Table 9. Multivariate Logistic Regression Analysis on Bleeding Complications within 72 Hours in Patients without Cardiogenic Shock.

	Univariate			Multivariate		
	OR	95% CI	p Value	OR	95% CI	p Value
Age	1.04	1.03–1.05	<0.001	1.02	1.01–1.04	<0.001
Female gender	2.29	1.77–2.96	<0.001	1.82	1.38–2.38	<0.001
BMI	0.89	0.86–0.93	<0.001	0.95	0.91–0.98	0.006
Previous PCI	0.60	0.45–0.78	<0.001	0.69	0.51–0.92	0.012
Previous HF	2.12	1.50–2.93	<0.001	1.55	1.07–2.20	0.021
PAD	1.27	0.82–1.88	0.273			
COPD	1.59	0.83–2.74	0.151			
Hemodialysis	2.97	1.97–4.34	<0.001	2.20	1.40–3.34	<0.001
STEMI	1.61	1.22–2.11	<0.001	1.65	1.19–2.29	0.003
non-STEMI	1.98	1.36–2.80	<0.001	1.97	1.31–2.89	0.001
IABP use	4.52	3.22–6.21	<0.001	3.07	2.15–4.32	<0.001
Transradial Intervention	0.37	0.26–0.51	<0.001	0.55	0.38–0.78	<0.001
Closure device	1.01	0.70–1.42	0.944			
CTO	2.06	1.38–2.99	<0.001	2.39	1.57–3.54	<0.001
Rotablator	3.42	2.29–4.95	<0.001	2.67	1.73–4.01	<0.001

OR = odds ratio; CI = confidence interval; BMI = body mass index; PCI = percutaneous coronary intervention; HF = heart failure; PAD = peripheral artery disease; COPD = chronic obstructive pulmonary disease; STEMI = ST elevation myocardial infarction; IABP = intra-aortic balloon pumping; CTO = chronic total occlusion.

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reported that Asian patients were more likely to receive excess doses of antithrombotic agents compared with non-Asians. Appropriate doses of antiplatelets or anticoagulants may reduce bleeding complications. Furthermore, patients with a low BMI were older ($p<0.001$), more likely to have end-stage renal disease ($p<0.001$) and systemic atherosclerotic disease including cerebrovascular disease ($p<0.001$) and peripheral artery disease ($p<0.001$), than those with a high BMI in our cohort. These results are consistent with previous studies [9,13,14,40], and indicate that patients with a low BMI in our present study tended to have progressive atherosclerosis in the arterial system of the whole body. Arterial stiffness due to progressive atherosclerosis might be associated with a higher risk of bleeding in patients with a low BMI [9,14], although we performed multivariate analysis to adjust for possible confounding variables.

Because bleeding complications are associated with short- and long-term adverse outcomes after PCI [39,41], efforts for reducing bleeding complications are important. Bivalirudin, TRI, and use of a closure device are considered as bleeding avoidance strategies [42]. Bivalirudin is not available in Japan. Therefore, appropriate use of a closure device and TRI may be useful for reducing bleeding complications after PCI. In our study, there was no difference in the frequency of using a closure device in each BMI group, and use of a closure device was not a predictor of reducing bleeding complications by univariate analysis. TRI has been reported as a useful method for reducing bleeding complications compared with conventional transfemoral intervention [24,43]. In our study, TRI was an independent predictor of preventing overall complications in the total cohort. TRI was also associated with a small risk of bleeding in a subgroup analysis of patients without cardiogenic shock in multivariate logistic regression analysis. Approximately one-third of all of the PCIs in our dataset were performed with the transradial approach. Furthermore, TRI is performed more frequently in patients with a high BMI than in those with a low BMI [36]. Although TRI is more commonly performed in Japan than in Western countries [24], more frequent use of radial access in patients with a low BMI for reducing

bleeding complications should be considered. Because patients with a low BMI have small vessels compared with patients with a high BMI, an unfavorable arterial sheath size has been reported as a possible explanation for increased access site bleeding complications in those with a low BMI [7,40,44]. Kang et al. reported that a high BMI was associated with a large diameter of the coronary arteries, and was associated with a large stent area after intravascular ultrasound-guided stent implantation [45]. They concluded that a high BMI is not associated with worse outcomes after drug-eluting stent implantation, despite more comorbidities, greater plaque burden, and more plaque rupture. A large vessel diameter in patients with a high BMI is one of the potential causes of the obesity paradox after PCI. Endovascular techniques and devices have evolved over the years, and smaller sheaths, guiding catheters, stents, and balloons have become available in recent years. However, physicians should be aware that lean patients are at greater risk for complications during and after PCI.

Obesity is an independent risk factor of advanced cardiovascular disease and mortality [1–3]. Although the obesity paradox may be a real phenomenon, physicians should be aware that patients with an increased body mass remain at high risk for development of CAD and poor outcomes over the long term [2,3,32]. Current guidelines recommend weight reduction to a BMI <25 as a second prevention for patients with CAD [46,47]. However, there is no clear evidence that a reduction in weight improves the prognosis of patients after PCI. Further long-term studies are needed in the future regarding this important issue.

Study limitations

The first limitation of our study is that it was an observational clinical trial. The study population was heterogenous, including patients with different severities of coronary artery disease, ranging from acute coronary syndrome with cardiogenic shock to stable angina. Although we performed multivariate logistic regression analysis to adjust for possible confounding variables, some selection bias might not have been completely adjusted for in our statistical model, and the heterogeneity of the patients may have affected the incidence of complications in each of the BMI groups. Furthermore, we excluded 646 patients with missing data of basic information, including sex, height and/or body weight, which might have affected selection bias. Another limitation is that the duration of antiplatelet therapy and the size of the sheaths and guiding catheters were not recorded, and patients with cancer or other serious comorbidities were not excluded in our registry. These factors might have been associated with the rate of bleeding complications. Finally, the impact of BMI and in-hospital bleeding complications on long-term clinical outcomes in patients who undergo PCI should be investigated in our registry in the future.

Conclusions

Lean patients, rather than obese patients are at greater risk for in-hospital complications during and after PCI, particularly for bleeding complications.

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ORIGINAL ARTICLE

Nomogram Prediction of Metachronous Colorectal Neoplasms in Patients With Colorectal Cancer

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Objective: To construct a predictive model of postoperative colorectal neoplasm development using a nomogram.

Background: Although patients with colorectal cancer (CRC) are known to be at high risk of developing metachronous adenoma or CRC, no statistical model for predicting the incidence of postoperative colorectal lesions has been reported.

Methods: A total of 309 CRC patients who underwent surgical resection received regular endoscopic follow-up to detect the development of metachronous adenoma or adenocarcinoma. The patients were divided into the derivation set (n = 209) and the validation set (n = 100). The nomogram to predict the 3- and 5-year adenoma-free survival rates was constructed using the derivation set, and a calibration plot and concordance index (c-index) were calculated. The predictive utility of the nomogram was validated in the validation set.

Results: Sex, age, and number of synchronous lesions at the time of surgery for primary CRC were adopted as variables for the nomogram. The nomogram showed moderate calibration, with a c-index of 0.709 in the derivation set and 0.712 in the validation set.

Conclusions: A nomogram based on sex, age, and number of synchronous lesions at the time of surgery has the ability to predict postoperative adenoma-free survival.

Keywords: colonoscopy, colorectal adenoma, colorectal cancer, nomogram, postoperative surveillance

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Colorectal cancer (CRC) is one of the most common malignancies in Japan and in Western countries.[1] Furthermore, those with a history of CRC are at a higher risk for developing second metachronous adenomas or CRC recurrence during the follow-up period.[2–5] Chen et al[6] reported that 0.7% of patients develop metachronous CRC during the 3 years after surgical resection for the initial CRC.

