Analysis of Risk Factors for High-dose Cisplatin-induced Renal Impairment in Head and Neck Cancer Patients

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Analysis of Risk Factors for High-dose Cisplatin-induced Renal Impairment in Head and Neck Cancer Patients

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Abstract. *Background/Aim: Concurrent chemoradiotherapy with high-dose cisplatin (CDDP-RT) is the standard therapy for advanced head and neck cancer; however, due to CDDP-induced renal impairment, dose reduction or discontinuation is frequently required. Therefore, the identification of risk factors for renal impairment is of importance to improve the efficacy and safety of CDDP-RT. Patients and Methods: We retrospectively investigated risk factors for renal impairment in advanced head and neck cancer patients receiving CDDP-RT. Renal impairment was defined as a >25% decrease from baseline in estimated glomerular filtration rate within 14 days after CDDP administration in the first cycle. Results: Of the 82 patients analyzed in this study, 21 (26%) patients developed renal impairment. Multivariate logistic regression analysis showed that concomitant use of a calcium channel blocker or lower hemoglobin levels significantly contributed to the increased risk of CDDP-induced renal impairment (odds ratio=3.60, 95% confidence interval=1.04-12.40; odds ratio=0.71, 95% confidence interval=0.50-0.99, respectively), while concomitant use of proton pump inhibitors was a factor associated with a decreased risk of CDDP-induced renal impairment (odds ratio=0.20, 95% confidence interval=0.04-0.86). Conclusion: Renal function of patients receiving calcium channel blocker or patients with lower hemoglobin levels should be monitored cautiously when receiving CDDP-RT.*

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Concurrent chemoradiotherapy with high dose-cisplatin (CDDP-RT) is considered to be the standard therapy for advanced head and neck cancer (1-4). The standard CDDP-RT regimen for head and neck cancer consists of three cycles of CDDP at 100 mg/m^2 every 3 weeks and RT (70 Gy for curative treatment and 60-66 Gy for postoperative adjuvant chemotherapy), CDDP is used at higher doses than in regimens for other cancer types, requiring more attention for CDDP-induced toxicity. Despite the many clinical effects of this CDDP-RT therapy, renal impairment results in dose reduction or discontinuation of CDDP. In clinical practice, the completion rate of the CDDP-RT regimen in Japan is lower than that in the West (5-7). Some groups have considered that a reduced dose CDDP-RT regimen is needed because of intolerance in clinical practice (8-10). Therefore, identifying risk factors for renal impairment is of importance to improve the efficacy and safety of CDDP-RT.

Acute kidney injury is observed in approximately 30% of CDDP-administered cases (11, 12), and CDDP is known to cause chronic kidney disease because of further progression of renal injury. CDDP is transported to the renal tubules via renal transporters, resulting in renal impairment (13). Previous studies including various cancer types and regimens have shown that female sex, age, hypoalbuminemia, smoking, cardiovascular disease, diabetes, or diagnosis of cancer stage 4 are risk factors for the development of CDDP-induced renal impairment in cancer patients (14, 15). In addition, previous studies on 5-fluorouracil and CDDP therapy have reported that the combination of calcium channel blocker (CCB) and angiotensin-converting enzyme inhibitors/angiotensin II receptor blocker (ARB) increases the risk of CDDP-induced renal impairment (16), while magnesium sulfate or proton pump inhibitors (PPI) reduces it (17, 18). Thus, patient characteristics and concomitant drug administration may influence the development of renal impairment in CDDP-RT. However, there is currently insufficient evidence on factors associated with renal impairment of CDDP-RT. Therefore, it is important to

prevent nephrotoxic events during CDDP-RT and to maintain high treatment intensity and the patients' quality of life in advanced head and neck cancer.

In the current study, a retrospective analysis was conducted to clarify the effects of patient background factors, including concomitant use of drugs, on the development of renal impairment in head and neck cancer patients treated with CDDP-RT therapy.

