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A risk scoring model to predict renal progression associated with postcontrast acute kidney injury in chronic kidney disease patients

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Abstract

Postcontrast acute kidney injury (AKI) occurs more frequently in patients with lower estimated glomerular filtration rate. We hypothesized that postcontrast AKI in chronic kidney disease (CKD) patients with distinct risk factors might be associated with accelerated renal progression.

We undertook this retrospective cohort study to develop and validate a risk scoring model for predicting renal progression. In a development dataset, 18,278 contrast-enhanced CT scans were performed in 9097 patients with CKD (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2) who were not undergoing dialysis. Postcontrast AKI was observed in 5.8% (1051/18,278) of all contrast-enhanced CTs with 7.6% (689/9097) of the total CKD patients. We investigated the 1-year renal outcome in 224 eligible patients. A risk scoring model was developed with multivariate regression analysis and was assessed in external validation (independent 154 patients).

Among 224 patients, 70 (31.3%) patients had progression of renal dysfunction at 1 year (defined as reduction in estimated GFR ≥25% at 1 year). A risk score of 4, 4, 6, 6, 7, or 6 was assigned to diabetes, baseline estimated GFR < 45 mL/min/1.73 m^2, hypertension, repeated contrast exposure, congestive heart failure, and persistent renal injury (defined as an elevation of serum creatinine ≥25% at 3 months), respectively. An increasing risk score was associated with renal progression. Of note, persistent renal injury was more prevalent in the progression group than in the non-progression group. The AUROC of the model in the development population was 0.765. In the validation dataset, however, the discriminative power decreased (AUROC = 0.653).

Our suggested model provided the risk of renal progression, aiding in predicting prognosis, counseling, and improving outcomes in CKD patients complicated by postcontrast AKI.

Abbreviations: AKI = acute kidney Injury, BUN = blood urea nitrogen, CI =confidence interval, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease, OR = Odds ratios, SD = standard deviation.

Keywords: chronic kidney disease, postcontrast acute kidney injury, renal outcomes, risk factors

1. Introduction

Postcontrast acute kidney injury (AKI) is a common iatrogenic complication. Kidney injury is usually transient and the patients recover within 7 to 10 days. However, persistent renal damage after contrast nephropathy has been reported in patients with high risk factors such as reduced renal function.[1] Postcontrast AKI could also cause severe kidney injury requiring dialysis and it has poor outcomes.

In particular, patients with chronic kidney disease (CKD) are at risk of developing postcontrast AKI.[2] Considering other diseases that cause CKD or are complicated by CKD, patients with CKD are easily exposed to contrast medium in various clinical situations such as contrast-enhanced computed tomography (CT), interventional procedure, or cardiac angiography. Currently, there are limited renoprotective strategies against postcontrast AKI. It is also difficult to assess the risk-benefit balance before performing contrast-enhanced CT in CKD patients due to lack of prediction probability of renal progression after postcontrast AKI. Previously, most of the studies were limited to evaluation of risk factors for postcontrast AKI occurrence and consecutive outcomes. Although recent observations about overestimation of contrast nephropathy exist,[3] the risks of nephrotoxicity are significant, especially in CKD

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population.[4] The aim of the present study was to identify the risk factors for renal progression in patients with CKD complicated by postcontrast AKI and to provide a clinical risk assessment tool for predicting 1-year renal outcome.

2. Materials and methods

2.1. Population and study protocol

From January 2013 to December 2014, 18,278 contrast-enhanced CTs were performed in 9097 patients with CKD with an estimated glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2, at least, for 3 months and not on dialysis in Asan Medical Center, a tertiary referral hospital. The development of postcontrast AKI was noted in 1051 (5.8%) contrast-enhanced CTs of 689 (7.5%) patients with CKD. From among these 689 patients, 465 patients were excluded due to incomplete data (n = 252), loss to follow-up (n = 145), subsequent kidney transplantation (n = 45), or death (n = 23). The 1st episode of postcontrast AKI in the remaining 224 patients was analyzed to identify the risk factors for renal progression and to develop a risk scoring model.

