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

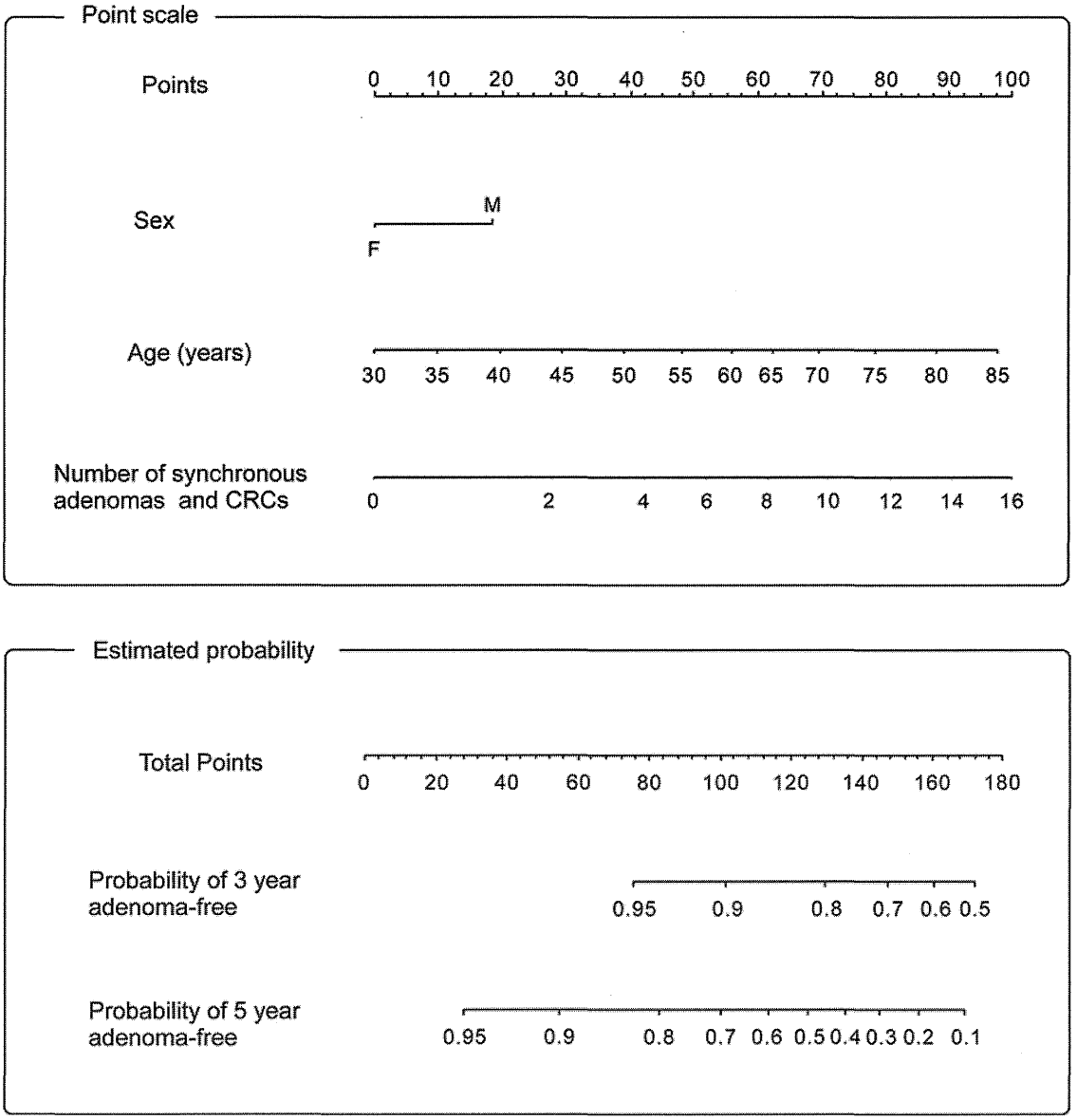


FIGURE 1. Nomogram for predicting postoperative adenoma-free survival after surgery for colorectal cancer. The 3- and 5-year probabilities of survival without adenoma or CRC development is estimated by summing the score of the 3 variables, that is, sex, age, and the number of synchronous adenomas and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