It is generally accepted that most CRCs develop through a continuous process, transforming from normal mucosa to adenoma to carcinoma,[7–9] a process known as the adenoma-carcinoma sequence. Therefore, the early detection and endoscopic resection of newly developed adenomas constitute an important preventive strategy, especially in patients who have undergone surgical resection for primary CRC. However, there are no definite guidelines for adenoma surveillance after the surgical resection of primary CRC. The 2006 guidelines issued by the American Cancer Society indicate that a postoperative colonoscopy should be performed 1, 4, and 9 years after the initial surgical procedure,[10] but these guidelines also state that the currently available evidence does not fully address any clinical, genetic, or biologic markers that may predict the development of metachronous CRC. Therefore, the development of a prediction model of metachronous colorectal lesions after resection of initial CRC is very important.

Several studies have previously attempted to identify risk factors for the development of metachronous adenomas after resection of initial CRC. The location of CRC in the proximal colon and previous or synchronous adenoma presence were reported to be risk factors for the early development of metachronous lesions.[5,11] However, there have been no previous studies investigating the time course of adenoma formation after surgery using the log-rank test or Cox proportional hazard model. Recently, we demonstrated that age, presence of a synchronous lesion, and diabetes mellitus were independent predictive variables affecting the development of postoperative colorectal neoplasms.[11] By extending the previously reported regression results, we have designed the present study to construct a predictive model of postoperative colorectal neoplasm development using a nomogram, a tool widely used among clinicians because of its utility as a prediction model and its user-friendly interface.[12,13]

MATERIALS AND METHODS

Patient Selection

We retrospectively evaluated the medical records of 552 consecutive patients with colorectal adenocarcinoma, diagnosed between January 2004 and December 2007, who underwent surgical resection at the Department of Surgical Oncology, the University of Tokyo Hospital. Patients with adenomatous polyposis (>30 lesions at the time of surgery or familial adenomatous polyposis), those with hereditary non-polyposis colon cancer, and those with inflammatory bowel disease were excluded from the study. After surgical resection, all specimens were histopathologically reviewed, and the pathological TNM class and stage were determined according to the classification established by the American Joint Committee on Cancer.[14] In cases of multifocal disease, the histopathological variables were determined by assessing the dominant lesion (the most extensive lesion based on tumor invasion or size). Primary colon cancer located proximal to the splenic flexure was defined as right-sided, and the distally located one was defined as left-sided; all variables were assessed at the time of surgery. This study was approved by the institutional review board, and all patients gave written informed consent.

The first colonoscopy was scheduled at 1 year after surgery, and adenomas detected during the first colonoscopy were treated as synchronous lesions. Polyps larger than 5 mm were removed by endoscopic mucosal resection and were histopathologically analyzed. Hyperplastic polyps and other nonneoplastic colorectal lesions were recorded but not included in the analysis. After confirming the absence of colonic lesions (clean colon) by perioperative colonoscopy, endoscopic surveillance was conducted every 1 to 2 years. Patients who failed to undergo the second colonoscopy, which was usually scheduled 2 years after surgery, were excluded from the study; the final number of patients enrolled in this surveillance program was

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309. The patients were divided into 2 groups: the derivation and validation groups. The derivation group consisted of 209 patients who underwent surgery from January 2004 to June 2006, and the validation group consisted of 100 patients who underwent surgery from July 2006 to December 2007. The nomogram was constructed on the basis of derivation group data, and its predictive utility was validated in the validation group.

Statistical Analysis

The Kaplan-Meier method was used to estimate overall survival and recurrence-free survival, and the log-rank test was used to analyze differences in survival between groups. For the derivation group, the following potential prognostic variables were assessed: sex, age, and sex (general characteristics); tumor location, depth of invasion, regional lymph node metastasis, distant metastasis, lymphatic invasion, venous invasion, histologic differentiation, and the presence of concomitant CRCs and/or adenomas at the time of surgery (cancer-related variables); and smoking, body mass index greater than 25 kg/m^2, history of previous malignancies (CRC or extracolic malignancy), first-degree family history of CRC, hypertension, hyperlipidemia, and diabetes mellitus (patient background variables). A multivariate Cox proportional hazards analysis was performed using variables whose P value was less than 0.2 in univariate analysis. By following the method of Wang et al,[15] we built nomograms for predicting the probability of 3- and 5-year adenoma-free survival rates after surgery. The nomogram was subjected to 100 bootstrap resamples for calculating the estimated Harrell concordance index (c-index) as an index of model performance.[16] The c-index estimates the probability of concordance between predicted and observed outcomes in rank order and is equivalent to the area under the receiver operating characteristic curve, if there are no censored cases.[16] It represents the ability of the model to discriminate between patients who survived without adenoma development and those who did not. Higher values indicate better discrimination: a value of 0.5 indicates no predictive discrimination, whereas a value of 1.0 indicates perfect separation of patients with different outcomes.

We also performed calibration using a calibration curve, a graphic representation of the relationship between the observed outcome frequencies and the predicted probabilities, with both the derivation and validation groups. Using the constructed nomogram, the score of predicting the 5-year adenoma-free survival rate was calculated for both groups. All statistical analyses were performed using the statistical software program R 3.0.1 with rms and Hmisc packages (http://www.r-project.org/).

RESULTS

Of the 552 patients enrolled in the study, 243 were excluded for the following reasons: 227 patients did not undergo colonoscopic surveillance (CRC progression in 108 patients, other disease progression in 64 patients, and a move or change of hospital in 55 patients), 4 patients had colitic cancers, 3 patients had polyposis, and 3 patients died during the perioperative period. The differences between the included and excluded patients are presented in Table 1. Because a large proportion of the patients excluded from the analysis had residual cancer or recurrence, and most of the remaining excluded patients failed to receive surveillance because of the development of diseases other than CRC, the age and stage of initial CRC were higher in the excluded group than in the included group. General characteristics related to adenoma formation are also presented in Table 2. The characteristics of patients in the derivation and validation groups were comparable. The incidence of CRC formation per year was 0.0064 in both groups, and that of adenoma formation was approximately 0.084 in both groups. Although the 5-year adenoma-free rate was a little lower in the validation group, this difference was not statistically significant ($P = 0.077$).

TABLE 1. Differences Between Included and Excluded Patients

	Included	Excluded	P
Total, n	309	243	
Sex, n			
Male	199	149	
Female	110	94	0.4564
Age, mean ± SD, yr	63.2 ± 10.3	68.0 ± 11.7	<0.001
Location, n (%)			
Right hemicolon	68 (22.0)	78 (32.1)	
Left hemicolon	112 (36.2)	76 (31.3)	
Rectum	129 (41.7)	89 (36.6)	0.0288
Stage, n (%)			
0/I	99 (32.0)	45 (18.5)	
II	105 (34.0)	69 (28.4)	
III	84 (27.2)	70 (28.8)	
IV	21 (6.8)	59 (24.3)	<0.001

TABLE 2. Patient Characteristics

	Derivation Data Set	Validation Data Set
No. patients	209	100
Sex, n (%)		
Male	134 (64.1)	64 (64)
Female	75 (35.9)	36 (36)
Median follow-up time, yr	5.57	5.04
Total follow-up time, yr	1097.0	466.5
Total colorectal cancer cases developed during follow-up time, n	7	3
Incidence per year	0.00638	0.00643
Total colorectal adenoma cases developed during follow-up time, n	93	39
Incidence per year	0.08470	0.08359
Cumulative 5-yr adenoma-free rate	75.35%	71.71%
95% CI	68.31–81.25	61.30–80.22

CI indicates confidence interval.