Before performing contrast-enhanced CT, hydration was given with N-acetylcysteine administration via oral or intravenous depending on whether performed in an inpatient or outpatient setting. The hydration volume and N-acetylcysteine dosage were not standardized. In general, 1 L of 0.9% saline was administered to the patient with N-acetylcysteine 600 mg 2 times a day for 2 days. Nonionic low-osmolarity iodinated contrast agents were used in all cases. The amount of contrast agent varied from 80 mL to 150 mL depending on different body regions, patient weight, and CT protocols.

External validation was performed in Dankook University Hospital. Among the 2031 patients with CKD who underwent contrast-enhanced CT scans from January 2010 to December 2014, a total of 154 (7.6%) patients who were complicated by postcontrast AKI and had available data were enrolled.

This study was approved by the Institutional Review Board of the Asan Medical Center and Dankook University Hospital. Informed consent was waived for electrical health record review.

2.2. Data collection and definitions

The study protocol was approved by the Local Ethics Committee. Baseline demographics included age, sex, body mass index, smoking habits (any smoking vs never smoking), mean blood pressure, diabetes, hypertension, congestive heart failure (ejection fraction below the normal range), liver cirrhosis, active cancer, peripheral vascular disease, solid organ transplantation, glomerulonephritis, vesicoureteral reflux, repeat contrast exposure (≥2 contrast- enhanced CT scans), and laboratory variables. Anemia was defined as a baseline hematocrit value < 39% for men and < 36% for women.[5] The risk factors were chosen based on previous studies.[6,7]

Postcontrast AKI was defined as an absolute increase in serum creatinine concentration of at least 0.5 mg/dL and/or a relative increase of at least 25% above the baseline serum creatinine level within 3 days after the administration of contrast medium.[8] Persistent renal injury was defined as an elevation of serum creatinine ≥25% at 3 months in comparison with baseline .[1] Transient renal injury was defined as partial or complete recovery of renal function (serum creatinine elevation < 25% at 3 months in comparison with baseline). Progression of renal dysfunction was defined as reduction in the estimated glomerular filtration rate (eGFR) ≥25% at 1 year in comparison with baseline.[9]

The eGFR was calculated using the re-expressed four-variable Modification of Diet in Renal Disease (MDRD) study equation with standardized serum creatinine concentration as follows: GFR = 186 × creatinine − 1.154 × age − 0.203 × (0.742 if female).[10]

2.3. Statistical analysis

Patient characteristics were compared using descriptive statistics. Categorical variables were presented as numbers with percentages and continuous variables were presented as means with standard deviations. Differences between the 2 groups were assessed by the Chi-square test or Fisher exact test for categorical variables and by Student *t* test for continuous variables. The development population was used for identifying univariate associations between clinical characteristics and renal progression. Multivariate logistic regression analysis was then performed to identify independent predictors of renal progression and to estimate odds ratios (OR) and tested for multicollinearity. Risk factors that were significant in the univariate analysis ($P \leq 0.1$) were available for selection in the final model. The estimated ORs from the logistic model were converted into an integer for the development of an easy-to-use risk score. The estimated ORs from the logistic model were used to give an integer of 2 to each 1 value of OR. The final risk score represented the sum of integer coefficients. Based on the frequencies of progression rate in relation to different risk scores, the patients were categorized into low-, moderate-, high-, and very high-risk groups corresponding to risk scores ≤ 7, 8–14, 15–21, and ≥22, respectively. The model 2 which had a larger AUROC was selected as the final model. Finally, the prognostic significance of risk score in 1-year renal progression rates was calculated. The risk scoring model was tested in the validation population. Model discrimination was assessed by the goodness-of-fit Hosmer–Lemeshow statistic, and its predictive performance was assessed by the c-statistic. All analyses were performed using R 2.10.1 (R Foundation for Statistical Computing, Vienna, Austria). Two-sided *P* values with a statistical significance level of .05 were used.

3. Results

Postcontrast AKI was observed in 1051 of the 18,278 (5.8%) CT scans performed in 689 of the 9097 (7.6%) patients with CKD. A total of 224 patients were analyzed and followed up for a year (Fig. 1). At the 1-year follow-up, 70 of the 224 (31.3%) patients showed progression of renal dysfunction. Detailed characteristics are shown in Table 1. The patients in the validation cohorts were older and had lower eGFR than those in the development cohorts. Between the progression and non-progression groups, diabetes, hypertension, congestive heart failure, repeat contrast exposure, blood urea nitrogen (BUN), creatinine, and eGFR were significantly different. Anemia was not significantly different between the progression and non-progression groups (85.7% vs 85.1%, $P = .899$). Severe postcontrast AKI requiring dialysis was also not significantly different between the 2 groups (20.0% *vs*. 18.8%, $P = .837$).