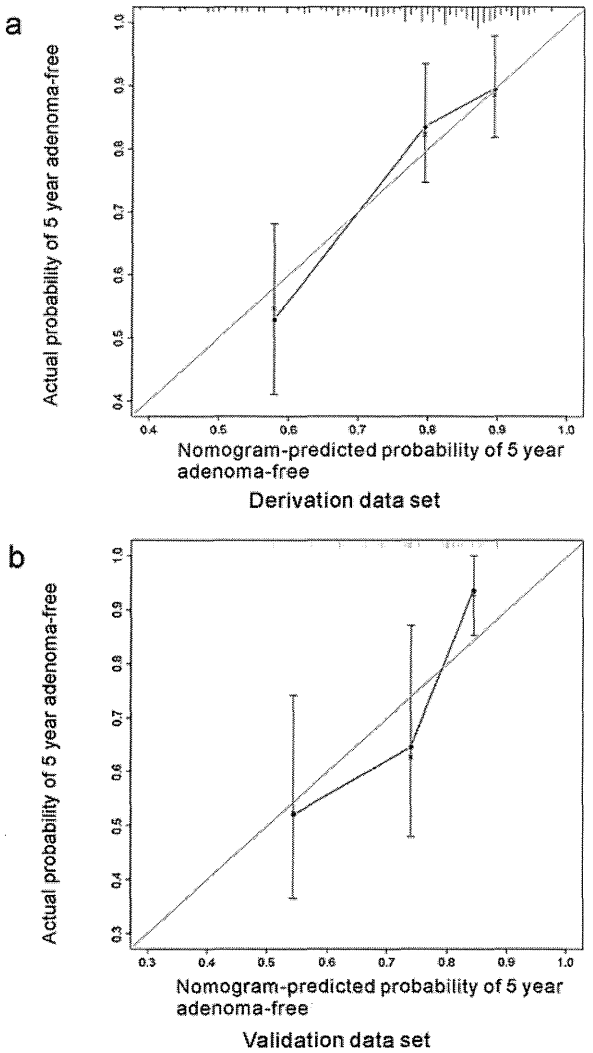


FIGURE 2. Calibration of the nomogram in the derivation (A) and validation (B) data sets. The horizontal axis is the nomogram-predicted probability of adenoma-free survival at 5 years, and the vertical axis is the actual adenoma-free survival rate estimated at 5 years using the Kaplan-Meier method. The 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.