Patients and Methods

Patient selection and data collection. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Shiga University of Medical Science Ethics Committee (reference number: R2019-253). This study was retrospective. Data were collected from 88 patients with head and neck cancer who underwent CDDP-RT from September 2014 to December 2021 at the Shiga University of Medical Science Hospital. Eligible patients were treated with CDDP-RT; high-dose CDDP was planned every 3 weeks up to three cycles. In this study, the initial dose of CDDP was 100 mg/m^2 in 19 patients, 90 mg/m^2 in one patient, 80 mg/m^2 in 49 patients, 70 mg/m^2 in 10 patients, and 60 mg/m^2 in three patients. All patients received hydration with >1,000 ml saline each pre and post cisplatin infusion, respectively, and 300 ml of 15% mannitol infused over 1.5 h post cisplatin administration as an enforced diuresis. All doses of cisplatin were diluted in 500 ml saline and infused over 2 h.

Data including basic demographic information, such as age, sex, and body surface area, CDDP dose, laboratory test values, such as serum creatinine level (Scr, mg/dl), serum urea nitrogen level (BUN, mg/dl), alanine transaminase level (ALT, IU/l), estimated glomerular filtration rate (eGFR, ml/min/1.73 m^2), albumin (Alb, mg/dl), white blood cell count (WBC, 10^3/μl), hemoglobin concentration (Hb, g/dl), platelet count (PLT, 10^3/μl), serum sodium level (Na, mmol/l), serum potassium level (K, mmol/l), serum chloride (Cl, mmol/l), and concomitant medications (*e.g.*, ARB, CCB, PPI) were collected. Six patients receiving non-steroidal anti-inflammatory drugs, which are known to be risk factors for renal damage (19, 20), were excluded. Information on concomitantly used drugs was extracted as drugs administered on the same day as CDDP administration. Drugs were classified based on efficacy.

Toxicity evaluation. In this study, renal impairment was defined as a >25% reduction from baseline in eGFR within 14 days after CDDP administration in the first cycle (14, 21-23).

Data analysis. Differences in patient background factors between the two groups with or without renal impairment were compared using Fisher's exact test or the Mann–Whitney *U*-test. When the *p*-value was <0.20, the odds ratio (95% confidence interval) was calculated using univariate logistic regression analysis. At least five outcome events are needed for each independent variable in multivariate logistic regression analysis (24). Multivariate logistic regression using a model with four covariates was performed. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal threshold value for the predicted probability of the model for predicting CDDP-induced renal impairment in CDDP-RT, as well as to calculate the specificity, sensitivity, and area under the curve (AUC). The value maximizing the Youden index (sensitivity + specificity-1) was used to determine the optimal threshold value.

The significance level was set at $p<0.05$. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (25). EZR is a statistical software extending the functionality of the R command-line tool.

Results

The degree and timing of the maximal decrease in eGFR after CDDP administration. The timing of the maximal decrease in eGFR after CDDP administration in the first cycle is shown in Figure 1A. CDDP was administered to patients on day 1. The maximum decrease in eGFR was observed after 8 days of CDDP administration (day 9) in many patients, and the median (interquartile range, IQR) time to maximum decrease in eGFR after CDDP administration was 9 days (range=7-14 days). The degree of the maximal decrease in eGFR during 14 days after CDDP administration in the first cycle is shown in Figure 1B. Of the 82 patients analyzed, 21 (25.6%) patients developed renal impairment. Among them, 2 patients developed a >50% reduction from baseline in eGFR.

Patient characteristics with or without renal impairment after CDDP administration. A comparison of patient characteristics with or without CDDP-induced renal impairment in the first cycle is presented in Table I. Age (p=0.003), Hb level (p=0.033), and concomitant treatment with CCB (p=0.005) were statistically significantly different between the groups with or without renal impairment. No significant difference was observed in any of the other factors including eGFR between the groups with or without renal impairment.

Univariate and multivariate logistic regression analysis of each factor for renal impairment. The results of the univariate and multivariate logistic regression analysis of each factor for renal impairment after the first administration of CDDP are presented in Table II. Univariate logistic regression analysis identified concomitant treatment with CCB (p=0.003), age (p=0.007), and Hb level (p=0.031) as significant risk factors; the other factors including eGFR were not significantly different between the two groups. For further analysis, based on sample size, previous findings, and *p*-value in univariate logistic regression analysis, concomitant use of CCB, age, Hb levels, and concomitant use of PPI were evaluated as potential covariates in multivariate logistic regression analysis. Hypertension/cardiovascular comorbidity was excluded due to multicollinearity with the concomitant use of CCB. Concomitant treatment with PPI (p=0.031), concomitant treatment with CCB (p=0.043), and Hb level (p=0.046) were found to be significant; however, age was not significant (p=0.120).