3.1. Renal outcomes

Figure 2 shows the time course of creatinine values in the 2 groups. Baseline creatinine values were 1.84 ± 0.75 mg/dL and 1.67 ± 0.60 mg/dL in the progression and non-progression groups, respectively ($P = .025$). Day 3 creatinine values were 3.22 ± 1.15 mg/dL and 2.87 ± 1.04 mg/dL in the respective groups

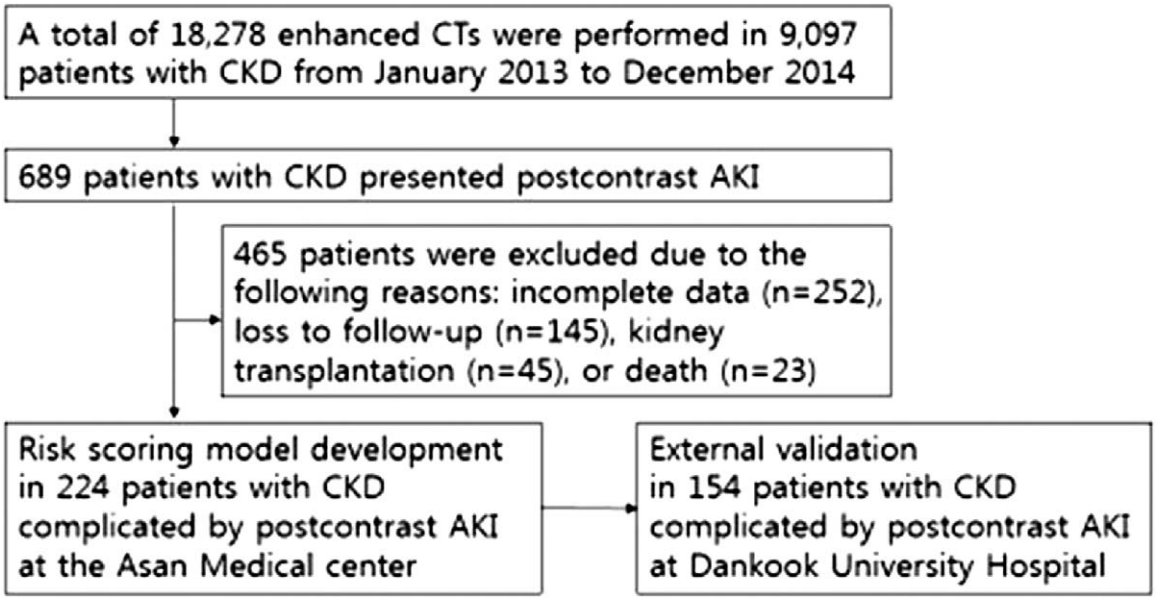

Figure 1. Flow of the inclusion of the study population.

($P = .064$), and the mean difference was 1.09 ± 1.00 mg/dL and 1.05 ± 0.66 mg/dL in the respective groups ($P = .788$). Thirty-day, 90-day, and 1-year creatinine values were 2.46 ± 1.13 mg/dL and 1.69 ± 0.84 mg/dL ($P < .001$), 2.38 ± 1.18 mg/dL and 1.55 ± 0.84 mg/dL ($P = .001$), and 3.25 ± 1.70 mg/dL and 1.43 ± 0.55 mg/dL ($P < .001$) in the respective groups. Although the mean difference was not significantly different, renal recovery status at 3 months (i.e., persistent renal injury) was significantly different between the 2 groups (40.0% vs 13.6%, $P < .001$).

3.2. Risk factors of renal progression

Univariate logistic regression identified 6 risk factors which were also valid in multivariate analysis (Table 2). We then developed a

Table 1

Baseline characteristics of the study population.