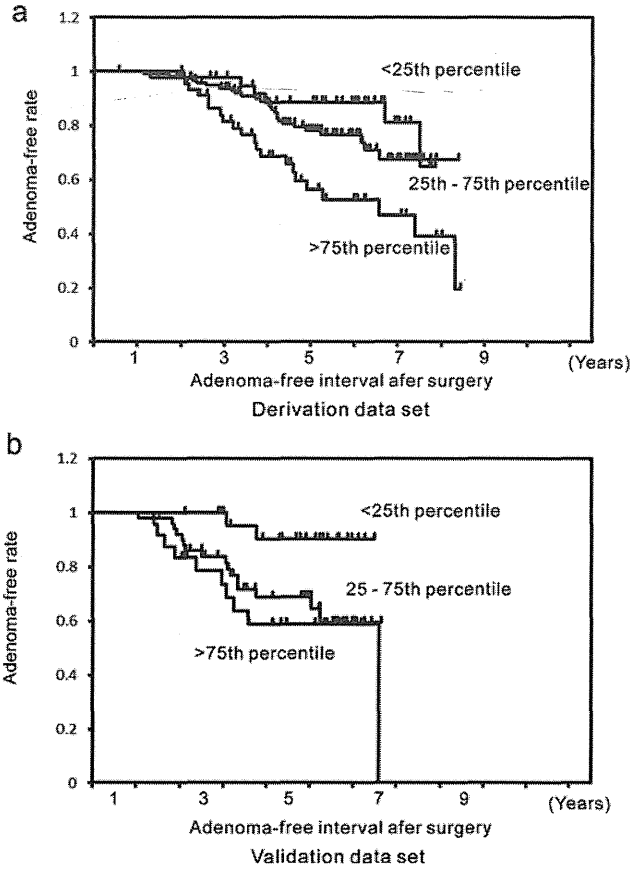


FIGURE 3. Actual adenoma-free survival curves of patients in the derivation (A) and validation (B) sets stratified by quartiles of the nomogram-predicted score. The patients were stratified into 3 groups according to their percentile of the nomogram-predicted score: <25th, 25th–75th, and >75th percentile.

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.

ACKNOWLEDGMENT

The authors thank Yukihide Kanemitsu from the National Cancer Center Hospital for providing statistical assistance.

REFERENCES

1. Hyodo I, Suzuki H, Takahashi K, et al. Present status and perspectives of colorectal cancer in Asia: Colorectal Cancer Working Group report in 30th Asia-Pacific Cancer Conference. *Jpn J Clin Oncol.* 2010;40(Suppl 1):i38–i43.
2. Cali RL, Pitsch RM, Thorson AG, et al. Cumulative incidence of metachronous colorectal cancer. *Dis Colon Rectum.* 1993;36:388–393.
3. Bulow S, Svendsen LB, Mellemgaard A. Metachronous colorectal carcinoma. *Br J Surg.* 1990;77:502–505.
4. Lockhart-Mummery HE, Heald RJ. Metachronous cancer of the large intestine. *Dis Colon Rectum.* 1972;15:261–264.
5. Fajobi O, Yiu CY, Sen-Gupta SB, et al. Metachronous colorectal cancers. *Br J Surg.* 1998;85:897–901.
6. Chen HS, Sheen-Chen SM. Synchronous and "early" metachronous colorectal adenocarcinoma: analysis of prognosis and current trends. *Dis Colon Rectum.* 2000;43:1093–1099.
7. Weitz J, Koch M, Debus J, et al. Colorectal cancer. *Lancet.* 2005;365:153–165.
8. Muto T, Bussey HJ, Morson BC. The evolution of cancer of the colon and rectum. *Cancer.* 1975;36:2251–2270.
9. Stryker SJ, Wolff BG, Culp CE, et al. Natural history of untreated colonic polyps. *Gastroenterology.* 1987;93:1009–1013.
10. Rex DK, Kahi CJ, Levin B, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology.* 2006;130:1865–1871.
11. Kawai K, Sunami E, Tsuno NH, et al. Polyp surveillance after surgery for colorectal cancer. *Int J Colorectal Dis.* 2012;27:1087–1093.
12. Kanemitsu Y, Kato T, Komori K, et al. Validation of a nomogram for predicting overall survival after resection of pulmonary metastases from colorectal cancer at a single center. *World J Surg.* 2010;34:2973–2978.
13. Gronchi A, Miceli R, Shurell E, et al. Outcome prediction in primary resected retroperitoneal soft tissue sarcoma: histology-specific overall survival and disease-free survival nomograms built on major sarcoma center data sets. *J Clin Oncol.* 2013;31:1649–1655.
14. Compton C, Fenoglio-Preiser CM, Pettigrew N, et al. American Joint Committee on Cancer Prognostic Factors Consensus Conference: Colorectal Working Group. *Cancer.* 2000;88:1739–1757.
15. Wang Y, Li J, Xia Y, et al. Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. *J Clin Oncol.* 2013;31:1188–1195.
16. Harrell FE, Jr, Califf RM, Pryor DB, et al. Evaluating the yield of medical tests. *JAMA.* 1982;247:2543–2546.
17. Balleste B, Bessa X, Pinol V, et al. Detection of metachronous neoplasms in colorectal cancer patients: identification of risk factors. *Dis Colon Rectum.* 2007;50:971–980.
18. Moon CM, Cheon JH, Choi EH, et al. Advanced synchronous adenoma but not simple adenoma predicts the future development of metachronous neoplasia in patients with resected colorectal cancer. *J Clin Gastroenterol.* 2010;44:495–501.
19. Bonithon-Kopp C, Piard F, Fenger C, et al. Colorectal adenoma characteristics as predictors of recurrence. *Dis Colon Rectum.* 2004;47:323–333.
20. Haggar FA, Boushey RP. Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. *Clin Colon Rectal Surg.* 2009;22:191–197.
21. Gervaz P, Bucher P, Neyroud-Caspar I, et al. Proximal location of colon cancer is a risk factor for development of metachronous colorectal cancer: a population-based study. *Dis Colon Rectum.* 2005;48:227–232.
22. Borda A, Martinez-Penuela JM, Borda F, et al. Drawing up an individual risk index for development of metachronous neoplastic lesions in resected colorectal cancer. *Rev Esp Enferm Dig.* 2012;104:291–297.
23. Bussey HJ, Wallace MH, Morson BC. Metachronous carcinoma of the large intestine and intestinal polyps. *Proc R Soc Med.* 1967;60:208–210.
24. Chu DZ, Giacco G, Martin RG, et al. The significance of synchronous carcinoma and polyps in the colon and rectum. *Cancer.* 1986;57:445–450.
25. Cunliffe WJ, Hasleton PS, Tweedle DE, et al. Incidence of synchronous and metachronous colorectal carcinoma. *Br J Surg.* 1984;71:941–943.
26. Giovannucci E. Modifiable risk factors for colon cancer. *Gastroenterol Clin North Am.* 2002;31:925–943.