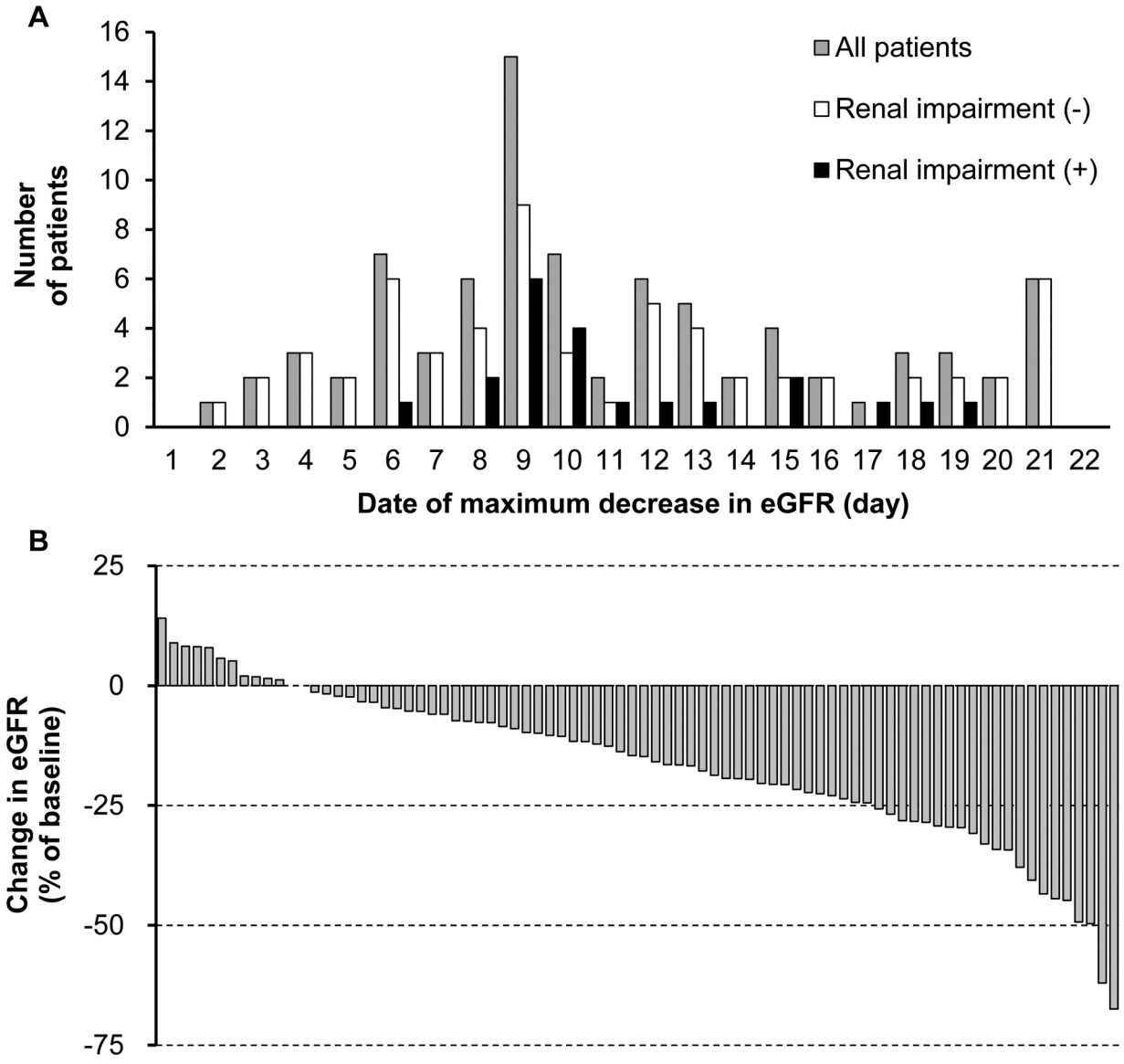

Figure 1. *The date of maximum decrease in estimated glomerular filtration rate (eGFR) and the change in eGFR after cisplatin (CDDP) administration in the first cycle. (A) Date of maximum decrease in eGFR during 21 days after CDDP administration. (B) Change in eGFR during 14 days after CDDP administration.*