Variables	Development population (n = 224)	Validation population (n = 154)	*P* value
Age	63.2 ± 13.3	67.7 ± 13.5	.002
Age >75 years, n (%)	51 (22.8)	61 (39.6)	.001
Gender (male), n (%)	142 (63.3)	42 (60)	.477
Body mass index	22.8 ± 4.3	23.0 ± 5.2	.708
Smoking, n (%)	64 (28.6)	21 (13.6)	.001
Mean blood pressure	90.9 ± 13.8	93.2 ± 13.6	.110
Diabetes mellitus	111 (49.6)	70 (45.5)	.497
Hypertension	138 (61.6)	116 (75.3)	.007
Congestive heart failure	16 (7.1)	16 (10.4)	.354
Liver cirrhosis	36 (16.1)	21 (13.6)	.614
Active cancer	125 (55.8)	25 (16.2)	.001
Peripheral vascular disease	3 (1.3)	2 (1.3)	1.000
Solid organ transplantation	77 (34.4)	0 (0)	.001
Glomerulonephritis	46 (20.5)	13 (8.4)	.002
Polycystic kidney disease	2 (0.9)	0 (0)	.650
Vesicoureteral reflux	1 (0.4)	0 (0)	1.000
Repeat contrast exposure	39 (17.4)	4 (2.6)	.001
Laboratory variables			
Hemoglobin level (g/dL)	10.6 ± 1.9	10.5 ± 1.8	.669
Hematocrit (%)	31.1 ± 5.9	30.9 ± 8.2	.836
Platelet count (x10^3/mm^3)	174.5 ± 98.9	200.9 ± 113.0	.086
Albumin level (g/dL)	3.6 ± 0.7	3.4 ± 0.6	.014
BUN level (mg/dL)	29.2 ± 15.3	32.6 ± 15.2	.033
Creatinine level (mg/dL)	1.7 ± 0.7	1.9 ± 0.9	.002
eGFR (mL/min/1.73 m^2)	42.6 ± 13.3	38.8 ± 14.6	.010
Microscopic hematuria	110 (49.1)	59 (38.3)	.019

Data were expressed as mean ± SD or number and percentage (%).
BUN = blood urea nitrogen, eGFR = estimated glomerular filtration rate.

