1{,}000$
	Female	< 25	> 50
		$\geq 25, < 125$	> 125
		$\geq 125, < 375$	> 375
		≥ 375	$> 1{,}000$
Hepatic dysfunction in ALP		Baseline ALP (IU/L)	Maximum ALP during the follow-up period (IU/L)
		< 325	> 650
		$\geq 325, < 1{,}625$	$> 1{,}625$
		$\geq 1{,}625, < 4{,}875$	$> 4{,}875$
		$\geq 4{,}875$	$> 10{,}000$

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; eGFR, estimated glomerular filtration rate.

baseline in the logistic regression models for RD and HD, and linear regression models for changes in measurements with dummy variables for each phase was used to estimate the adjusted p-values.

Continuous variables are presented as mean $\pm$ standard deviation or median (interquartile range) and compared with the analysis of variance. Categorical variables are shown as numbers and percentages and compared using the Chi-square test. All reported p-values were two-tailed, and p-values less than 0.01 were considered statistically significant considering the many outcomes. JMP 14.2 (SAS Institute Inc., Cary, North Carolina, United States) was used for all statistical analyses.

Results

During the study periods, there were 10,903 inpatients (phase I, 3,648; phase II, 3,597; phase III, 3,658) admitted to the hospital. We included 6,767 patients (phase I, 2,205; phase II, 2,279; and phase III, 2,283) who met the inclusion criteria (►Figure 1). Among them, 3,044 (45%) were males, and the mean age was 69 (standard deviation = 17) years.

The patients' characteristics were similar between phases, and those with RD (< 60 mL/min/1.73 m^2) were one-third of all admitted patients (►Table 2). The median (interquartile range) length of hospital stay was 11 (6–21) days.

The appropriate rates of prescribed drugs which necessitate the adjustment for renal function were improved from 90.7% (4,174/4,602) during phase I to 95.8% (4,789/4,999) phase II among all admitted patients; they were 78.5% (1,429/1,820) and 89.5% (1,729/1,931) of patients with Cr clearance less than 50 mL/min during phase I to phase II, respectively.[17]

Effect of Clinical Decision Support System Implementation on Renal and Hepatic Function
The incidence rates of RI and the changes in eGFR were similar among phases, but the decrease in eGFR ≥ 15 mL/min/1.73 m^2 increased in phase III (phase I, 228 [10.3%]; phase II, 260 [11.4%]; phase III, 296 [13.0%]; $p = 0.02$), compared with that in phase I. However, after adjusting for eGFR and age at baseline, the incidences of RD were not statistically significant (►Table 2).

On the contrary, the incidences of HD were similar among phases (phase I, 175 [13.2%]; phase II, 171 [12.9%]; phase III,