Development of the Nomogram

The results of the univariate and multivariate analyses of the association between variables and the 5-year adenoma-free survival rate are shown in Table 3. In the univariate analysis, male patients and older patients had a significantly shorter adenoma-free survival time. The variables associated with progression of the primary cancer, such as T stage and presence of lymph node or distant metastasis, showed no correlation with postoperative adenoma development, consistent with our previous report. Although the presence of second or additional primary CRC showed no correlation, if both synchronous CRC and adenomas were included in the category sublesions, the presence of sublesions was strongly associated with postoperative adenoma development. We previously reported that the presence of diabetes mellitus correlated with postoperative development[11]; however, in this study, no variables concerning patient background, including diabetes mellitus, correlated with adenoma development.

Therefore, we performed multivariate analysis using the variables of sex, age, and the presence of concomitant colorectal

TABLE 3. Univariate and Multivariate Analyses of the Association Between Clinicopathological Factors and Postoperative Adenoma-free Intervals

	Univariate Analysis		Multivariate Analysis		
	5-yr Adenoma-free Survival	*P*	Hazard Ratio	95% CI	*P*
Sex					
Female	84.5%				
Male	68.2%	0.0404	1.75	0.89–3.71	0.1102
Age					
<70 yr	76.6%				
≥70 yr	62.4%	0.0188	1.95	1.04–3.54	0.0387
Cancer-related variables					
Tumor location					
Right-sided colon	74.9%				
Left-sided colon	74.6%				
Rectum	73.1%	0.7888			
Depth of invasion					
T1/2	72.7%				
T3/4	74.1%	0.9003			
Regional lymph node metastasis					
N0	72.2%				
≥N1	76.9%	0.3909			
Distant metastasis					
M0	73.3%				
M1	80.9%	0.503			
Lymphatic invasion					
Absent	74.5%				
Present	71.4%	0.8254			
Venous invasion					
Absent	73.9%				
Present	74.3%	0.957			
Histopathology					
Well or moderate	73.0%				
Other	90.9%	0.106	2.54	0.54–45.43	0.2874
Concomitant colorectal cancers at the time of surgery					
Absent	75.0%				
Present	64.0%	0.1367	1.45	0.66–2.93	0.3394
Concomitant colorectal cancers and adenomas at the time of surgery					
Absent	84.2%				
Present	61.0%	<0.0001	1.95	1.04–3.54	0.0387
Patient background variables					
Smoking					
Absent	77.6%				
Present	69.2%	0.1768	1.23	0.69–2.23	0.4825
Body mass index ≥25 kg/m^2					
Absent	72.2%				
Present	77.2%	0.5937			
History of malignancies					
Absent	74.8%				
Present	64.6%	0.1307	1.39	0.60–2.81	0.4158
Family history of colorectal cancer					
Absent	72.6%				
Present	83.8%	0.2803			
Hypertension					
Absent	77.2%				
Present	66.8%	0.0994	1.03	0.57–1.91	0.9314
Hyperlipidemia					
Absent	74.3%				
Present	69.6%	0.6153			
Diabetes mellitus					
Absent	75.4%				
Present	66.9%	0.399			

CI indicates confidence interval.

sublesions. Because the latter 2 variables were independent predictive factors in the prediction of adenoma development and sex also showed a trend toward correlation, we constructed the nomogram with point scales of these 3 variables (Fig. 1). The sum of the each variable point was plotted on the total point axis, and the estimated median 3- and 5-year adenoma-free survival rates were obtained by drawing a vertical line from the plotted total point axis straight down to the outcome axis. The c-index of this model was 0.709, indicating good discrimination. Figure 2A shows the calibration graph for the nomogram, in which the probability of 5-year adenoma-free survival as predicted by the nomogram is plotted against the corresponding observed survival rates obtained by the Kaplan-Meier method. This illustration demonstrates good calibration of the nomogram. Furthermore, the derivation group was further stratified into 3 groups according to the score calculated using the nomogram: the high-risk (>75th percentile of the group), low-risk (<25th percentile), and intermediate-risk (25th–75th percentile) groups. Figure 3A demonstrates that scoring with the nomogram effectively discriminated the risk of postoperative adenoma development.

Validation

To validate whether the nomogram would be applicable to other data sets, we conducted a validation study using data from the 100 CRC patients in the validation group. The c-index of the validation group was 0.712, demonstrating that the nomogram also showed good prediction in the validation patient group. Moreover, the calibration plot of the validation group demonstrated good calibration (Fig. 2B). Patients in the validation group were also stratified by percentile into 3

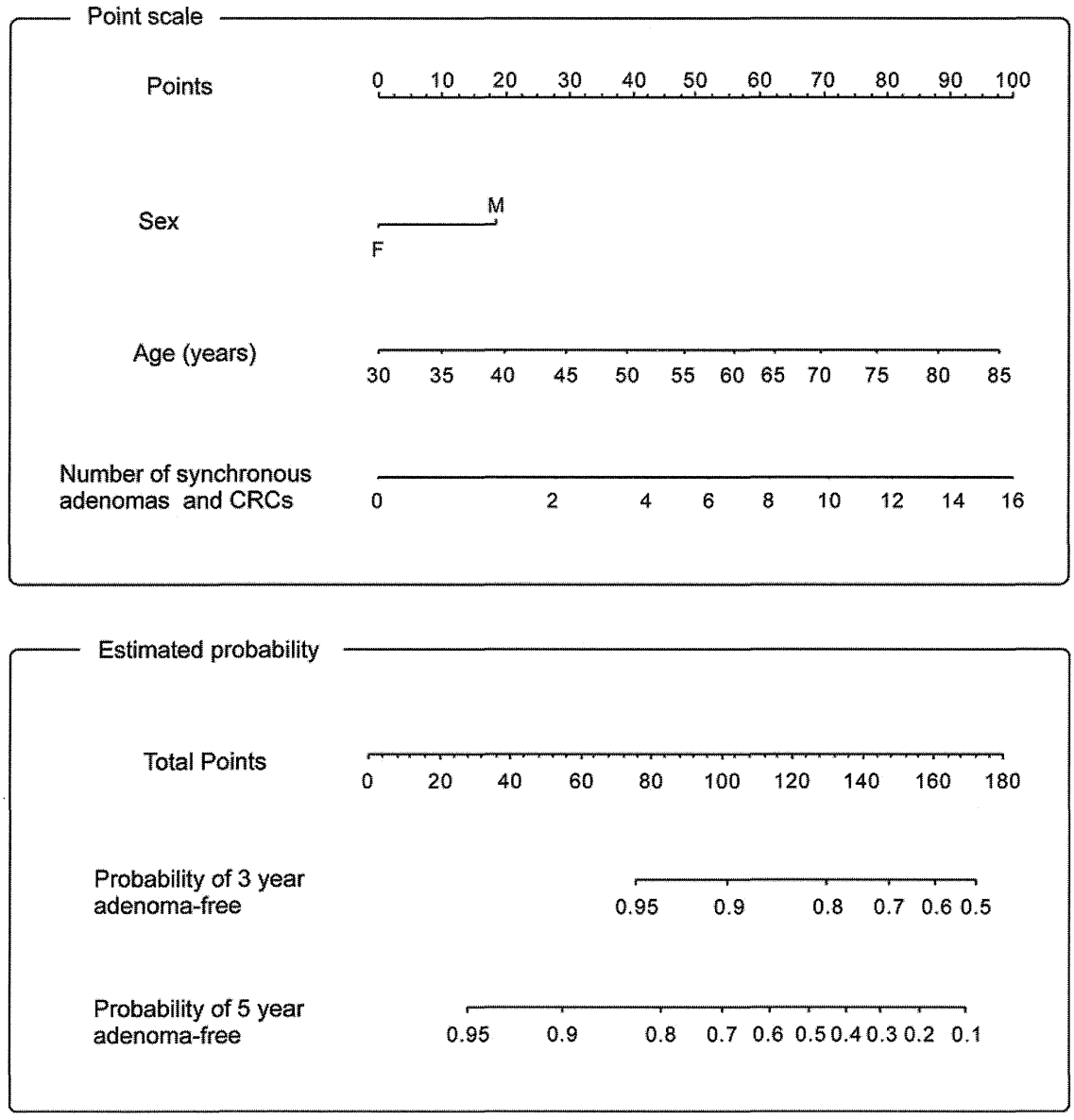

FIGURE 1. Nomogram for predicting postoperative adenoma-free survival after surgery for colorectal cancer. The 3- and 5-year probabilities of survival without adenoma or CRC development is estimated by summing the score of the 3 variables, that is, sex, age, and the number of synchronous adenomas and CRCs at the time of surgery.