The logit function of CDDP-induced renal impairment in CDDP-RT, obtained by multivariate logistic regression using a model with four covariates, was as follows:

logit=−1.30 −1.63×PPI (use:1, no use: 0)+
1.28×CCB (use:1, no use: 0) −0.349×Hb+0.0693×Age

Based on the analysis of the ROC curve (Figure 2), the AUC and the threshold value for the predicted probability of the model for predicting CDDP-induced renal impairment in CDDP-RT were 0.813 (95% confidence interval=0.719-0.908) and 0.286 (sensitivity, 81.0%; specificity, 70.5%), respectively.

Discussion

We conducted a retrospective study to assess the relationship between the development of high-dose CDDP-induced renal impairment in CDDP-RT and patient-related factors in patients with head and neck cancer. Of the 82 patients

Table I. *Comparison of patient characteristics with or without renal impairment at the time of cisplatin (CDDP) administration in the first cycle.*

Variable	Renal impairment (–) n=61	Renal impairment (+) n=21	*p*-Value
Age (years)	62 (52-69)	68 (65-72)	0.003
Sex (Female)	6 (10)	5 (24)	0.139
BSA (m^2)	1.68 (1.57-1.77)	1.63 (1.55-1.71)	0.281
CDDP dose (mg/m^2)	80 (80-80)	80 (80-100)	0.558
Chemotherapy history with regimens including CDDP	17 (28)	3 (14)	0.254
Clinical disease stage			
Stage 3	9 (15)	5 (24)	0.503
Stage 4	35 (58)	9 (43)	0.309
Hypertension/cardiovascular disease	24 (39)	13 (62)	0.082
Diabetes	8 (13)	4 (19)	0.493
Scr (mg/dl)	0.77 (0.67-0.85)	0.76 (0.59-0.91)	0.852
BUN (mg/dl)	12.5 (10.9-14.5)	14.5 (10.2-17.1)	0.286
eGFR (ml/min/1.73 m^2)	80.1 (70.2-88.5)	73.5 (63.0-85.4)	0.144
ALT (U/I)	21 (14-28)	17 (12-26)	0.145
Alb (<3.5 g/dl)	17 (28)	10 (48)	0.113
WBC ($10^3/\mu l$)	5.7 (4.5-7.4)	5.7 (4.5-6.8)	0.873
Hb (g/dl)	13.2 (11.7-14.4)	11.9 (10.7-13.1)	0.033
PLT ($10^3/\mu l$)	250 (216-295)	231 (196-285)	0.369
Na (mEq/l)	141 (139-143)	141 (140-143)	0.368
K (mEq/l)	4.3 (4.0-4.5)	4.2 (4.0-4.4)	0.448
Cl (mEq/l)	105 (104-107)	107 (105-108)	0.211
Furosemide intravenous (+)	48 (79)	18 (86)	0.750
PPI (+)	24 (39)	4 (19)	0.114
Vonoprazan (+)	2 (3)	2 (10)	0.270
CCB (+)	13 (21)	12 (57)	0.005
ARB (+)	10 (16)	6 (29)	0.337
CCB (+) and ARB (+)	6 (10)	5 (24)	0.139
Magnesium sulfate (+)	18 (30)	4 (19)	0.407

Values are presented as number (%) or median (interquartile range). Statistical analyses between two groups were performed using Fisher's exact test or Mann–Whitney *U*-test. BSA: Body surface area; Scr: creatinine; BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; ALT: alanine transaminase; Alb: albumin; WBC: white blood cell; Hb: hemoglobin; PLT: platelet; PPI: proton pump inhibitor; CCB: calcium channel blocker; ARB: angiotensin II receptor blocker.