27. Nguyen SP, Bent S, Chen YH, et al. Gender as a risk factor for advanced neoplasia and colorectal cancer: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol.* 2009;7:676.e1–681.e3.
28. He J, Stram DO, Kolonel LN, et al. The association of diabetes with colorectal cancer risk: the Multiethnic Cohort. *Br J Cancer.* 2010;103:120–126.
29. Marugame T, Lee K, Eguchi H, et al. Relation of impaired glucose tolerance and diabetes mellitus to colorectal adenomas in Japan. *Cancer Causes Control.* 2002;13:917–921.
30. Zhao J, Halfyard B, Roebothan B, et al. Tobacco smoking and colorectal cancer: a population-based case-control study in Newfoundland and Labrador. *Can J Public Health.* 2010;101:281–289.
31. Kang KJ, Sinn DH, Park SH, et al. Adenoma incidence after resection of sporadic colorectal cancer with microsatellite instability. *J Surg Oncol.* 2010;101:577–581.
32. Chung SJ, Kim YS, Yang SY, et al. Five-year risk for advanced colorectal neoplasia after initial colonoscopy according to the baseline risk stratification: a prospective study in 2452 asymptomatic Koreans. *Gut.* 2011;60:1537–1543.
33. Bond JH. Polyp guideline: diagnosis, treatment, and surveillance for patients with colorectal polyps. Practice Parameters Committee of the American College of Gastroenterology. *Am J Gastroenterol.* 2000;95:3053–3063.
34. Winawer SJ, Zauber AG, Fletcher RH, et al. Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. *Gastroenterology.* 2006;130:1872–1885.
35. Smith RA, von Eschenbach AC, Wender R, et al. American Cancer Society guidelines for the early detection of cancer: update of early detection guidelines for prostate, colorectal, and endometrial cancers. Also: update 2001—testing for early lung cancer detection. *CA Cancer J Clin.* 2001;51:38–75; quiz 77–80.
36. Valentini V, van Stiphout RG, Lammering G, et al. Nomograms for predicting local recurrence, distant metastases, and overall survival for patients with locally advanced rectal cancer on the basis of European randomized clinical trials. *J Clin Oncol.* 2011;29:3163–3172.
37. Rudloff U, Jacks LM, Goldberg JI, et al. Nomogram for predicting the risk of local recurrence after breast-conserving surgery for ductal carcinoma in situ. *J Clin Oncol.* 2010;28:3762–3769.
38. Crago AM, Denton B, Salas S, et al. A prognostic nomogram for prediction of recurrence in desmoid fibromatosis. *Ann Surg.* 2013;258:347–353.