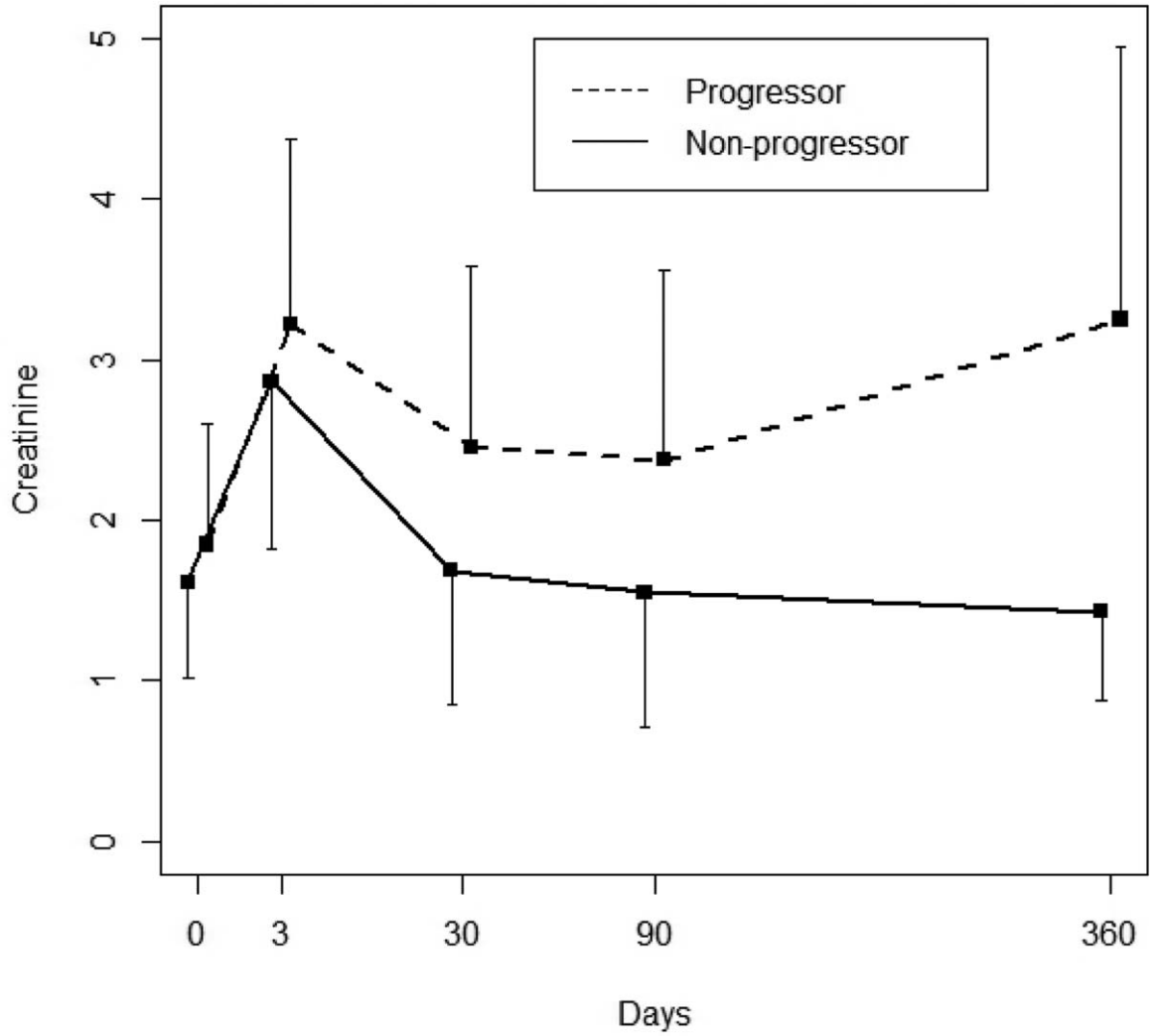

Figure 2. The time course of mean creatinine values. The bars give the standard deviation for each measurement.

risk scoring model based on a logistic analysis. A risk score of 4, 4, 6, 6, 7, or 6 was assigned to diabetes, baseline eGFR < 45 mL/min/1.73 m^2, hypertension, repeat contrast exposure, congestive heart failure, and persistent renal injury, respectively. An increasing risk score was associated with renal progression (value 10.1%, 29.5%, 65.8%, and 76.9% for a low, moderate, high, and very high risk score, respectively). Table 3 show the association of higher sum of the risk score with renal progression ($P < .001$). Figure 3 shows renal progression according to the risk score in the development and validation datasets. No significant change was observed in the AUROC after converting the regression coefficient-based model to the risk scoring model in a direct AUC–ROC comparison using the DeLong's test ($P > .05$). The AUROC of the model 1 and 2 in the development population was 0.712 (95% CI: 0.648–0.770) and 0.765 (95% CI: 0.697–0.833), respectively ($P < .05$ in a direct AUC-ROC comparison by

Table 2

Univariate and multivariate analyses of the risk factors of renal progression.

					Model 1: baseline parameters			Model 2: baseline and clinical course parameters		
		Univariate analysis			Multivariate analysis			Multivariate analysis		
Variables	Progression rate n (%)	β	OR (95% CI)	*P* value	β	OR (95% CI)	*P* value	β	OR (95% CI)	*P* value
Intercept					−2.247		<.001	−2.781		<.001
Diabetes mellitus	44 (39.6)	0.787	2.197 (1.230–3.925)	.008	0.673	1.960 (1.055–3.643)	.033	0.705	2.024 (1.049–3.903)	.035
Hypertension	54 (39.1)	1.034	2.812 (1.480–5.343)	.002	0.950	2.585 (1.324–5.047)	.005	1.004	2.728 (1.338–5.562)	.006
Congestive heart failure	10 (62.5)	1.414	3.639 (1.242–10.665)	.019	1.159	3.185 (1.020–9.943)	.046	1.244	3.471 (1.052–11.454)	.041
eGFR <45 mL/min/1.73 m^2	40 (40.4)	0.764	2.147 (1.209–3.812)	.009	6.597	2.226 (1.209–4.098)	0.010	0.723	2.061 (1.081–3.929)	.028
Repeat contrast exposure	20 (51.3)	1.045	2.680 (1.331–5.395)	.006				1.176	3.241 (1.445–7.266)	.004
Persistent renal injury	28 (57.1)	1.440	4.222 (2.174–8.199)	<.001				1.116	3.053 (1.475–6.322)	.003

β = regression coefficient, CI = confidence interval, eGFR = estimated glomerular filtration rate, OR = odds ratio

Table 3

Risk of renal progression in the development (A) and validation (B) population assessed using the sum of risk score.