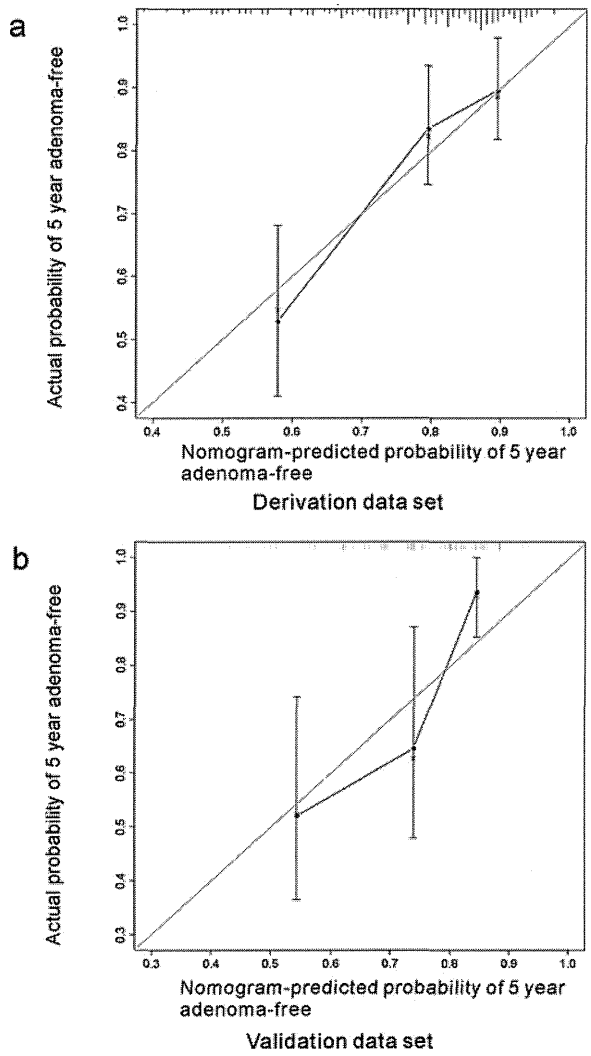

FIGURE 2. Calibration of the nomogram in the derivation (A) and validation (B) data sets. The horizontal axis is the nomogram-predicted probability of adenoma-free survival at 5 years, and the vertical axis is the actual adenoma-free survival rate estimated at 5 years using the Kaplan-Meier method. The line from the lower left to the upper right corner of the plot area is the reference line that indicates ideal prediction. Bars indicate 95% confidence intervals.

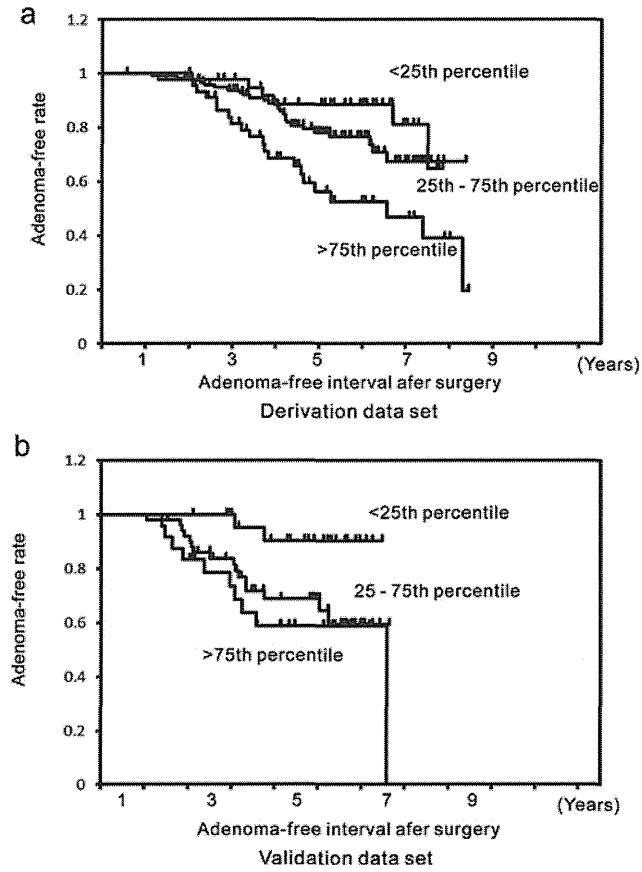

FIGURE 3. Actual adenoma-free survival curves of patients in the derivation (A) and validation (B) sets stratified by quartiles of the nomogram-predicted score. The patients were stratified into 3 groups according to their percentile of the nomogram-predicted score: <25th, 25th–75th, and >75th percentile.

groups (<25th, 25th–75th, and >75th percentile), and the adenoma-free survival in each group was found to increase in this order of patient groups, similar to the result of the derivation group (Fig. 3B).

DISCUSSION

Because CRC patients are at high risk for developing metachronous colorectal adenoma or carcinoma after resection of the primary tumor,[5,17] many studies have attempted to identify the risk factors predicting the development of postoperative neoplasms, but only a few factors have been reported. In the present study, we evaluated possible risk factors by dividing them into sex, age, cancer-related variables, and patient background variables. Initially, in our analysis, male sex was a higher risk factor for postoperative neoplasm development, but the correlation was not strong in the multivariate analysis. This may be explained by the fact that the male patients were on average older than the female patients and advanced age was a strong risk factor. Moon et al[18] also reported that male sex correlated with postoperative adenoma development in a univariate analysis; however, similar to our study, the correlation was not statistically significant by multivariate analysis. Furthermore, they found that age was a risk factor for adenoma development,[18–20] also corroborating our results.

The variables related to cancer progression or malignant potential, such as depth of invasion or presence of metastasis, showed no correlation with postoperative adenoma development. Although several studies have reported that the location of the primary CRC in the proximal colon is a risk factor for metachronous adenoma,[21,22] we failed to find any correlation between primary CRC location and the incidence of postoperative adenoma development. On the contrary, similar to the results of this study, the presence of synchronous colorectal adenomas has been reported to be a risk factor in many studies.[3,11,17,22,23] Chu et al[24] reported that 6.5% of patients with synchronous polyps had metachronous large bowel cancer whereas 3.4% of those without polyps developed metachronous large bowel cancer. Moreover, multiple polyps are associated with a higher risk of metachronous colorectal cancer than single polyps.[25] Correlations between other variables related to patient background and postoperative polyp development were also investigated. We evaluated a variety of

factors reported to be associated with adenoma formation, including previous cancer history, family history of CRC, hyperlipidemia, hypertension, diabetes mellitus, obesity, and smoking habits,[20,26–30] but no correlations were observed with any of these variables. In our previous study, we reported that diabetes was an independent predictive factor for adenoma development[11]; however, there was no correlation in the present study.