Table 2 Patient characteristics on admission

	Phase I	Phase II	Phase III
	(2,205 patients)	(2,279 patients)	(2,283 patients)
Age (y)[a]	68.9 ± 17.1	69.3 ± 16.8	70.3 ± 16.9
< 65 (n %)	748 (33.9)	751 (33.0)	677 (29.7)
≥ 65 (n %)	1,457 (66.1)	1,528 (67.0)	1,606 (70.3)
Male (n %)[c]	1,195 (54.2)	1,250 (54.9)	1,278 (56.0)
Height (cm)[a]	157.8 ± 10.1	158.0 ± 9.6	158.0 ± 10.0
Weight (kg)[a]	54.5 ± 12.2	55.4 ± 12.2	54.9 ± 12.2
BMI (kg/m^2)[a]	21.9 ± 3.8	22.2 ± 3.9	22.0 ± 3.7
eGFR (mL/min/1.73m^2)[a]	69.4 ± 24.3	72.0 ± 25.9	72.5 ± 25.9
≥ 60 (n %)	1,464 (66.4)	1,552 (68.1)	1,573 (68.9)
< 60 (n %)	741 (33.6)	727 (31.9)	710 (31.1)
Cr (mg/dL)[b]	0.77 (0.63–0.96)	0.75 (0.6–0.94)	0.74 (0.6–0.95)
BUN (mg/dL)[b]	15.2 (11.7–20.7)	15.6 (12.1–21.2)	15.6 (12–21.3)
AST (IU/L)[b]	23 (17–32)	23 (18–34)	24 (18–35)
ALT (IU/L)[b]	17 (12–27)	18 (12–29)	18 (12–28)
ALP (IU/mL)[b]	246 (191–321)	248 (193–323)	255 (198–343)
T-Bil (mg/dL)[b]	0.7 (0.5–1.0)	0.7 (0.5–1.0)	0.7 (0.5–1.0)
Primary diseases for admission (ICD-10 classification; n %)[c]			
Neoplasms	598 (27.1)	585 (25.7)	661 (29.0)
Diseases of the circulatory system	420 (19.0)	495 (21.7)	414 (18.1)
Diseases of the digestive system	335 (15.2)	327 (14.3)	300 (13.2)
Injury and poisoning	260 (11.8)	248 (10.9)	242 (10.6)
Diseases of the respiratory system	167 (7.6)	185 (8.1)	210 (9.2)
Diseases of the genitourinary system	67 (3.0)	66 (2.9)	64 (2.8)
Endocrine, nutritional, and metabolic diseases	61 (2.8)	59 (2.6)	68 (3.0)
Mental and behavioral disorders	59 (2.7)	41 (1.8)	59 (2.6)
Symptoms, signs, abnormal clinical findings, and abnormal laboratory findings not otherwise classified	53 (2.4)	65 (2.9)	69 (3.0)
Certain infectious diseases	51 (2.3)	55 (2.4)	62 (2.7)
Diseases of the nervous system	39 (1.8)	69 (3.0)	39 (1.7)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular filtration rate; ICD-10, International Classification of Diseases-10.
[a]Mean ± standard deviation.
[b]Median (25% quartile and 75% quartile).

167 [12.2%]; $p = 0.72$), and they were similar after adjusting for eGFR and age at baseline.

Effect on Renal and Hepatic Function Stratified by Baseline Estimated Glomerular Filtration Rate

Among patients with eGFR ≥ 60 mL/min/1.73 m^2 on admission, decrease in eGFR ≥ 15 mL/min/1.73 m^2 and change in eGFR in phase III significantly increased compared with those in phase I (►Table 3). In the case of eGFR < 60 mL/min/1.73 m^2 on admission, there was no significant difference in the decrease in eGFR ≥ 15 mL/min/1.73 m^2 and change in eGFR among phases.

There was no significant difference in the incidence of HD among phases between patients with eGFR ≥ 60 and those with < 60.

Effect on the Renal and Hepatic Function Stratified by Age

Between patients aged < 65 and those ≥ 65 years, there was no significant difference in the decrease in eGFR ≥ 15 mL/min/1.73 m^2 and change in eGFR among phases (►Table 4).

Additionally, there was no significant difference in the incidence of HD among phases between patients aged < 65 and ≥ 65 years (►Table 5).

Table 3 Effect on renal and hepatic function through implementation of clinical decision support system