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

Taku Inohara, MD[a], Shun Kohsaka, MD[a,*], Takayuki Abe, PhD[b], Hiroaki Miyata, PhD[c], Yohei Numasawa, MD[d], Ikuko Ueda, PhD[a], Yutaro Nishi, MD[e], Kotaro Naito, MD[f], Masaru Shibata, MD[g], Kentaro Hayashida, MD[a], Yuichiro Maekawa, MD[a], Akio Kawamura, MD[a], Yuji Sato, MD[h], and Keiichi Fukuda, MD[a]

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

[a]Department of Cardiology and [b]Department of Preventive Medicine and Public Health, Center for Clinical Research, Keio University School of Medicine, Tokyo, Japan; [c]Department Healthcare Quality Assessment, The University of Tokyo, Tokyo, Japan; [d]Department of Cardiology, Ashikaga Red Cross Hospital, Ashikaga, Japan; [e]Department of Cardiology, St Luke's International Hospital, Tokyo, Japan; [f]Department of Cardiology, Keiyu Hospital, Yokohama, Japan; [g]Department of Cardiology, Tachikawa Hospital, Tachikawa, Japan; and [h]Center for Clinical Research, Keio University School of Medicine, Tokyo, Japan. Manuscript received December 23, 2014; revised manuscript received and accepted March 10, 2015.

See page 1641 for disclosure information.

*Corresponding author: Tel: +81-3-5843-6702; fax: +81-3-5363-3875.
E-mail address: kohsaka@cpnet.med.keio.ac.jp (S. Kohsaka).

0002-9149/15/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2015.03.004

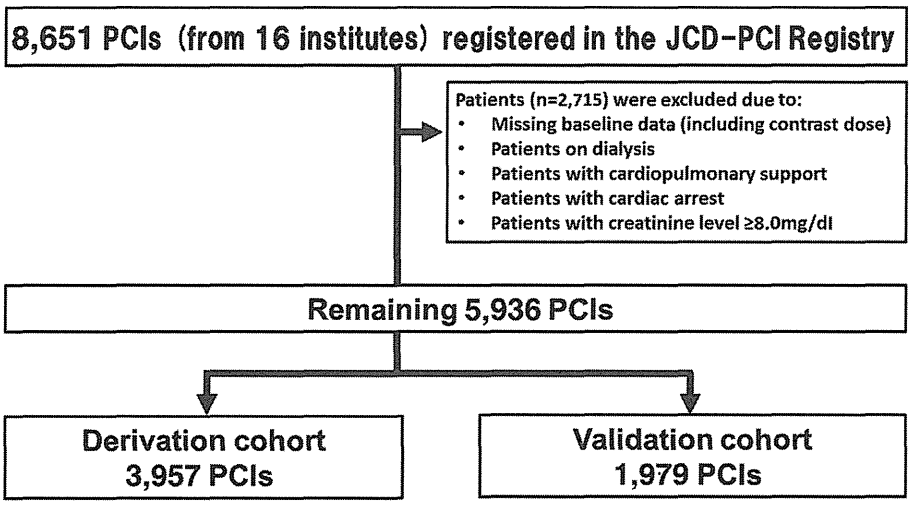


Figure 1. Study patient inclusion and exclusion.