Table II. *Univariate and multivariate analyses of risk factors for renal impairment in the first cycle of cisplatin (CDDP) administration.*

	Univariate			Multivariate			
Variable	Odds	95%CI	*p*-Value	Regression coefficient	Odds	95%CI	*p*-Value
CCB (+)	4.92	1.71-14.2	0.003	1.28	3.60	1.04-12.4	0.043
Age (years)	1.11	1.03-1.20	0.007	0.0693	1.07	0.982-1.17	0.120
Hb (g/dl)	0.738	0.560-0.973	0.031	–0.349	0.705	0.500-0.994	0.046
Hypertension/cardiovascular disease	2.51	0.904-6.94	0.078				
PPI (+)	0.363	0.109-1.21	0.099	–1.63	0.195	0.0443-0.862	0.031
Alb (<3.5 g/dl)	2.35	0.846-6.55	0.101				
ALT (U/I)	0.959	0.912-1.01	0.110				
Sex (Female)	2.86	0.772-10.6	0.116				
CCB (+) and ARB (+)	2.86	0.772-10.6	0.116				
eGFR (ml/min/1.73 m^2)	0.986	0.955-1.02	0.407				
Intercept				–1.30	0.274	0.00012-622	0.742

The odds ratio (95% confidence interval) was calculated using univariate or multivariate logistic regression analysis. Objective variable: renal impairment. CI: Confidence interval; Hb: hemoglobin; CCB: calcium channel blocker; CDDP: cisplatin; PPI: proton pump inhibitor; ALT: alanine transaminase; Alb: albumin; ARB: angiotensin II receptor blocker; eGFR: estimated glomerular filtration rate.

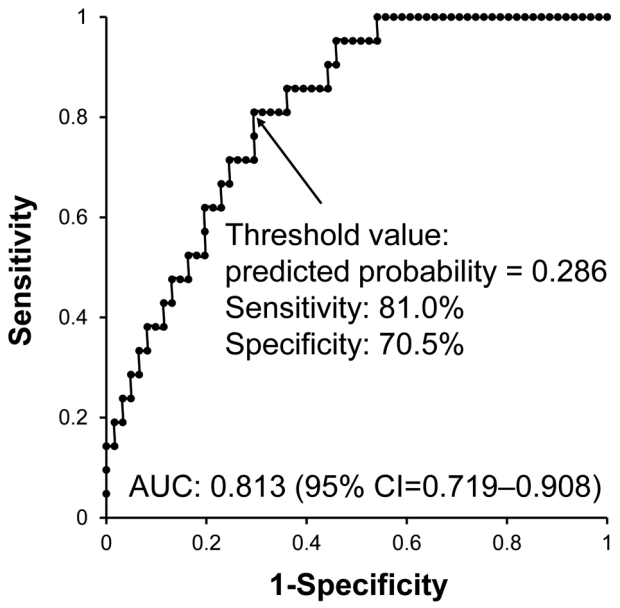

Figure 2. *Receiver operating characteristic curve of predicted probability of the model for predicting cisplatin-induced renal impairment in the first cycle. AUC: Area under the curve; CI: confidence interval.*

analyzed in this study, 21 (26%) patients developed renal impairment (Figure 1B). Previous studies have reported that a cumulative CDDP dose of approximately 200 mg/m^2 or more was sufficient to produce an antitumor effect in patients with head and neck cancer (7, 26, 27), and the therapeutic goals are set at a cumulative CDDP dose of 200 mg/m^2 or more. In this study, the renal impairment led to a much higher rate of dose reduction or discontinuation of CDDP administration in the second cycle (86% *vs*. 30%), a much lower completion rate of three cycles in CDDP-RT (24% *vs*. 75%), and a much lower rate of >200 mg/m^2 of total CDDP dosage (19% *vs*. 77%) compared to patients who did not develop renal impairment. The risk of renal impairment due to CDDP-RT was significantly higher in patients receiving CCB or patients with lower Hb levels and significantly lower in patients receiving PPI (Table II and Figure 2). Thus, the prevention of renal impairment by reducing risk factors may be helpful to improve the therapeutic efficacy of CDDP-RT therapy.