Because the nomogram is intended to be used for pragmatic postoperative surveillance in municipal hospitals, the variables included in the nomogram should be limited. Too many variables can make calculating the predictive score cumbersome, and variables with a lopsided risk group distribution will be less useful in clinical application, even if the variables are statistically significant. Although expression of MUC-5 in the initial CRC has been reported to have a protective effect,[22] and microsatellite instability has been reported to be a possible risk factor for the development of metachronous colorectal neoplastic lesions,[31] variables that require experimental techniques such as immunohistochemistry or gene analysis are inappropriate as parameters for a nomogram. Furthermore, a nomogram has an advantage over other statistic models because continuous variables can be directly converted to a prognosis-predicting score and therefore continuous variables are more desirable than categorized ones. From these perspectives, the variables we adopted for the nomogram in the present study are ideal (sex, age, and number of synchronous lesions).

Chung et al[32] evaluated the cumulative incidence of colorectal neoplasia development by stratifying patients according to risk factors. They recommended extending the surveillance interval beyond 5 years for the low-risk group, in which the 5-year incidence of adenoma development was 45.8%. A 3-year colonoscopic follow-up period was recommended for the high-risk group, in which the 5-year incidence of adenoma development as 57.8%. Similarly, a number of guidelines for polyp surveillance have been published and most of these recommend 3-year intervals for high-risk patients and intervals of 5 or more years for low-risk patients.[33–35] Further to these previous reports, we recommend extending the colonoscopic surveillance interval to 5 years for those whose probability of 5-year adenoma-free survival is more than 50%, that is, for those with fewer than 120 points according to the nomogram. Conversely, those with a probability of 5-year adenoma-free survival less than 50%, that is, with more than 120 points according to the nomogram, should undergo a colonoscopy at least every 3 years. However, there have been no published guidelines concerning the ideal colonoscopic interval after CRC resection. Therefore, the validity of the intervals recommended by our nomogram should be prospectively evaluated in the future.

The c-indexes of nomograms previously reported were approximately 0.7. For example, c-indexes were 0.68 to 0.73 for predicting the prognosis of rectal cancer,[36] 0.69 for predicting recurrence after surgery for breast cancer,[37] and 0.66 to 0.70 for predicting recurrence of desmoid fibromatosis.[38] The nomogram we constructed showed moderate prediction capability in the derivation set, comparable with these previous reports, as shown in both the calibration plot and the Kaplan-Meyer adenoma-free survival plot. The calibration plot showed a similar distribution to the ideal reference line, and the survival plot showed good stratification of metachronous lesion-free intervals by nomogram scoring. Because application of the nomogram to the validation set also showed moderate prediction capabilities in the calibration and survival plots, the nomogram may be applicable in other hospitals.

CONCLUSIONS

This nomogram is the first statistical model for predicting the development of metachronous colorectal lesions, and it may be of great assistance during postoperative surveillance after CRC surgery.

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Development and Validation of a Pre-Percutaneous Coronary Intervention Risk Model of Contrast-Induced Acute Kidney Injury With an Integer Scoring System

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Previous models for contrast-induced acute kidney injury (CI-AKI) after percutaneous coronary intervention (PCI) include procedure-related variables in addition to pre-procedural variables. We sought to develop a risk model for CI-AKI based on pre-procedural variables and compare its predictability with a conventional risk model and also to develop an integer score system based on selected variables. A total of 5,936 consecutive PCIs registered in the Japanese Cardiovascular Database were analyzed (derivation cohort, n = 3,957; validation cohort, n = 1,979). CI-AKI was defined as an increase in serum creatinine of 50% or 0.3 mg/dl compared with baseline. From the derivation cohort, 2 different CI-AKI risk models were generated using logistic regression analyses: a pre-procedural model and a conventional model including both pre-procedural and procedure-related variables. The predictabilities of the models were compared by c-statistics. An integer score was assigned to each variable in proportion to each estimated regression coefficient for the final model. In our derivation cohort, the proportion of CI-AKI was 9.0% (n = 358). Predictors for CI-AKI included older age, heart failure, diabetes, previous PCI, hypertension, higher baseline creatinine level, and acute coronary syndrome. Presence of procedure-related complications and insertion of intra-aortic balloon pumping were included as procedure-related variables in the conventional model. Both the conventional model (c-statistics 0.789) and the pre-procedural model (c-statistics 0.799) demonstrated reasonable discrimination. The integer risk-scoring method demonstrated good agreement between the expected and observed risks of CI-AKI in the validation cohort. In conclusion, the pre-procedural risk model for CI-AKI had acceptable discrimination compared with the conventional model and may aid in risk stratification of CI-AKI before PCI. **(Am J Cardiol 2015;115:1636–1642)**

Contrast-induced acute kidney injury (CI-AKI) is a common complication of percutaneous coronary intervention (PCI) and is associated with increased risk of morbidity and short- and long-term mortality.[1–3] Various risk score models have been proposed to identify the patients at risk of CI-AKI[4–6] as the therapeutic options are limited and a prophylactic approach is crucial for this entity.[7–10] However, the previously established risk scores have not been fully exploited in current clinical practice because they include not only pre-procedural but also procedure-related variables, which make it difficult to pre-procedurally identify the patients at risk of CI-AKI. Thus, to improve the pre-procedural stratification of patients at risk of CI-AKI, the development of a risk model without procedure-related variables is of utmost importance. Here, we sought to develop 2 different risk models, one based on pre-procedural variables only and the other based on all available variables, including both pre-procedure– and procedure-related variables, using data from a Japanese Multicenter PCI Registry, and to compare their predictive abilities. By demonstrating the sufficient predictive ability of a pre-procedural risk model of CI-AKI, pre-procedural stratification of patients at risk can be improved.

Methods

Data for the development and validation of CI-AKI risk models were derived from the Japan Cardiovascular Database Keio Inter-hospital Cardiovascular Studies (JCD-KICS), which is a prospective multicenter registry designed to collect clinical variables and outcome data on consecutive patients with PCI, with dedicated clinical research

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See page 1641 for disclosure information.

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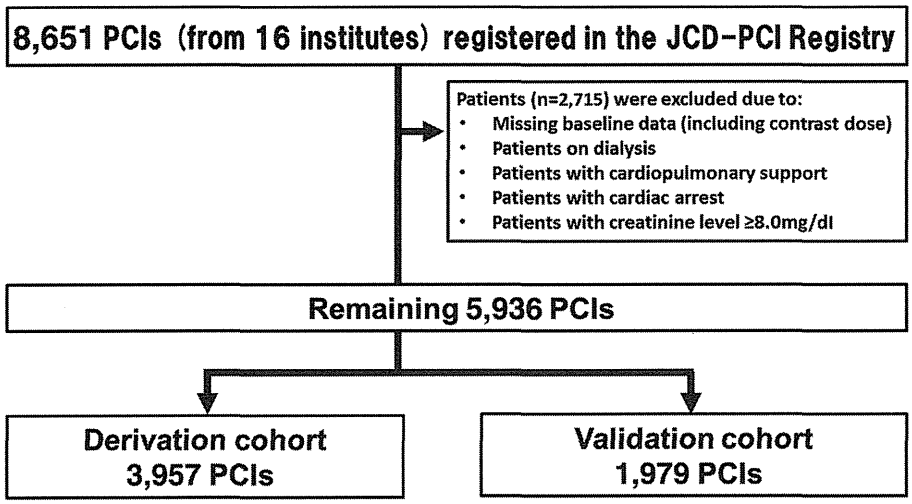

Figure 1. Study patient inclusion and exclusion.

co-ordinators assigned to each site.[11,12] Approximately 200 variables are collected for each patient. The clinical variables and in-hospital outcomes for JCD-KICS were defined in accordance with NCDR, version 4.1. This registry, sponsored by the American College of Cardiology,[13,14] is the largest national clinical registry program for diagnostic cardiac catheterization and PCI, with >1,500 centers currently participating across the United States. The JCD-KICS includes 16 teaching hospitals within the metropolitan Tokyo area, and the participating hospitals were instructed to record and register data from consecutive hospital visits for PCI using an Internet-based database system. All PCI procedures performed with any commercially available coronary device were included. The data entered were checked for completeness and internal consistency. Quality assurance of the data was achieved through automatic system validation and reporting of data completeness and through education and training for dedicated clinical research co-ordinators specifically trained for the present PCI registry. The senior study co-ordinator (IU) and exclusive on-site auditing by the investigators (SK and AK) ensured proper registration of each patient.