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

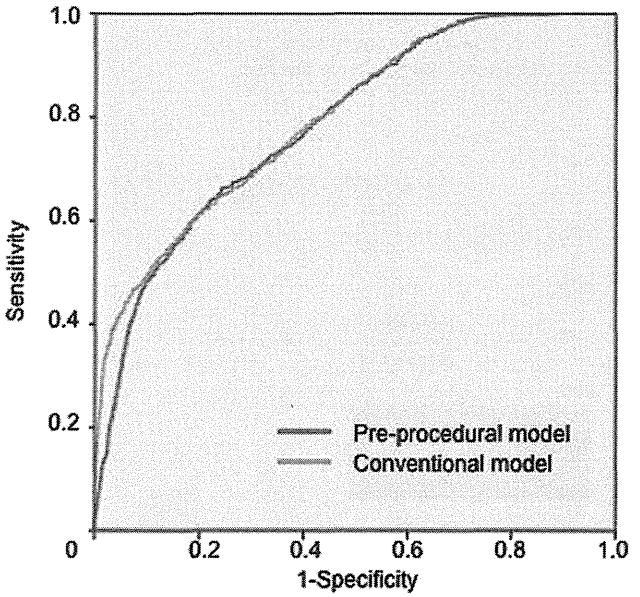
Of the 3,957 patients in the derivation cohort, 358 patients (9.0%) experienced CI-AKI after PCI. Table 1 shows the baseline characteristics of the patients. The patients with CI-AKI tended to be older and women and to have lower BMI, significant heart failure status (New York Heart Association 3 or 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)



	C-statistics (95% CI)
Pre-procedural model	0.799 (0.783-0.815)
Conventional model	0.789 (0.773-0.805)

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

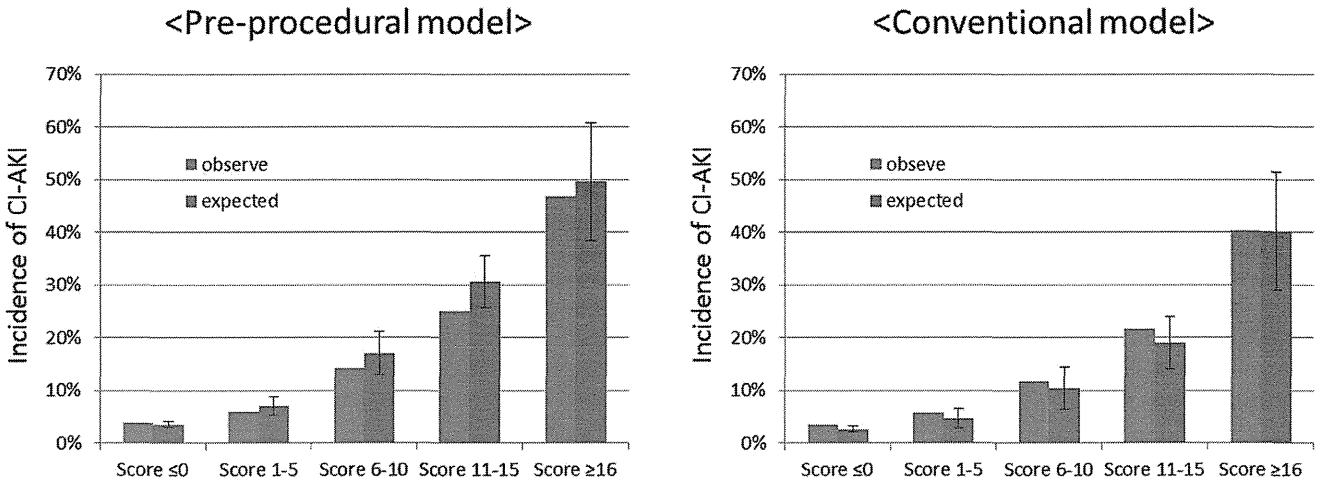


Figure 3. Internal validation of CI-AKI risk scores.

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.

Acknowledgment: The authors appreciate the contributions of all the investigators and clinical co-ordinators involved in the JCD-KICS registry, who are listed in a supplement file.

Disclosures

This study was funded by the Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (Grant Nos. 25460630, 80571398). The authors have no conflicts of interest to disclose.

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.