In this study, of the 25 patients receiving CCB undergoing CDDP-RT, 12 (48%) patients developed renal impairment (Table I). The risk of developing CDDP-induced renal impairment in patients receiving CCB was higher than that in patients not receiving CCB (Table II). Using a combination of antihypertensive agents (angiotensin-converting enzyme inhibitor/ARB and CCB) may increase the risk of renal impairment in esophageal cancer patients treated with fluorouracil and CDDP therapy (16). In addition, concomitant use of CCB reduces the relative dose intensity of CDDP and vinorelbine as adjuvant chemotherapy in patients with non-small cell lung cancer (28). Some CCBs are shown to increase renal accumulation of platinum in rats and enhance CDDP-induced renal impairment (29, 30). In addition, amlodipine increases CDDP-induced fibrosis area in a mouse model (31). The most common CCB administered to patients in this study was amlodipine (amlodipine for 24 patients and benidipine for one patient). Amlodipine mainly inhibits L-type calcium channels among all calcium channel subtypes (32). Inhibition of L-type calcium channel dilates afferent arterioles. Thus, the combined use of CCB (mainly amlodipine) may increase the risk of renal impairment possibly by increasing renal accumulation of platinum or by inducing glomerular hypertension through the dilation of renal afferent arterioles. Therefore, increased attention should be paid to the development of renal impairment when performing CDDP-RT for patients receiving CCB. There is also the possibility that other background factors, such as the presence of hypertension/cardiovascular disease, cause renal impairment. In this study, although concomitant use of ARB was not identified as a significant factor due to the small number of cases (Table I), unlike a previous report (16), caution should be applied to ARB, as well as CCB. Future studies should investigate the safety of regimens, such as weekly CDDP-RT with a less frequency of renal impairment for the above patients (10).

In contrast, of the 28 patients receiving PPI and CDDP-RT, only 4 (14%) patients developed renal impairment; however, the difference was not statistically significant (Table I). Multivariate analysis showed that the risk of developing CDDP-induced renal impairment in patients receiving PPI was lower than that in patients not receiving PPI (Table II). The combined use of some PPIs, such as lansoprazole and esomeprazole, reduces the risk of renal impairment in esophageal cancer or head and neck cancer patients treated with fluorouracil and CDDP therapy (18). Some PPIs inhibit organic cation transporter 2 transport (33), which is involved in CDDP uptake into renal tubular cells in *in vitro* cell experiments (13). Additionally, some PPIs have been shown to exert protective effects against CDDP-induced renal impairment in *in vitro* and *in vivo* experiments (34-37). These findings suggest that PPI may attenuate renal impairment by reducing renal accumulation of platinum. Recently, a randomized controlled trial has shown that pantoprazole prevents CDDP-induced renal impairment in patients with head and neck cancer (38). On the other hand, because association between PPI use and the development of acute kidney injury and chronic kidney disease has been reported (39, 40), it is necessary to re-evaluate the need for PPI in the case of chronic use, considering the risks and benefits. We hope that future studies will lead to the development of drugs that reduce CDDP-induced renal impairment.

In addition, Hb levels in patients who developed renal impairment were significantly lower than in those who did not develop renal impairment (Table I), and lower Hb level was a significant factor associated with the CDDP-induced renal impairment (Table II). This is consistent with previous findings that anemia is a risk factor for a steeper decline in GFR during CDDP chemotherapy (41). Anemia is often present in cancer patients either due to cancer treatment or the progression of cancer itself (42). The kidney is considered to be vulnerable to hypoxic damage because of the presence of an arterial-venous oxygen shunt. Continued chronic ischemia may damage kidney tissue, leading to renal impairment (43). Additionally, erythropoietin or hypoxia-inducible factor prolyl hydroxylase inhibitor has a protective effect against CDDP-induced renal impairment, as indicated by *in vitro* and *in vivo* experiments (44, 45). Therefore, more attention should be paid to the development of renal impairment when providing CDDP-RT to patients with lower Hb levels.

This study has a few limitations that must be considered. First, because this was a retrospective observational study with a limited number of patients, further research is needed to confirm our findings. Second, the concomitant drugs are classified according to their main pharmacological action, and the dosage and individual effects of drugs were not considered. To overcome the above-mentioned limitations, large-scale prospective studies are needed.

Conclusion

This study found that the risk of renal impairment due to CDDP-RT was significantly higher in patients receiving CCB or patients with lower Hb levels and significantly lower in patients receiving PPI. The results of the present study may contribute to devising therapeutic approaches to reduce the risk of CDDP-RT-induced renal impairment.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization: HK, SN, TT, SM; Data curation: HK, SN; Formal analysis; HK, SN; Investigation: HK, SN; Project administration: SM; Resources: SO, TS; Supervision: SM; Visualization: HK, SN; Writing – original draft: HK, SN; Writing – review & editing: YO, SO, TS, TT, SM.

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