A total of 8,651 patients who underwent PCI procedures from January 2011 to March 2013 for acute and nonacute indications were registered in the database. Although JCD-KICS have collected data from September 2008, we excluded data from September 2008 to December 2010 in this analysis because information regarding dosing of contract media has only been collected since January 2011. A total of 2,715 patients were excluded because they were on dialysis or cardiopulmonary support, had cardiac arrest, and had serious renal dysfunction (serum creatinine ≥8.0 mg/dl), or because of insufficient baseline data, resulting in 5,936 patients being included in our study (Figure 1).

An interventional team performed PCIs according to the standard clinical practice through the femoral or radial approach. Supportive pharmacologic therapies, mechanical support, contrast medium dose (nonionic low osmolar), and the angioplasty technique were left to the discretion of the operators, according to each institution's clinical protocols and the international guidelines. Whether to perform pre-procedural hydration and administer bicarbonate or N-acetylcysteine was also left to the operators. Cessation of the use of nephrotoxic medications, such as biguanide or nonsteroidal anti-inflammatory drugs, was encouraged before admission in elective cases and after admission in emergent cases.

CI-AKI was defined as increase in serum creatinine of 50% or 0.3 mg/dl after PCI compared with the baseline value.[15] Postprocedural creatinine value was defined as the highest value within 30 days after indexed procedure based on the definition of NCDR CathPCI registry[16]; therefore, if >1 postprocedural creatinine was measured, the highest value was used for CI-AKI calculation. Anemia was defined using the World Health Organization criteria as baseline hemoglobin value <13 g/dl for men and <12 g/dl for women.[17] Procedural complications included significant dissection, perforation, procedure-related myocardial infarction, cardiogenic shock, heart failure, ischemic or hemorrhagic stroke, tamponade, vascular complications requiring treatment, and bleeding. Bleeding was defined as follows: (1) occurring at the percutaneous entry site, during or after the catheterization laboratory visit until discharge, which may be external or a hematoma >10 cm for femoral, >5 cm for brachial, or >2 cm for radial access; (2) retroperitoneal; (3) gastrointestinal; (4) genitourinary; and (5) other/unknown origin during or after the catheterization laboratory visit until discharge. Only bleeding events requiring a transfusion and/or with a decrease in hemoglobin >3.0 g/dl were included. This bleeding criterion is also consistent with Bleeding Academic Research Consortium grade 3A to C.[18] The definition of these complications was in accordance with the NCDR CathPCI registry, and any additional data elements and definitions can be found at their Web site.[16]

The study cohort was randomly divided in a 2:1 ratio into derivation (n = 3,957) and validation (n = 1,979) cohorts, respectively. The demographic and clinical patient characteristics were summarized, and the data are presented as mean ± SD or as proportion (%), depending on the variables. In this study, we developed 2 different risk models: one based on pre-procedural variables only and one based on all available variables, including both pre- and

Table 1
Patients characteristics with and without contrast-induced acute kidney injury

Variable	Contrast-induced acute kidney injury		P value
	No	Yes	
	(N=3599)	(N=358)	
Mean Age (Years)	67.8±11.0	72.1±12.1	<0.001
Age ≥75	919 (25.5%)	167 (46.6%)	<0.001
Men	2866 (79.6%)	270 (75.4%)	0.065
Body mass index (kg/m^2)	24.2±3.6	23.7±4.0	0.005
<18.5	145 (4.1%)	33 (9.4%)	<0.001
New York Heart Association 3 or 4	200 (5.6%)	66 (18.6%)	<0.001
Diabetes Mellitus	1424 (39.6%)	168 (47.1%)	0.007
Previous Myocardial Infarction	855 (23.8%)	58 (16.2%)	0.001
Previous Percutaneous coronary Intervention	1308 (36.3%)	63 (17.6%)	<0.001
Previous Coronary Artery Bypass Grafting	186 (5.2%)	15 (4.2%)	0.527
Cerebrovascular Disease	301 (8.4%)	51 (14.2%)	<0.001
Peripheral Vascular Disease	306 (8.5%)	35 (9.8%)	0.429
Chronic Lung Disease	115 (3.2%)	13 (3.6%)	0.637
Hypertension	2688 (74.7%)	299 (83.5%)	<0.001
Current/Recent Smoker	1256 (34.9%)	130 (36.5%)	0.561
Dyslipidemia	2417 (67.2%)	215 (60.1%)	0.008
Atrial Fibrillation	139 (7.0%)	18 (9.2%)	0.247
Anemia	787 (28.0%)	134 (41.1%)	<0.001
Urgent or Emergent Procedure	1634 (45.4%)	269 (75.1%)	<0.001
Acute Coronary Syndrome	1743 (48.5%)	273 (76.3%)	<0.001
Radial approach	1373 (38.1%)	87 (24.3%)	<0.001
Chronic total Occlusion	106 (2.9%)	4 (1.1%)	0.042
Multivessel Percutaneous Coronary Intervention	312 (8.7%)	44 (12.3%)	0.019
Periprocedural Complication	226 (6.3%)	93 (26.0%)	<0.001
Periprocedural Bleeding	80 (2.2%)	9 (2.5%)	0.415
Cardiogenic shock	61 (1.7%)	22 (6.1%)	<0.001
Intra-aortic Balloon Pump Support	159 (4.4%)	76 (21.2%)	<0.001
Contrast dose (ml)	178±79	187±88	0.027
Creatinine	0.93±0.41	1.15±0.67	<0.001
Creatinine >1.0mg/dL	799 (22.2%)	157 (43.9%)	<0.001

Hypertension is defined by a prior documentation of blood pressure >140/90 mm Hg or current use of antihypertensive medication. Dyslipidemia is defined by a prior documentation of total cholesterol >200 mg/dL or low-density lipoprotein >130 mg/dL or high-density lipoprotein <40 mg/dL or current use of lipid-lowing agent. Anemia is defined by baseline hemoglobin value <13 g/dL for men and <12 g/dL for women.

procedure-related variables, from the derivation cohort, and compared their performance. Subsequently, we evaluated the validities of the developed risk models using the validation cohort.