	Number of patient (%)			Phase I vs. Phase II				Phase I vs. Phase III			
	Phase I	Phase II	Phase III	Crude OR or Difference (95% CI)[e]	p-Value	Adjusted OR or Difference (95% CI)[e]	p-Value	Crude OR or Difference (95% CI)[e]	p-Value	Adjusted OR or Difference (95% CI)[e]	p-Value
	2,205	2,279	2,283								
RI	267 (12.1)	259 (11.4)	295 (12.9)	0.93 (0.78–1.12)	0.44[a]	0.96 (0.80–1.16)	0.70[c]	1.08 (0.90–1.29)	0.41[a]	1.11 (0.93–1.33)	0.27[c]
Decrease in eGFR ≥ 15	228 (10.3)	260 (11.4)	296 (13.0)	1.12 (0.92–1.35)	0.25[a]	0.98 (0.81–1.19)	0.85[c]	1.29 (1.08–1.55)	0.006[a]	1.12 (0.92–1.35)	0.26[c]
RI or decrease in eGFR ≥ 15	388 (17.6)	412 (18.1)	452 (19.8)	1.03 (0.89–1.20)	0.67[a]	1.00 (0.85–1.16)	0.97[c]	1.16 (0.99–1.34)	0.059[a]	1.09 (0.93–1.27)	0.29[c]
Change in eGFR	4.27 ± 9.7	4.55 ± 10.1	5.21 ± 10.7	0.28 (−0.30 to 0.86)	0.34[b]	−0.08 (−0.63 to 0.48)	0.78[d]	0.94 (0.35–1.54)	0.002[b]	0.41 (−0.16 to 0.99)	0.16[d]
HD-ALT	165 (8.0)	161 (7.7)	159 (7.6)	0.96 (0.77–1.21)	0.74[a]	0.96 (0.77–1.20)	0.73[c]	0.95 (0.75–1.19)	0.63[a]	0.95 (0.76–1.19)	0.66[c]
HD-ALP	32 (2.3)	25 (1.8)	23 (1.6)	0.76 (0.45–1.30)	0.32[a]	0.77 (0.46–1.31)	0.34[c]	0.68 (0.40–1.17)	0.16[a]	0.69 (0.40–1.19)	0.18[c]
HD-ALT or HD-ALP	175 (13.2)	171 (12.9)	167 (12.2)	0.97 (0.77–1.22)	0.79[a]	0.97 (0.77–1.22)	0.80[c]	0.91 (0.73–1.14)	0.42[a]	0.92 (0.73–1.15)	0.45[c]
Difference of creatinine (mg/dL)											
Maximum-Minimum	0.191 ± 0.008	0.187 ± 0.008	0.198 ± 0.009	−0.004 (−0.027 to 0.018)	0.70[b]	0.009 (−0.012 to 0.030)	0.40[d]	0.006 (−0.017 to 0.030)	0.59[b]	0.023 (0.000–0.046)	0.046[d]
Baseline-discharge	0.050 ± 0.007	0.044 ± 0.007	0.036 ± 0.008	−0.007 (−0.027 to 0.013)	0.51[b]	−0.004 (−0.023 to 0.016)	0.73[d]	−0.014 (−0.036 to 0.007)	0.19[b]	−0.010 (−0.032 to 0.011)	0.34[d]
Difference of eGFR (mL/min/1.73 m²)											
Maximum-Minimum	14.53 ± 0.43	14.73 ± 0.46	15.81 ± 0.46	0.21 (−1.04 to 1.45)	0.75[b]	−0.22 (−1.45 to 1.02)	0.73[d]	1.28 (0.039–2.52)	0.04[b]	0.62 (−0.61 to 1.85)	0.32[d]
Baseline-Discharge	−5.70 ± 0.41	−5.16 ± 0.42	−4.30 ± 0.45	0.54 (−0.61 to 1.69)	0.36[b]	0.57 (−0.58 to 1.72)	0.33[d]	1.40 (0.21–2.59)	0.02[b]	1.35 (0.16–2.54)	0.03[d]

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; CI, confidence interval; eGFR, estimated glomerular filtration rate; HD-ALP, hepatic dysfunction-alkaline phosphatase; HD-ALT, hepatic dysfunction-alanine transaminase; OR, odds ratio; RI, renal impairment.

[a]Chi-square test.

[b]t-test.

[c]Logistic regression model adjusted for age and eGFR at baseline.

[d]Linear regression model adjusted for age and eGFR at baseline.

[e]Odds ratio (95% CI) for categorical variable; difference (95% CI) for continuous variable. Missing data number (Phase I, II, and III) for ALT and ALP: 2,751 (883, 953, and 915).

Table 4 Effect on renal and hepatic function through implementation of clinical decision support system in patients with or without baseline renal impairment

