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【 ORIGINAL ARTICLE 】

Applicable Machine Learning Model for Predicting Contrast-induced Nephropathy Based on Pre-catheterization Variables

Heejung Choi[1], Byungjin Choi[2], Sungdam Han[3], Minjeong Lee[1], Gyu-Tae Shin[1], Heungsoo Kim[1], Minkook Son[4], Kyung-Hee Kim[5], Joon-myoung Kwon[6-8], Rae Woong Park[2,9] and Inwhee Park[1]

Abstract:

Objective Contrast agents used for radiological examinations are an important cause of acute kidney injury (AKI). We developed and validated a machine learning and clinical scoring prediction model to stratify the risk of contrast-induced nephropathy, considering the limitations of current classical and machine learning models.

Methods This retrospective study included 38,481 percutaneous coronary intervention cases from 23,703 patients in a tertiary hospital. We divided the cases into development and internal test sets (8:2). Using the development set, we trained a gradient boosting machine prediction model (complex model). We then developed a simple model using seven variables based on variable importance. We validated the performance of the models using an internal test set and tested them externally in two other hospitals.

Results The complex model had the best area under the receiver operating characteristic (AUROC) curve at 0.885 [95% confidence interval (CI) 0.876-0.894] in the internal test set and 0.837 (95% CI 0.819-0.854) and 0.850 (95% CI 0.781-0.918) in two different external validation sets. The simple model showed an AUROC of 0.795 (95% CI 0.781-0.808) in the internal test set and 0.766 (95% CI 0.744-0.789) and 0.782 (95% CI 0.687-0.877) in the two different external validation sets. This was higher than the value in the well-known scoring system (Mehran criteria, AUROC=0.67). The seven precatheterization variables selected for the simple model were age, known chronic kidney disease, hematocrit, troponin I, blood urea nitrogen, base excess, and N-terminal pro-brain natriuretic peptide. The simple model is available at http://52.78.230.235:8081/

Conclusions We developed an AKI prediction machine learning model with reliable performance. This can aid in bedside clinical decision making.

Key words: acute kidney injury, contrast-induced nephropathy, percutaneous coronary intervention, machine learning, risk assessment, clinical decision making

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[1]Department of Nephrology, Ajou University School of Medicine, Korea, [2]Department of Biomedical Informatics, Ajou University School of Medicine, Korea, [3]Malgundam Internal Medicine Clinic, Korea, [4]Department of Physiology, College of Medicine, Dong-A University, Korea, [5]Department of Cardiology, Cardiovascular Center, Incheon Sejong Hospital, Korea, [6]Department of Critical Care and Emergency Medicine, Incheon Sejong Hospital, Korea, [7]Artificial Intelligence and Big Data Research Center, Sejong Medical Research Institute, Korea, [8]Medical Research Team, Medical AI, Korea and [9]Department of Biomedical Sciences, Ajou University Graduate School of Medicine, Korea
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Correspondence to Dr. Inwhee Park, inwhee@aumc.ac.kr

Introduction

Iodine contrast agents used for radiological examinations are an important cause of acute kidney injury (AKI) in hospitals (1). Contrast angiography is currently widely applied for diagnostic and therapeutic purposes, and its use is increasing. This has led to an increased risk of iatrogenic kidney dysfunction due to exposure to contrast agents, a condition known as contrast-induced nephropathy (CIN). In a previous report, CIN accounted for 11% of hospital-acquired kidney insufficiency cases and was the third-most common cause of hospital-induced AKI (2). Coronary angiography and percutaneous coronary intervention (PCI) are among the most common causes of CIN (2). Although CIN is generally reversible, active prevention and treatment are needed, as CIN can lead to an extended hospital stay and an increased occurrence of complications and mortality (3-5).