A 2-step approach was used to identify the independent predictors of CI-AKI. First, from the derivation cohort, univariate analysis was performed to select significant risk factors of CI-AKI. Second, the set of identified predictors ($p < 0.10$) was used as a pool of variables in constructing a final model using a backward stepwise multivariate logistic regression model, and the regression coefficients were estimated. In this model, age and body mass index (BMI) were treated as continuous covariates, and serum creatinine level (>1.0 mg/dl) and contrast dose (per 100 ml) were treated as categorical variables to make the model more clinically meaningful. We repeated the earlier mentioned method for the 2 different risk models, and c-statistics were used to compare the predictabilities of the 2 risk models. An integer score was assigned to each variable selected in the final model in proportion to the estimated regression coefficient defined from an incremental risk ratio per unit from the referencing age (50 years). This unit risk increment from the referencing age (0.024 for the pre-procedural risk model and 0.019 for the conventional risk model) was multiplied by 10, and the regression coefficient for each level of every risk factor was subsequently divided by this value (0.24 for pre-procedural risk model and 0.19 for conventional risk model) to compute its weights for the risk score.[19]

Using the validation cohort data, the validities of the risk models with the integer scoring were also evaluated by examining the agreement between the predicted and observed proportions of CI-AKI in 5 groups defined with quintiles of the point totals. All data were analyzed using SPSS, version 21 (SPSS Inc., Chicago, Illinois), and the 2-sided significance level (α) was 0.05 for all analyses.

Results

Of the 3,957 patients in the derivation cohort, 358 patients (9.0%) experienced CI-AKI after PCI. Table 1 shows the baseline characteristics of the patients. The patients with CI-AKI tended to be older and women and to have lower BMI, significant heart failure status (New York Heart Association 3 or 4 equivalents), higher baseline creatinine level, and high proportion of co-morbidities, whereas patients without CI-AKI tended to have a higher prevalence of dyslipidemia and histories of myocardial infarction and PCI. There were also procedural differences between the patients with and without CI-AKI. Cardiogenic shock with or without intra-aortic balloon pump (IABP) support, emergent cases such as PCI for acute coronary syndrome, and procedural complications were more frequently observed in the patients with CI-AKI. Meanwhile, the patients without CI-AKI tended to undergo PCI through radial approach. Furthermore, in patients with CI-AKI, a higher amount of contrast media was used.

Table 2 shows the results of the multivariate logistic regression analyses. The clinical variables selected in the final model were older age, heart failure status, diabetes mellitus, no previous PCI, hypertension, higher baseline creatinine level (>1.0 mg/dl), and acute coronary syndrome. As procedure-related variables, presence of procedure-related complications and insertion of IABP were identified and included in the conventional model. Age was the only factor used as a continuous variable (>50 years), whereas all other factors were represented as categorical variables. Figure 2 demonstrates the receiver-operating characteristic curves. The c-statistics of pre-procedural and conventional models were 0.799 (95% confidence interval [CI] 0.783 to 0.815) and 0.789 (95% CI 0.773 to 0.805), respectively.

The integer points for each variable by means of estimated coefficients in the logistic regression models are listed in Table 3. The highest number of points was 6 for procedural complications, whereas the lowest was −4 for history

Table 2
Multivariate analysis for independent predictors of contrast-induced acute kidney injury

Pre-procedural risk model			Conventional risk model		
	β	OR (95% CI)		β	Odds Ratio
Number of years > 50	0.024	1.02 (1.01-1.04)	Number of years > 50	0.019	1.02 (1.01-1.03)
New York Heart Association 3 or 4	0.725	2.10 (1.46-2.92)	New York Heart Association 3 or 4	0.533	1.70 (1.18-2.46)
Diabetes Mellitus	0.39	1.48 (1.15-1.90)	Diabetes Mellitus	0.335	1.40 (1.08-1.81)
Previous Percutaneous Coronary Intervention	-0.751	0.47 (0.34-0.66)	Previous Percutaneous Coronary Intervention	-0.695	0.50 (0.35-0.71)
Hypertension	0.383	1.47 (1.06-2.02)	Hypertension	0.35	1.42 (1.02-1.97)
Pre-creatinine >1.0mg/dL	0.845	2.33 (1.80-3.02)	Pre-creatinine >1.0mg/dL	0.796	2.22 (1.70-2.89)
Acute Coronary Syndrome	1.129	3.09 (2.25-4.25)	Acute Coronary Syndrome	0.986	2.68 (1.94-3.71)
Not Applicable			Procedural Complication	1.195	3.30 (2.37-4.60)
			Intra-aortic Balloon Pump Insertion	0.895	2.45 (1.70-3.52)

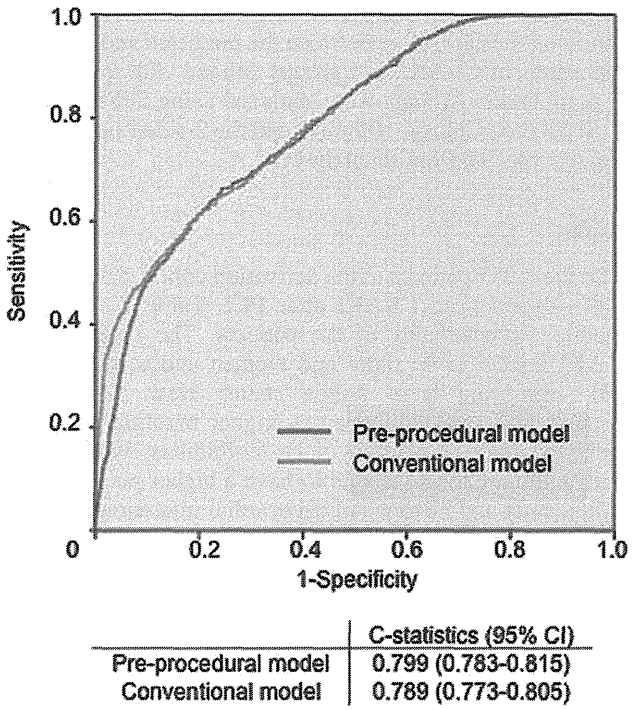

Figure 2. C-statistics of the pre-procedural and conventional models.

of PCI in the convention model because this factor was negatively associated with CI-AKI. The possible total points ranged from −3 to 21 in the pre-procedural risk score and from −4 to 32 in the conventional risk score.

The agreements between the observed and predicted risks of CI-AKI with the developed risk-scoring methods were assessed across 5 groups defined with quintiles of the total points in the validation cohort (Figure 3). Among a total of 10 pairs of observed and predicted risks compared, only 1 observed group (score ≤0 in the conventional risk model) was outside the 95% CIs of the corresponding predicted risk of CI-AKI.

Discussion

Our study demonstrated a sufficient predictability of the CI-AKI risk model developed solely based on pre-procedural variables. The predictability of the model, as calculated by c-statistics, was comparable with a conventional risk model developed using both pre-procedure— and procedure-related variables. The calibration plots showed no relevant departures from the ideal predictions. This finding may lead to better stratification of patients at risk for CI-AKI before the procedures. Furthermore, our study clarified the current incident rate and unique characteristics of CI-AKI in a Japanese population.

Despite the wide recognition of CI-AKI and the importance of preventative measures against CI-AKI, the occurrence of CI-AKI remains unsolved. In this study, despite the same definition of CI-AKI (increase in serum creatinine of 50% or 0.3 mg/dl after PCI compared with the baseline value) or postprocedural highest creatinine value (highest value within 30 days after indexed procedure), the rate of CI-AKI was slightly higher than that of the study from NCDR Cath-PCI registry (9.0% vs 7.1%).[20] The precise reasons for this remain unclear; however, this could be potentially explained by the unique demographic characteristics in our study population. The CI-AKI cohort of our study was likely to be older and to have lower BMI compared with the cohorts of these previous reports, which might explain the higher incidence of CI-AKI in our study despite the similar volumes of contrast media used. Furthermore, the rate of CI-AKI in the recent report from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC) 2 was significantly lower than that of our study; however, the definition of CI-AKI (0.5 mg/dl absolute increase in serum creatinine level from baseline) was quite different.[21] When CI-AKI was evaluated on the basis of the same definition as the study from BMC2, the rate of CI-AKI in our population decreased substantially (from 9.0% to 3.9%), which was the similar proportion of the report from BMC2.