eGFR ≥ 60 mL/min/1.73 m²

	Number of patient (%)			Phase I vs. Phase II				Phase I vs. Phase III			
	Phase I	Phase II	Phase III	Crude OR or Difference (95% CI)[e]	p-Value	Age-Adjusted OR or Difference (95% CI)[e]	p-Value	Crude OR or Difference (95% CI)[e]	p-Value	Age-Adjusted OR or Difference (95% CI)[e]	p-Value
	(1,464)	(1,552)	(1,573)								
RI	139 (9.5)	133 (8.6)	172 (10.9)	0.89 (0.70–1.15)	0.38[a]	0.87 (0.67–1.11)	0.26[c]	1.17 (0.92–1.48)	0.19[a]	1.07 (0.84–1.36)	0.60[c]
Decrease in eGFR ≥ 15	182 (12.4)	225 (14.5)	257 (16.3)	1.19 (0.97–1.47)	0.10[a]	1.19 (0.96–1.47)	0.10[c]	1.38 (1.12–1.69)	0.002[a]	1.34 (1.09–1.65)	0.005[c]
RI or decrease in eGFR ≥ 15	260 (17.8)	286 (18.4)	329 (20.9)	1.05 (0.87–1.26)	0.63[a]	1.03 (0.86–1.24)	0.74[c]	1.22 (1.02–1.47)	0.03[a]	1.17 (0.98–1.41)	0.09[c]
Change in eGFR	5.1 ± 10.7	5.5 ± 11.3	6.3 ± 12.1	0.39 (−0.39 to 1.18)	0.32[b]	0.35 (−0.44 to 1.13)	0.38[d]	1.21 (0.40–2.01)	0.004[b]	1.08 (0.27–1.90)	0.009[d]
HD-ALT	106 (7.8)	111 (7.8)	100 (6.9)	1.00 (0.76–1.31)	0.98[a]	0.99 (0.75–1.31)	0.96[c]	0.88 (0.66–1.17)	0.38[a]	0.87 (0.65–1.16)	0.34[c]
HD-ALP	18 (2.0)	16 (1.7)	13 (1.3)	0.85 (0.43–1.68)	0.64[a]	0.85 (0.43–1.68)	0.65[c]	0.66 (0.32–1.35)	0.25[a]	0.66 (0.32–1.35)	0.25[c]
HD-ALT or HD-ALP	110 (12.7)	118 (12.9)	106 (11.2)	1.02 (0.77–1.35)	0.87[a]	1.02 (0.77–1.35)	0.88[c]	0.87 (0.66–1.16)	0.34[a]	0.87 (0.65–1.16)	0.33[c]

eGFR < 60 mL/min/1.73m²

	Number of patient (%)			Phase I vs. Phase II				Phase I vs. Phase III			
	Phase I	Phase II	Phase III	Crude OR or Difference (95% CI)[e]	p-Value	Age-Adjusted OR or Difference (95% CI)[e]	p-Value	Crude OR or Difference (95% CI)[e]	p-Value	Age-Adjusted OR or Difference (95% CI)[e]	p-Value
	(741 patients)	(727 patients)	(710 patients)								
RI	128 (17.3)	126 (17.3)	123 (17.3)	1.00 (0.77–1.32)	0.98[a]	1.00 (0.77–1.32)	0.98[c]	1.00 (0.76–1.32)	0.98[a]	1.00 (0.76–1.32)	0.98[c]
Decrease in eGFR ≥ 15	46 (6.2)	35 (4.8)	39 (5.5)	0.76 (0.49–1.20)	0.24[a]	0.76 (0.49–1.20)	0.24[c]	0.88 (0.57–1.36)	0.56[a]	0.88 (0.58–1.37)	0.58[c]
RI or Decrease in eGFR ≥ 15	128 (17.3)	126 (17.3)	123 (17.3)	1.00 (0.77–1.32)	0.98[a]	1.00 (0.77–1.32)	0.98[c]	1.00 (0.76–1.32)	0.98[a]	1.00 (0.76–1.32)	0.98[c]
Change in eGFR	2.7 ± 7.1	2.6 ± 6.5	2.9 ± 6.4	−0.08 (−0.78 to 0.62)	0.82[b]	−0.08 (−0.78 to 0.62)	0.82[d]	0.18 (−0.52 to 0.87)	0.62[b]	0.18 (−0.52 to 0.88)	0.61[d]
HD-ALT	59 (8.4)	50 (7.7)	59 (9.1)	0.90 (0.61–1.33)	0.60[a]	0.90 (0.61–1.33)	0.60[c]	1.09 (0.75–1.60)	0.64[a]	1.11 (0.76–1.62)	0.60[c]
HD-ALP	14 (3.1)	9 (2.1)	10 (2.3)	0.66 (0.28–1.54)	0.33[a]	0.66 (0.27–1.51)	0.33[c]	0.74 (0.33–1.69)	0.47[a]	0.74 (0.32–1.68)	0.48[c]
HD-ALT or HD-ALP	65 (14.3)	53 (12.8)	61 (14.4)	0.88 (0.60–1.30)	0.52[a]	0.88 (0.59–1.30)	0.52[c]	1.01 (0.69–1.47)	0.98[a]	1.00 (0.69–1.47)	0.98[c]