Multiple strategies have been successful in preventing CIN, including fluid administration (6, 7), minimizing the contrast dose (8), and using iso- and low-osmolar contrast media (9, 10). Therefore, it is important to identify patients who are likely to develop postinterventional CIN and subsequently initiate preventive strategies to preserve the kidney function. As a result, certain risk prediction tools or risk models have been reported as capable of predicting the incidence of CIN. The Mehran score is the most widely used prediction method for CIN in patients hospitalized for acute coronary syndrome who have undergone coronary angiography (11). However, because the Mehran criteria use intraintervention variables, such as contrast volume, there are limitations in accurately predicting the preprocedural risk. Although CIN prediction models using other variables have recently been developed (12, 13), they have been limited to classical statistical techniques. The adoption of electronic medical record (EMR) technology has led to the notable accumulation of medical data. Recent machine learning techniques have been employed more frequently than classical statistical methods for identifying reliable predictive patterns in EMR and improving predictive performance (14-16). Furthermore, machine learning techniques have been used to predict CIN after PCI (17-19). Although machine learning-based predictive models have been shown to have better predictive capabilities, they typically use large numbers of variables, which makes their use in actual clinical practice difficult.

The present study developed a CIN prediction machine learning model with high accuracy using only an applicable number of variables.

Materials and Methods

Data preparation

From January 1994 to January 2021, we extracted all PCI cases at tertiary education hospitals regardless of whether they were inpatients or outpatients [Ajou University Medical Center (AUMC), Suwon, South Korea], and the intervention date was set as the index date. We divided the AUMC data into development and internal test cohorts (8:2) on a patient basis. We excluded patients who had a history of end-stage renal disease or hemodialysis and a history of PCI within one year prior to the index date and those who did not have a medical record for at least one year before the PCI. For external validation of the model, we extracted patient data from March 2010 to December 2019 from two hospitals - a government-certified cardiology hospital [Bucheon Sejong Hospital (BSH), Bucheon, South Korea] and a community-based general hospital [Incheon Sejong Hospital (ISH), Incheon, South Korea] - by applying the same inclusion and exclusion criteria.

We extracted data regarding 23,703 patients and 38,481 PCI procedures from AUMC, 9,364 patients and 433 cases from BSH, and 874 patients and 27 cases from ISH.

We extracted the patients' sex, age, drug, diagnosis, and laboratory records from electronic medical records. The age covariate was divided into five-years groups; drug covariates were grouped by the drug ingredient, regardless of drug brand; and use in the past year was considered as a binary variable. As a disease covariate, we used whether or not a patient had been diagnosed with a specific International Classification of Diseases code in the last year. For laboratory records, based on whether the test value was above, within, or below the normal range, the nearest laboratory value was categorized and used as a variable. To avoid a postintervention data gap due to data entry inconsistency in hospitals, variables from the day of the procedure were removed.

For the imputation of missing data, MissForest was used (20). It imputes missing values using a random forest trained on the observed values of a data matrix to predict the missing values. It can be used to impute continuous and categorical data.

The clinical outcome was the occurrence of AKI within three days after PCI. AKI was judged to have occurred when one of the following two conditions was satisfied based on individual creatinine tests, according to the Kidney Disease Improving Global Outcomes criteria: an individual creatinine test result higher than the minimum creatinine test value of the past 2 days by ≥0.3 mg/dL; or an increase in creatinine ≥1.5× the average value of the past seven days (21).

This study followed the Declaration of Helsinki and was approved by the Institutional Review Board of Ajou University Medical Center (approval No. AJIRB-MED-MDB-21-196). The requirement for informed patient consent was waived. All data transformed into the common data model were deidentified.

The database used in this study was standardized with the observational medical outcomes partnership common data model, which is an international clinical standardization system maintained by the Observational Health Data Sciences

and Informatics community (22).

Model development

A total of 11,092 diagnosis, prescription, and laboratory variables were extracted from the EMR. We applied a total of five machine learning algorithms: gradient boosting machine (GBM), random forest, lasso logistic regression, decision tree, and Adaboost (23-27). In addition, we constructed a classical logistic regression model as a baseline to provide a comparative benchmark for our machine learning algorithm (28). We performed five-fold validation of the development dataset for algorithm selection. The performance of each algorithm was ranked according to the mean area under the receiver operating characteristic (AUROC) curve of the cross-validation set. A grid search was used for the optimal hyperparameters for each algorithm. Additional details on the hyperparameter selection are provided in Supplementary material 1.