A				
Sum of risk score		**Progression**	**Non-progression**	**Risk of progression**
Low	≤7	8	71	10.1%
Moderate	8–14	28	67	29.5%
High	15–21	13	25	65.8%
Very high	≥22	10	3	76.9%
B				
Sum of risk score		**Progression**	**Non-progression**	**Risk of progression**
Low	≤7	27	18	60.0%
Moderate	8–14	53	31	63.1%
High	15–21	18	3	85.7%
Very high	≥22	4	0	100%

Delong's test between the models). The Hosmer–Lemeshow Chi-square value of model 2 was 3.366 ($P = .909$).

3.3. Model validation

In the validation population, because of poor performance when using baseline parameters alone (Model 1: AUC–ROC: 0.592, 95% CI: 0.510–0.671), we adopted the model that included baseline and clinical course parameters as the final model (Model 2: AUC–ROC: 0.653, 95% CI: 0.572–0.728, $P < .05$ in a direct AUC–ROC comparison with Model 1 using the Delong's test). The Hosmer–Lemeshow Chi-square value of model 2 was 4.401 ($P = .733$).

4. Discussion

The present study showed that overall postcontrast AKI incidence in patients with CKD was 7.6%, and among those, renal progression rate was as high as 31.3%. Risk factors for progression identified in our study were similar to those for postcontrast AKI occurrence in previous studies. We scored the risk factors that were easily measured in clinical practice and then provided a model to predict the risk of renal progression. Of note, the patients who did not recover renal function at 3 months, in comparison with those who recovered, were at a higher risk of renal progression.

Postcontrast AKI occurred in 7 to 15% of patients in a heterogeneous population who needed a diagnostic or therapeutic evaluation,[2] which was comparable with that in our study. Among them, patients with CKD who had multiple co-morbidities were at high risk of developing postcontrast AKI. Compared with non-enhanced CT, contrast-enhanced CT is rated higher in the evaluation of acute abdominal pain and fever or suspected abdominal mass, urogenital cancer diagnosis and follow-up, and bowel obstruction.[11] However, clinicians are also concerned about the risk of contrast reaction that offsets the benefit of contrast enhancement. For facilitating a decision, we developed a practical model to stratify the risk of renal progression.

In the present study, we found 6 risk factors for renal progression. The patient- related characteristics (i.e. diabetes, hypertension, congestive heart failure, and low eGFR) are well-known risk factors for postcontrast AKI occurrence.[12–14] In addition, clinical course-related characteristics (i.e. repeat contrast exposure and persistent renal injury) were identified. Previously, repeated contrast exposure was a significant risk factor for postcontrast AKI in subjects with even relatively

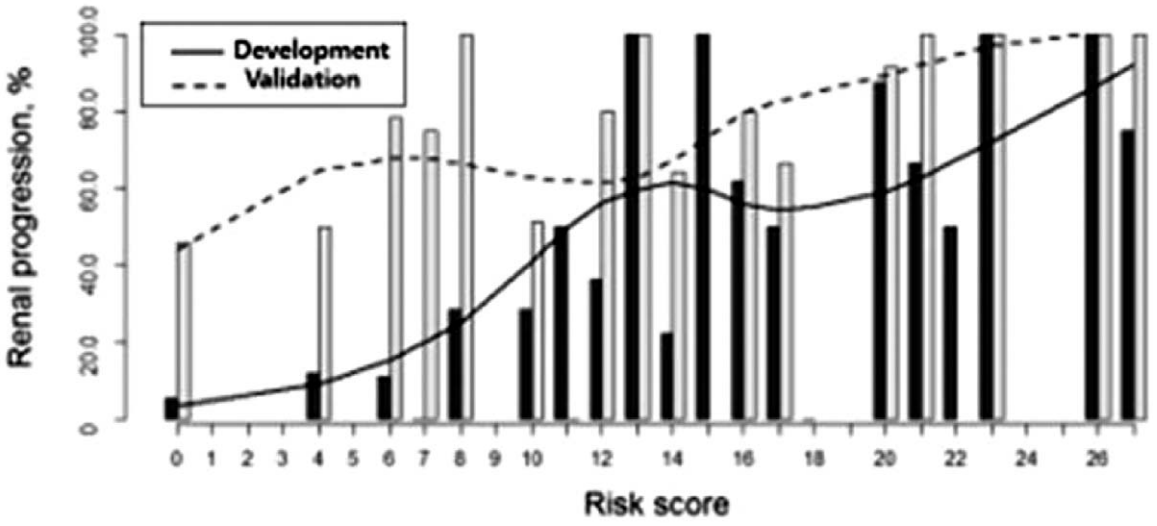

Figure 3. The association between risk score and renal progression in the development and validation datasets.