[a]Chi-square test.
[b]t-test.
[c]Logistic regression.
[d]Linear regression.
[e]Odds ratio (95% CI) for categorical variable; difference (95% CI) for continuous variable.
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HD-ALP, hepatic dysfunction-alkaline phosphatase; HD-ALT, hepatic dysfunction-alanine transaminase; OR, odds ratio; RI, renal impairment.

Table 5 Effect on renal and hepatic function through implementation of clinical decision support system in elderly or nonelderly patients

Age < 65 years

| | Number of patient (%) | | | Phase I vs. Phase II | | | | Phase I vs. Phase III | | | |
| | Phase I | Phase II | Phase III | Crude | | Baseline eGFR-Adjusted | | Crude | | Baseline eGFR-Adjusted | |
	(748 patients)	(751 patients)	(677 patients)	OR or Difference (95% CI)[e]	p-Value	OR or Difference (95% CI)[e]	p-Value	OR or Difference (95% CI)[e]	p-Value	OR or Difference (95% CI)[e]	p-Value
RI	49 (6.6%)	49 (6.5%)	43 (6.4%)	1.00 (0.66–1.50)	0.98[a]	1.01 (0.66–1.55)	0.95[c]	0.97 (0.63–1.48)	0.88[a]	1.04 (0.67–1.61)	0.87[c]
Decrease in eGFR ≥ 15	88 (11.8%)	93 (12.4%)	91 (13.4%)	1.06 (0.78–1.45)	0.71[a]	0.97 (0.70–1.33)	0.84[c]	1.16 (0.85–1.59)	0.34[a]	1.00 (0.72–1.38)	0.98[c]
RI or Decrease in eGFR ≥ 15	109 (14.6%)	111 (14.8%)	106 (15.7%)	1.02 (0.76–1.35)	0.91[a]	0.98 (0.74–1.31)	0.91[c]	1.09 (0.81–1.45)	0.57[a]	1.02 (0.76–1.37)	0.87[c]
Change in eGFR	4.3 ± 10.1	4.4 ± 10.9	5.3 ± 11.5	0.07 (−0.99 to 1.14)	0.89[b]	−0.15 (−1.18 to 0.89)	0.78[d]	0.97 (−0.17 to 2.10)	0.09[b]	0.42 (−0.68 to 1.51)	0.45[d]
HD-ALT	53 (7.6%)	54 (7.8%)	48 (7.8%)	1.03 (0.69–1.52)	0.90[a]	1.04 (0.70–1.54)	0.86[c]	1.02 (0.68–1.53)	0.92[a]	1.06 (0.71–1.60)	0.77[c]
HD-ALP	13 (2.9%)	9 (2.0%)	4 (1.0%)	0.67 (0.28–1.57)	0.35[a]	0.66 (0.27–1.55)	0.34[c]	0.32 (0.10–1.0001)	0.04[a]	0.32 (0.09–0.93)	0.04[c]
HD-ALT or HD-ALP	57 (13.6%)	58 (13.2%)	49 (12.2%)	0.97 (0.65–1.44)	0.88[a]	0.97 (0.65–1.43)	0.86[c]	0.89 (0.59–1.33)	0.56[a]	0.89 (0.59–1.34)	0.57[c]