Based on variable importance, the top seven variables were selected from the complex model. The Mehran criteria, the most popular CIN prediction model, uses eight variables (29). Using machine learning algorithms, we attempted to develop a higher-performance model with even fewer pre-intervention variables. We then trained the machine learning model using only the seven selected variables (simple model). Finally, we validated the performance of the complex and simple models using the internal test set and two external validation sets.

After model development, we calculated feature importance by implementing the gain importance method and created a feature importance plot. To validate the robustness of the model, subgroup analyses were conducted for sex and age. Sex was divided into "man" and "woman," and age was divided into 5 categories of <50, 50-60, 60-70, 70-80, and ≥ 80 years.

Due to concerns about the different cohort data collection periods for the model development hospitals and the external validation hospitals, we developed a subanalysis model that only used the time-synchronized data from the training dataset (collected from 2010-2019) and validated it in the validation dataset before comparing it to the main model.

As a subanalysis, we generated a balanced dataset by resampling the 1:1 ratio of outcomes from the training dataset and developed a machine learning model. We then compared the model developed with the balanced dataset (balanced model) and the model developed with the whole dataset (original model).

Statistical analyses

To validate the performance of the machine learning model, we compared the predictive probability of the machine learning model with the actual occurrence of AKI in the test dataset. For this purpose, the AUROC and average precision (AP) were calculated. The confidence interval of the AUROC was calculated using the DeLong test (30).

We computed the optimal threshold using Youden-J statistics for a detailed model performance evaluation. We plotted a confusion matrix using the optimal threshold and calculated the recall, precision, J statistic, and F1 score for the internal and external validation datasets.

For baseline characteristics, we used the unpaired Student's *t*-test to compare and present the mean values and standard deviations of the continuous variables. The categorical variables were described as percentages and compared using the χ^2 test.

This study was designed using the patient-level prediction R package version 4.0.5, and R 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for the statistical analysis.

Results

Baseline characteristics of the patients

A flowchart of the patients is shown in Fig. 1. In total, 24,187 patients from AUMC underwent PCI during the study period. A total of 484 patients were excluded owing to the exclusion criteria or hemodialysis. A total of 23,703 patients and 38,481 cases were included in the study. CIN occurred after 1,185 procedures (3.1%). In the external validation dataset from BSH, 9,364 patients underwent 11,105 PCI procedures, of whom 433 developed CIN (3.9%). In the ISH dataset, 874 patients underwent 960 PCI procedures, of whom 27 developed CIN (2.8%).

Detailed baseline characteristics of the study cohort are presented in Table 1. We observed statistically significant differences in the baseline characteristics between groups with and without CIN. Chronic kidney disease (CKD) patients showed the largest difference, with only 2% being noted in the group without CIN and 31.7% in the group with CIN.

Model development

As a result of the algorithm selection, GBM showed the best performance in 5-fold cross validation. The performance of each algorithm is summarized in Supplementary material 2.

We applied the GBM algorithm to all extracted variables. Seven variables were selected to produce a simple model based on the variable importance of the complex model, including the age, history of CKD, hematocrit result, troponin I level, blood urea nitrogen (BUN) level, base excess, and N-terminal pro-brain natriuretic peptide (NT-proBNP) level. The feature importance plot is depicted in Supplementary material 3.