The importance of identifying patients at risk for CI-AKI before the procedures has been recognized, and accordingly, 2 recent studies, 1 from the NCDR and 1 from the BMC2, aimed to develop risk models for CI-AKI including only pre-procedural variables.[20–22] The databases used in these previous studies contained thorough and complete clinical information and were reflective of contemporary practice. However, despite its aim to focus on the pre-procedural variables, the NCDR model also included the volume of contrast agents. Additionally, the report from BMC2 only included 46 pre-procedural variables in the full model[21] and did not compare their predictabilities with the corresponding

Table 3
Simplified risk scores with and without pre-procedural variables for contrast-induced acute kidney injury

Pre-procedural risk model	Score	Conventional risk model	Score
Age		Age	
≤50	0	≤50	0
51-59	1	51-59	1
60-69	2	60-69	2
70-79	3	70-79	3
80-89	4	80-89	4
90-99	5	90-99	5
New York Heart Association 3 or 4	3	New York Heart Association 3 or 4	3
Diabetes Mellitus	2	Diabetes Mellitus	2
Previous Percutaneous Coronary Intervention	-3	Previous Percutaneous Coronary Intervention	-4
Hypertension	2	Hypertension	2
Pre-creatinine >1.0mg/dL	4	Pre-creatinine >1.0mg/dL	4
Acute Coronary Syndrome	5	Acute Coronary Syndrome	5
Not Applicable		Procedural Complication	6
		Intra-aortic Balloon Pump Insertion	5

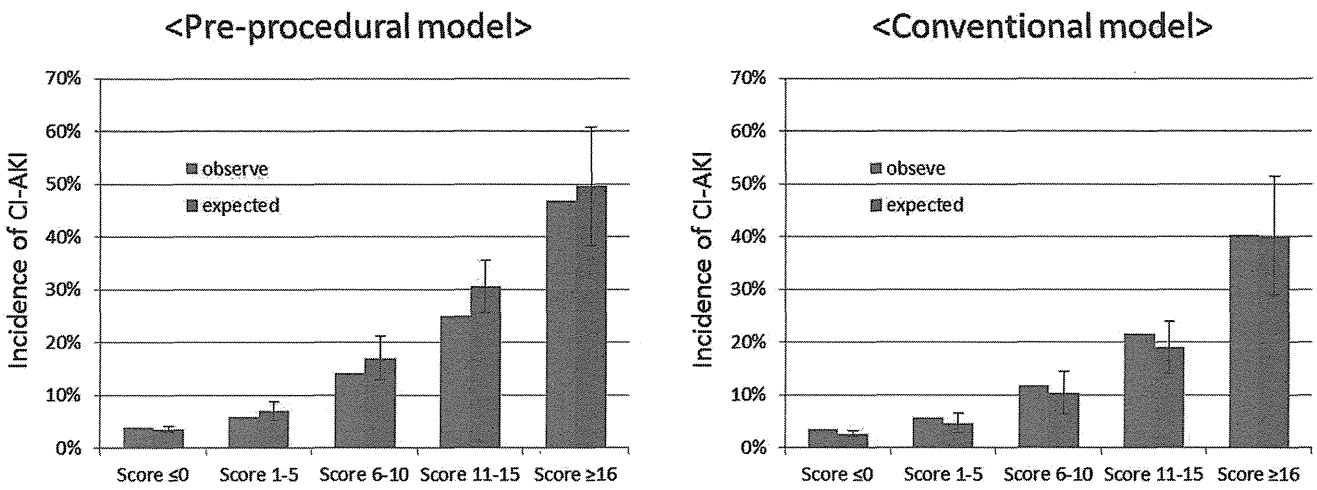

Figure 3. Internal validation of CI-AKI risk scores.

conventional models including both pre-procedure— and procedure-related variables. Our findings further reinforced the viewpoints of these previous studies; moreover, we tested the validity of our pre-procedural method against a previously established risk model in a large set of Japanese patients with PCI.

As opposed to the findings from other reports, and despite the similar volumes of contrast media used, we found that the use of increasing volumes of contrast media was not independently associated with an increased risk of CI-AKI in the multivariate analysis. However, in the univariate analysis, the amount of contrast media was found to be significantly higher in patients with CI-AKI, which is similar to the results of previous studies. Because AKI can occur in patients with acute myocardial infarction in the absence of contrast media use,[23] it is, hence, likely that our cohorts were influenced by factors other than the volumes of contrast media use.

The main strength of our study was the sufficient predictability of the pre-procedural risk model. This means that the current trend toward simplified pre-procedural risk models is on the right track. Moreover, this study demonstrated a relatively high incidence rate of CI-AKI and the unique demographic characteristics of the patients with complicated CI-AKI, such as older age, lower BMI, and higher prevalence of cardiogenic shock, in a Japanese population. These trends were also observed in the previous study based on the other Japanese PCI registry and considered as common features of the Japanese population.[24] Further investigations are required to compare the adjusted incidence of CI-AKI using the same definition.

For a thorough understanding of our results, several limitations should be acknowledged. First, although our registry was created with an observational prospective design, it does not focus on CI-AKI; therefore, we did not have access to any information regarding intravenous hydration before PCIs, the types of contrast media used, and the preventive medications administered. Considering that a prophylactic approach is crucial for reducing the risk of

CI-AKI, such uncollected information could affect the incidence rate derived. Moreover, other unknown confounders also might have existed even after adjustment in the multivariate analyses. However, the aim of this study was to compare the performances of pre-procedural and conventional risk models. Therefore, our results remain robust regardless of unknown confounders. Second, the definition of postprocedural peak creatinine level in our study might have affected the incidence of CI-AKI. In the previous studies, CI-AKI was usually defined based on the peak creatinine level within 48 or 72 hours after the indexed procedure.[1,2,4,7] However, in our registry, the postprocedural peak creatinine level was determined based on the highest level within 30 days after the indexed PCI in our registry; this definition was based on that serum creatinine level typically peaks at 3 to 5 days after contrast medium administration and returns to its baseline level after 1 to 3 weeks.[25] Indeed, the incidence of CI-AKI might have been overestimated in this study compared with the previous reports. However, the previous investigation in a Japanese population demonstrated a similar incidence of CI-AKI.[24] Moreover, we believe that most of the creatinine measurements were, indeed, performed within the index hospitalization (e.g., within 48 to 72 hours after the procedure) in our registry as well. Third, not all hospitals that perform PCI in Japan participate in our registry. Our registry, however, is a multicenter registry and includes a relatively large number of procedures. We believe that this is one of the most representative Japanese databases on patients with PCI and that our results comprise the most complete assessment of practice patterns throughout Japan to date. Fourth, we excluded patients with missing baseline and postprocedural serum creatinine values from our analyses. Generally, patients with a relatively stable status were likely to be omitted to evaluate the creatinine value pre- and post-procedural settings, and therefore, this excluding process may have led to overestimation of the incidence of CI-AKI. Lastly, although we emphasized that the discrimination and calibration of the pre-procedural risk model was comparable with those of the conventional risk model, the impact of procedural complications and the use of IABP on the occurrence of CI-AKI should not be ignored in clinical practice, and this was underscored by their high odds ratios in our conventional statistical model. Conventional efforts for the prevention of CI-AKI, such as procedure-related complication avoidance strategies and minimum use of IABP or contrast media, remain of considerable importance.

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Disclosures

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Supplementary Data

Supplementary data related with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2015.03.004.

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