Age ≥ 65 years

| | Number of patient (%) | | | Phase I vs. Phase II | | | | Phase I vs. Phase III | | | |
| | Phase I | Phase II | Phase III | Crude | | Baseline eGFR-Adjusted | | Crude | | Baseline eGFR-Adjusted | |
	(1,457 patients)	(1,528 patients)	(1,606 patients)	OR Difference (95% CI)[e]	p-Value	OR Difference (95% CI)[e]	p-Value	OR Difference (95% CI)[e]	p-Value	OR or Difference (95% CI)[e]	p-Value
RI	218 (15.0%)	210 (13.7%)	252 (15.7%)	0.91 (0.74–1.11)	0.34[a]	0.95 (0.77–1.17)	0.64[c]	1.06 (0.87–1.29)	0.58[a]	1.12 (0.92–1.37)	0.26[c]
Decrease in eGFR ≥ 15	140 (9.6%)	167 (10.9%)	205 (12.8%)	1.15 (0.91–1.46)	0.24[a]	1.00 (0.78–1.29)	0.98[c]	1.38 (1.10–1.73)	0.006[a]	1.23 (0.97–1.57)	0.08[c]
RI or decrease in eGFR ≥ 15	279 (19.2%)	301 (19.7%)	346 (21.5%)	1.04 (0.86–1.24)	0.70[a]	1.01 (0.84–1.21)	0.90[c]	1.16 (0.97–1.38)	0.10[a]	1.13 (0.95–1.35)	0.18[c]
Change in eGFR	4.2 ± 9.5	4.6 ± 9.7	5.2 ± 10.4	0.39 (-0.30–1.08)	0.27[b]	0.04 (-0.63–0.70)	0.91[d]	0.94 (0.24–1.65)	0.009[b]	0.53 (0.15–1.21)	0.13[d]
HD-ALT	112 (8.2%)	107 (7.7%)	111 (7.5%)	0.93 (0.71–1.23)	0.62[a]	0.93 (0.70–1.22)	0.59[c]	0.91 (0.69–1.20)	0.51[a]	0.90 (0.69–1.19)	0.47[c]
HD-ALP	19 (2.1%)	16 (1.7%)	19 (1.9%)	0.83 (0.42–1.63)	0.59[a]	0.84 (0.43–1.65)	0.62[c]	0.91 (0.48–1.73)	0.77[a]	0.92 (0.48–1.75)	0.80[c]
HD-ALT or HD-ALP	118 (13.1%)	113 (12.7%)	118 (12.2%)	0.97 (0.74–1.28)	0.83[a]	0.97 (0.73–1.28)	0.82[c]	0.92 (0.70–1.21)	0.57[a]	0.92 (0.70–1.21)	0.55[c]

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HD-ALP, hepatic dysfunction-alkaline phosphatase; HD-ALT, hepatic dysfunction-alanine transaminase; OR, odds ratio; RI, renal impairment.

[a]Chi-square test.
[b]t-test.
[c]Logistic regression.
[d]Linear regression.
[e]Odds ratio (95% CI) for categorical variable and difference (95% CI) for continuous variable.

Discussion

We investigated the effectiveness of the CDSS implementation on renal and hepatic function of inpatients. The amount of eGFR change during the study period and the proportion of patients with eGFR changes ≥ 15 mL/min/1.73 m^2 were significantly greater 1 year after the implementation of the system (phase III) than before the implementation (phase I). However, this difference was not observed when the baseline age and eGFR were adjusted. In contrast, in the stratified group without RI (eGFR ≥ 60 mL/min/1.73 m^2), the amount of eGFR changes during the study period and the proportion of patients with eGFR changes ≥ 15 mL/min/1.73 m^2 were significantly larger 1 year after the system implementation than before the implementation. However, there was no significant difference between phases in the stratified groups with RI (eGFR < 60 mL/min/1.73 m^2) and the stratified groups of elderly (age ≥ 65 years) and nonelderly (age < 65 years) patients. Thus, the CDSS implementation with renal adjustment did not prevent the deterioration of renal and hepatic function during hospital stay.

Our findings suggested that the improved prescription did not improve renal and hepatic outcomes. The discrepancy between the improved prescription rate and unchanged RD or HD during the hospital stay should be carefully interpreted. Medications that necessitate the dose adjustment based on renal function were limited in the hospital. In addition, the follow-up period in the study (median hospital days, 11) was short because renal function is generally observed in the longer term. Therefore, this function may be improved when these measurements are followed up after discharge.