Model performance

The performance of the models is illustrated in Fig. 2. The complex model had the best AUROC at 0.885 [95% confidence interval (CI) 0.876-0.894] and AP at 0.393. In the external test, the AUROC was 0.837 (95% CI 0.819-0.854) for an AP of 0.204 and 0.850 (95% CI 0.781-0.918)

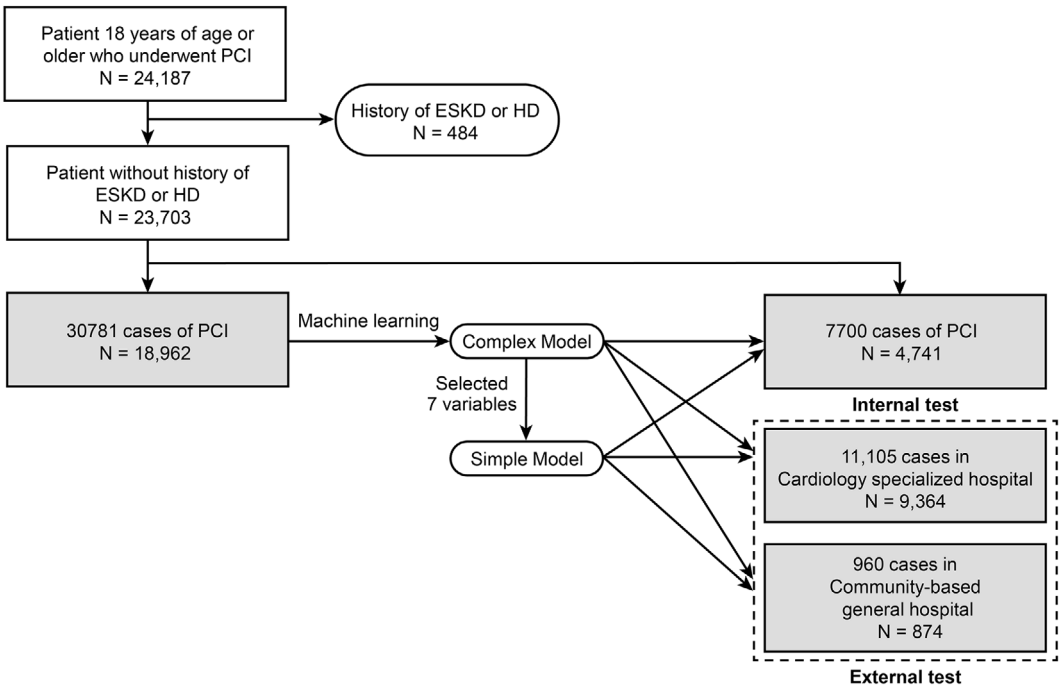

Figure 1. Flow chart of participants. All coronary intervention cases in a tertiary teaching hospital between January 1994 and January 2021 (AUMC: Ajou University Medical Center, Suwon, South Korea). In total, 24,187 patients underwent PCI during the study period in AUMC. Patients who had a history of ESRD, HD, or PCI within one year prior to the index date and patients who did not have a medical record for at least one year before the coronary intervention were excluded. After exclusion, 23,703 patients and 38,481 cases were included in the study. The AUMC data were divided into development and internal test cohorts (8:2) on a patient basis. ESRD: end-stage renal disease, HD: hemodialysis, PCI: percutaneous coronary intervention

Table 1. Baseline Characteristics of Patients.

	No CIN	CIN	p value
Total, cases (%)	37,296 (96.9)	1,185 (3.1)	
Age, mean (SD)	62.4 (11.2)	66.4 (12.4)	<0.001
Sex (male), n (%)	24,541 (65.8)	742 (62.6)	0.016
Heart valve disorder, n (%)	904 (2.4)	122 (10.3)	<0.001
Type 2 DM, n (%)	6,567 (17.6)	345 (29.1)	<0.001
Use of furosemide on the day of the coronary intervention, n (%)	2,171 (5.8)	507 (42.8)	<0.001
Use of artificial respiration on the day of the coronary intervention, n (%)	294 (0.8)	158 (13.3)	<0.001
Transfusion on the day of the coronary intervention, n (%)	380 (1.0)	190 (16.0)	<0.001
Central venous catheter on the day of the coronary intervention, n (%)	323 (0.9)	127 (10.7)	<0.001
ACE inhibitor or ARB, n (%)	5,774 (15.5)	291 (24.6)	<0.001
NT-pro-BNP level >115 pg/mL, n (%)	1,363 (3.7)	281 (23.7)	<0.001
Chronic kidney disease, n (%)	732 (2.0)	376 (31.7)	<0.001

Baseline characteristics calculated from hospital patients were used in model development and internal validation (AUMC: Ajou University Medical Center).