preserved renal function.[15] Anemia was suggested as one of the risk factors for postcontrast AKI.[6] However, we could not identify the association of anemia with renal progression. Anemia was already prevalent (85.3%) before performing contrast-enhanced CT, which was one of the inherent characteristics of the CKD population.

Postcontrast AKI portends major adverse events including renal and patient outcomes.[16] Although a transient decrease in GFR occurs after contrast administration in most patients,[17] permanent[1] or even continuous deterioration[18] of renal function was documented in selected patients. Residual renal impairment has been observed in as many as 30% of those affected by postcontrast AKI,[19] which was similar to our findings. Maioli et al[1] reported that persistent renal damage was found in 18.6% of postcontrast patients with AKI undergoing coronary angiography. Long-term patient, renal, and cardiovascular outcomes in postcontrast patients with AKI were worse than those in patients with transient renal damage. Conversely, transient postcontrast acute kidney injury did not increase the risk of accelerated renal progression.[20] Contrast medium was not associated with an increased risk of end-stage renal disease (ESRD) in nonadvanced CKD.[21] However, 21.9% of patients with CKD including a broad range of renal dysfunction who developed postcontrast AKI in our present study did not recover renal function and were at risk of renal progression. A continuum of renal injury was suggested.[22]

The mechanisms of postcontrast AKI with permanent renal damage need further evaluation. The pathogenesis appeared to be the result of direct tubular epithelial cell toxicity and medullary ischemia.[12] The nature of the contrast, associated ions, concentration, and the osmolality also matter. In the present study, we observed that postcontrast AKI was not transient in all patients. It is clinically relevant that patients with multiple risk factors are endangered with renal progression even by single exposure to contrast-enhanced CT. Chronic kidney disease might be accelerated after postcontrast AKI in these vulnerable patients with a limited renal reserve and comorbidity that increase as CKD progresses. We suggest that the benefits of contrast CT should be weighed against the risks of accelerated renal progression in CKD population.

There were several limitations in the present study. First, the causal link between iodinated contrast and nephrotoxicity has been continuously questioned in recent studies.[3,23] The lack of information about clinical indications for the CT scan in the present study further limited the understanding of causality. However, although the incidence of postcontrast AKI might has been overestimated in real-world practice, preexisting renal impairment is undoubtedly at high risk of postcontrast AKI.[12] An increased risk of dialysis was observed in patients with eGFR < 45 in the critical care setting ,[24] although there was no increased risk of postcontrast AKI in patients with mildly reduced renal function. Second, we could not investigate the amount of proteinuria, which is a strong indicator of renal progression. Third, although the model showed fair discrimination performance in the development population, progression in the validation population was found to be more prevalent than we had predicted, thus leading to inferior model performance in the validation population. We acknowledged that a large proportion of the population was excluded inadvertently. Although considering both populations were heterogeneous, further identification of predictors of renal progression is needed. Finally, we added the parameters that could be obtained only during the clinical course because baseline parameters alone showed a poor model performance.

5. Conclusions

The renal progression in patients with CKD who were at risk of postcontrast AKI occurrence was not negligible and the renal trajectories after postcontrast AKI were different among patients. The progression group did not show renal recovery from postcontrast AKI at 3 months in contrast to non-progression group, suggesting the possibility of development of permanent renal damage after postcontrast AKI. It is not always possible to avoid performing a contrast-enhanced-CT scan at the cost of the diagnostic accuracy, especially during a critical situation. Our validated tool might help clinicians who are counselling patients with CKD to decide on ordering contrast-enhanced CT and to predict renal progression.

Author contributions

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Writing – review & editing: Seung Don Baek, So Mi Kim, Jae-Young Kang, Eun Kyoung Lee, Jai Won Chang.

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