Several studies investigated the effectiveness of the CDSS with the prescription guide for renal adjustment.[18–22] Most of these studies reported the process, including the appropriateness of prescription, but not the patient outcomes, such as renal function. In addition, there were no reports on the relationship between the CDSS with renal adjustment and subsequent HD. However, we also could not demonstrate the effectiveness of the CDSS in the prevention of ADEs.

The appropriate prescription rate certainly improved with the CDSS implementation, which alerts the physicians' prescriptions in our study. As the study center was a tertiary care hospital, many physicians in charge were senior physicians. The effectiveness of the CDSS may be elucidated if there were more physicians in training. Therefore, the effectiveness of the CDSS on clinical outcomes should be evaluated in other settings such as a teaching hospital or primary care.

Our study has several limitations. First, this study was a before and after design; thus, the backgrounds of the patients were unnecessarily similar among phases although we adjusted for age and the baseline renal function. We should consider many other factors, such as patients' conditions that could contribute to a decline in renal and hepatic functions during hospitalization to establish the effectiveness of CDSS on RD and HD. However, we included all admitted patients in a general hospital, and the patient conditions were too diverse to be adjusted. Therefore, other studies among patients with simple or uniform diseases could be conducted to reinforce our findings. Second, we set several outcomes based on the eGFR, ALT, and ALP values because the magnitude of changes over a 3-month period was too small to evaluate the clinically meaningful dysfunctions. For instance, one of the definitions of CKD was the measurements of eGFR on at least two occasions, 90 days apart (with or without the markers of kidney damage).[31] Therefore, further studies need to evaluate the effectiveness of the CDSS with renal adjustment on renal and hepatic functions for inpatients after the discharge or those in for longer term.[32] Third, we observed RD and HD incidences of the overall cohorts, and two-third of the included patients did not have RD on admission and were not the target population of the CDSS. Therefore, if we analyzed only patients with actual guide for existing RD, the effectiveness of CDSS should be more prominent. However, we conducted this research on all patients to measure the overall impact of CDSS on hospital administration. Fourth, medications registered in the master list of this study were limited. The master list of drugs necessitating renal adjustment had initially been developed; however, it was not updated during the study period. If a new drug requiring dose adjustment for renal function was prescribed during the study period, the physician may not have been alerted and would not have been aware of the inappropriate prescription. In clinical practice, it is necessary to update the medication lists with adjustment for renal function. Fifth, the study setting was a general hospital and the background characteristics of admitted patients were too diverse. Therefore, we could not evaluate the effectiveness of CDSS on patients with specific characteristics. Finally, we conducted this study at a single center, and the generalizability was limited. If we could implement the CDSS at multiple centers, the generalizability of this study could be established.

Conclusion

The CDSS with renal adjustment did not improve the RD and HD during hospital stay. The effectiveness of the CDSS with renal adjustment on RD and HD for a short term remains undetermined and should be evaluated in long-term studies and from other perspectives.

Clinical Relevance Statement

Many CDSS are equipped with medication dose adjustment based on renal function, but their effectiveness was assessed by process measures such as appropriate prescription rates.

The prospective cohort study at inpatient setting showed implementation of CDSS with medication dose adjustment based on renal function did not decrease the incidences of renal and HD during the hospitalization.

The effectiveness of the CDSS with medication dose adjustment based on renal function should be investigated with respect to other endpoints and longer perspectives.

Multiple Choice Questions

1. When physicians prescribed any drug necessitate the dose adjustment, what measurement of patient was used to calculate the appropriate dose with the CDSS?
   a. Cr clearance
   b. eGFR
   c. BMI
   d. Body surface area

   Correct Answer: The correct answer is option a. The master list of drugs necessitating renal adjustment was developed based on the package inserts, and many package inserts set appropriate doses by Cr clearance in Japan.

2. Which of the following was the targeted patients to be analyzed in the study?
   a. Patients with RD
   b. Patients with HD
   c. Patients with RD and without RD
   d. Patients with RD and without HD

   Correct Answer: The correct answer is option c. We included all patients with RD and without RD because we should show the impact of CDSS on the hospital as whole.

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