Continuous variables were compared using Student's *t*-test. Categorical variables were compared using the χ^2te*st.*

ACE: angiotensin-converting enzyme, ARB: angiotensin II receptor blocker, CIN: contrast-induced nephropathy, DM: diabetes mellitus, NT-proBNP: N-terminal pro-brain natriuretic peptide

for an AP of 0.231. The simple model showed an AUROC of 0.795 (95% CI 0.781-0.808) and AP of 0.235 in the internal test and 0.766 (95% CI 0.744-0.789) for an AP of 0.127 and 0.782 (95% CI 0.687-0.877) for an AP of 0.158 for the BSH and ISH datasets. Otherwise, the baseline model, which was developed with the classical logistic regression algorithm, showed an AUROC of 0.652 (95% CI 0.615-0.689) and AP of 0.083. In the external test, the AUROC was 0.673 (95% CI 0.612-0.735) with an AP of 0.093 and 0.671 (95% CI 0.65-0.693) with an AP of 0.1. More model metrics, including the confusion matrix and J-statistics, are detailed in Supplementary material 4. In addi-

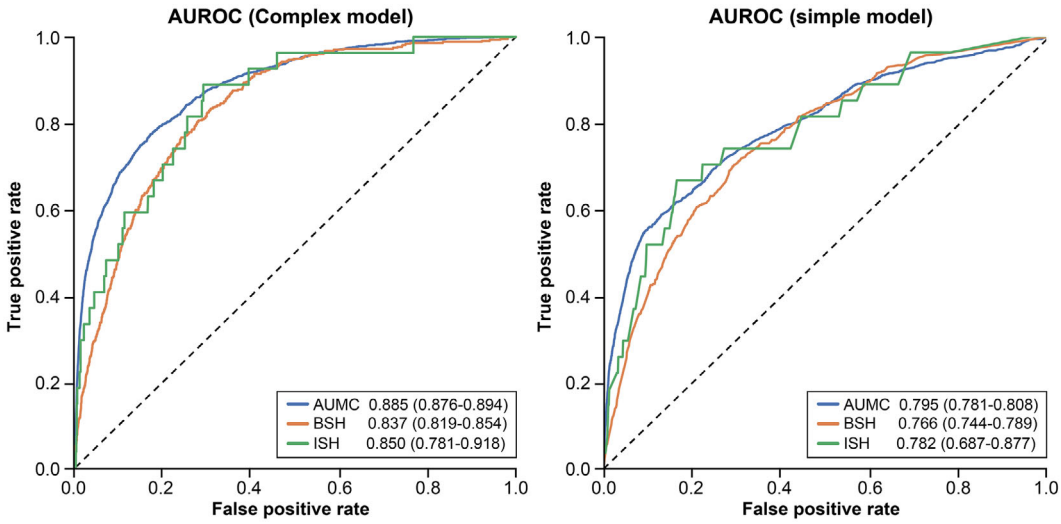

Figure 2. Performance of models. Machine learning models with all extracted variables from electronic medical records (complex model) and by restricting the number of variables to seven (simple model) were developed. After development, the predictions were calculated from the model using an internal test set (AUMC: Ajou University Medical Center) and two external test sets (BSH: Bucheon Sejong Hospital, ISH: Incheon Sejong Hospital). Finally, an AUROC (area under the receiver operating characteristic) curve was illustrated for each model.

Table 2. Subgroup Analysis.

	AUMC	BSH	ISH
Complex model			
Male	0.881 (0.870-0.893)	0.843 (0.819-0.868)	0.876 (0.819-0.932)
Female	0.892 (0.878-0.905)	0.822 (0.796-0.848)	0.818 (0.655-0.981)
Age < 50	0.886 (0.858-0.914)	0.899 (0.852-0.945)	0.972 (0.956-0.999)
50 ≤ Age < 60	0.894 (0.872-0.916)	0.836 (0.784-0.888)	0.957 (0.929-0.985)
60 ≤ Age < 70	0.902 (0.886-0.919)	0.87 (0.838-0.902)	0.892 (0.818-0.966)
70 ≤ Age < 80	0.847 (0.828-0.865)	0.797 (0.765-0.830)	0.618 (0.372-0.864)
80 ≤ Age	0.823 (0.792-0.853)	0.775 (0.723-0.828)	0.874 (0.749-0.999)
Simple model			
Male	0.786 (0.769-0.803)	0.785 (0.755-0.814)	0.797 (0.682-0.912)
Female	0.809 (0.788-0.830)	0.738 (0.703-0.774)	0.759 (0.577-0.940)
Age < 50	0.777 (0.733-0.821)	0.766 (0.640-0.892)	0.992 (0.971-1.000)
50 ≤ Age < 60	0.792 (0.758-0.827)	0.752 (0.685-0.819)	0.856 (0.660-1.000)
60 ≤ Age < 70	0.804 (0.778-0.830)	0.784 (0.741-0.827)	0.815 (0.645-0.985)
70 ≤ Age < 80	0.769 (0.744-0.793)	0.717 (0.677-0.757)	0.524 (0.220-0.828)
80 ≤ Age	0.729 (0.689-0.769)	0.692 (0.633-0.752)	0.804 (0.666-0.943)

A machine learning model with all extracted variables from electronic medical records (complex model), and a simplified model developed by restricting the number of variables to seven (simple model). To validate the robustness of the developed models regardless of sex and age, the area under the receiver operating characteristic curve and 95% confidence interval in each subgroup were calculated. Each calculation was performed using an internal test set (AUMC: Ajou University Medical Center) and two external test sets (BSH: Bucheon Sejong Hospital, ISH: Incheon Sejong Hospital).

tion, we publicly opened the simple model as a web application (http://52.78.230.235:8081/).

In the subgroup analysis, the performance of the complex model was >0.775, except for in the 70 to <80 years old group for the ISH dataset. In addition, the performance of the simple model was >0.692, except for in the 70 to <80 years old group for the ISH dataset. Detailed results of the subgroup analysis for sex and age are presented in Table 2.

Detailed results of the subanalysis are depicted in Supplementary material 5. In subanalyses of synchronizing the collection time of hospitals, the model without synchronization shows superior performance to the synchronized model.

In subanalyses with outcome balancing, the model without outcome balancing surpasses the model developed on the balanced dataset in internal and external validation. Detailed results of the subanalysis are depicted in Supplemen-

tary material 6.

Discussion

We developed a machine learning model to predict AKI in patients after PCI. The complex prediction model showed an AUROC of 0.885 (95% CI 0.876-0.894) in the internal test set and 0.837 (95% CI 0.819-0.854) and 0.850 (95% CI 0.781-0.918) in two different external validation sets. Based on the complex model, we created an easy-to-use prediction model. The seven variables selected for the simple model were the age, history of CKD, hematocrit result, troponin I level, BUN level, base excess, and NT-pro-BNP level. The simple model showed an AUROC of 0.795 in the internal test set and 0.766 (95% CI 0.744-0.789) and 0.782 (95% CI 0.687-0.877) in the two different external validation sets. In addition, we publicly opened up the simple model as a web application for convenient application in clinical practice.

Predicting CIN has important clinical implications. The Mehran score is the most widely used prediction method for CIN in patients undergoing coronary angiography (11). However, the score includes intraprocedural variables, such as contrast medium volume, which limits the preprocedural risk evaluation (11). To overcome these limitations, Tsai et al. (12) proposed a risk prediction model that used only preprocedural variables; however, the prediction performance was insufficient, with an AUROC of 0.72.

Recently, high-performance predictive models based on machine learning have been developed. However, their application in clinical practice is difficult, as numerous variables are required for prediction (17-19, 31). For applicability, a high-performance model using a small number of variables was needed.

In our study, we developed a complex prediction model initially created with 11,092 variables extracted from EMRs. Subsequently, we distilled the complex model using a data-driven method and finally developed a simple model. The simple model can predict AKI by using 7 variables, which is fewer than the number of variables in the Mehran score (8 variables) or Tsai's model (11 variables), but the risk prediction yielded an AUROC of 0.795, which is superior to that of the Mehran score (AUROC=0.67) or Tsai's model (AUROC=0.72). In addition, unlike the Mehran score, which requires intraprocedural variables, this simple model included only preprocedural variables, which makes it possible to predict the risk of CIN before using contrast.

Furthermore, our model requires fewer variables than the previously developed CIN risk prediction model based on machine learning, which requires more than 12 variables (17-19, 31). Yin's model (18) exhibits impressive performance with a parsimonious set of 13 variables. However, it is noteworthy that the study was conducted exclusively in a single hospital without any external validation. Yin's model outperforms Gurm's model (17), which is the second-best, by a margin of 0.067 AUROC units, despite having fewer variables. This observation raises a concern about potential overfitting. Sun's model (31) was similarly developed within a single hospital. Otherwise, our model showed robust performance metrics in multiple hospitals, demonstrating an AUROC of 0.795 in internal validation and 0.782 and 0.766 in external validation settings. In addition, Gurm's model has been evaluated in several medical institutions, requiring specialized assessments such as left ventricular ejection fraction (LVEF) measurements, which may incur additional costs and medical procedures. Our research findings led us to assert that our model exhibits greater clinical utility than Gurm's model, given its reliance on routine laboratory and diagnostic tests.

Our model was developed at a tertiary teaching hospital. However, it received multicenter validation in hospitals of various levels, showing particularly favorable results in community-based hospitals, which often have a shortage of medical resources (AUROC=0.782).

In the subgroup analysis, the difference in model performance according to sex was insignificant. When grouped by age, the AUROC in the subgroup did not fall more than 0.05 for the entire group, except for the 70 to <80 years old group for the ISH dataset and the ≥ 80 years old group for the BSH dataset. This result is thought to be mainly because 50- to 70-year-old patients comprised the majority of participants. Further studies are needed to obtain more data on older adults.

The seven variables used in the simple model were selected from the complex model based on variable importance and included the age, history of CKD, hematocrit, troponin I level, BUN level, base excess, and NT-pro-BNP level. Age and CKD are well-known risk factors for CIN (32, 33) and have been included in many previously developed CIN predictive models (34). Several studies have reported that the hematocrit result (35), BUN level (36, 37), and pro-BNP level (38-40) are related to CIN. In addition, as CIN is more common in emergent PCI following ST segment-elevation myocardial infarction than in elective PCI (41, 42), we can speculate that troponin I levels may be a risk factor for developing CIN. Base excess is not a well-known risk factor for CIN. This might be the first study to include base excess to estimate the risk of CIN. Nonetheless, as base excess is an indicator of hypoperfusion and hypotension (leading to hypoperfusion) can be a risk factor for CIN (43, 44), we can hypothesize that base excess is related to CIN. Further studies are needed to determine the association between base excess and the risk of CIN.

Several limitations associated with the present study warrant mention. First, it was a retrospective, single-nation study. We conducted multicenter validation in hospitals of various levels, and the model robustness for other countries or ethnic groups has not been validated. Further multinational studies are needed. Second, we did not include the amount of urine output because of incomplete urine output data. Although urine output was also excluded in several AKI studies (18, 45), this omission may have excluded AKI patients with decreased urine output but not increased cre-

atinine levels (46, 47). Third, it was challenging to extract information from patients without pre-PCI hospital records. To avoid this limitation, we only included patients who had medical records for at least one year before the index date of PCI.

In conclusion, we developed an applicable and simple CIN prediction model. Using machine learning techniques, our model requires fewer variables than do the Mehran criteria and shows a higher performance as well. We also validated the robustness of the model at multiple centers at various levels. In addition, we opened our model publicly as a web application for easy clinical applications.

The authors state that they have no Conflict of Interest (COI).

Heejung Choi and Byungjin Choi contributed equally to this work.

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