1. Rihal CS. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation* 2002;105:2259–2264.
2. Gupta R, Gurm HS, Bhatt DL, Chew DP, Ellis SG. Renal failure after percutaneous coronary intervention is associated with high mortality. *Catheter Cardiovasc Interv* 2005;64:442–448.
3. Tepel M, Aspelin P, Lameire N. Contrast-induced nephropathy: a clinical and evidence-based approach. *Circulation* 2006;113:1799–1806.
4. Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, Mintz GS, Lansky AJ, Moses JW, Stone GW, Leon MB, Dangas G. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol* 2004;44:1393–1399.
5. Bartholomew BA, Harjai KJ, Dukkipati S, Boura JA, Yerkey MW, Glazier S, Grines CL, O'Neill WW. Impact of nephropathy after percutaneous coronary intervention and a method for risk stratification. *Am J Cardiol* 2004;93:1515–1519.
6. Brown JR, DeVries JT, Piper WD, Robb JF, Hearne MJ, Ver Lee PM, Kellet MA, Watkins MW, Ryan TJ, Silver MT, Ross CS, MacKenzie TA, O'Connor GT, Malenka DJ. Serious renal dysfunction after percutaneous coronary interventions can be predicted. *Am Heart J* 2008;155:260–266.
7. Mueller C, Buerkle G, Buettner HJ, Petersen J, Perruchoud AP, Eriksson U, Marsch S, Roskamm H. Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. *Arch Intern Med* 2002;162:329–336.
8. Meier P, Ko DT, Tamura A, Tamhane U, Gurm HS. Sodium bicarbonate-based hydration prevents contrast-induced nephropathy: a meta-analysis. *BMC Med* 2009;7:23.
9. Cigarroa RG, Lange RA, Williams RH, Hillis LD. Dosing of contrast material to prevent contrast nephropathy in patients with renal disease. *Am J Med* 1989;86:649–652.
10. Brown JR, Robb JF, Block CA, Schoolwerth AC, Kaplan AV, O'Connor GT, Solomon RJ, Malenka DJ. Does safe dosing of iodinated contrast prevent contrast-induced acute kidney injury? *Circ Cardiovasc Interv* 2010;3:346–350.
11. Ohno Y, Maekawa Y, Miyata H, Inoue S, Ishikawa S, Sueyoshi K, Noma S, Kawamura A, Kohsaka S, Fukuda K. Impact of periprocedural bleeding on incidence of contrast-induced acute kidney injury in patients treated with percutaneous coronary intervention. *J Am Coll Cardiol* 2013;62:1260–1266.
12. Inohara T, Kohsaka S, Miyata H, Ueda I, Ishikawa S, Ohki T, Nishi Y, Hayashida K, Maekawa Y, Kawamura A, Higashi T, Fukuda K. Appropriateness ratings of percutaneous coronary intervention in Japan and its association with the trend of noninvasive testing. *JACC Cardiovasc Interv* 2014;7:1000–1009.
13. Brindis RG, Fitzgerald S, Anderson HV, Shaw RE, Weintraub WS, Williams JF. The American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR): building a national clinical data repository. *J Am Coll Cardiol* 2001;37:2240–2245.
14. Weintraub WS, McKay CR, Riner RN, Ellis SG, Frommer PL, Carmichael DB, Hammermeister KE, Effros MN, Bost JE, Bodycombe DP. The American College of Cardiology National Database: progress and challenges. American College of Cardiology Database Committee. *J Am Coll Cardiol* 1997;29:459–465.
15. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A; Acute Kidney Injury Network. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007;11:R31.
16. National Cardiovascular Data Registry (NCDR) CathPCI Registry. Available at: *http://www.ncdr.com/webncdr/cathpci/*. Accessed on April 10, 2014.
17. Nutritional Anemias: Report of a WHO Scientific Group. Geneva: World Health Organization, 1968.

18. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011;123:2736–2747.
19. Wu C, Camacho FT, King SB III, Walford G, Holmes DR Jr, Stamato NJ, Berger PB, Sharma S, Curtis JP, Venditti FJ, Jacobs AK, Hannan EL. Risk stratification for long-term mortality after percutaneous coronary intervention. *Circ Cardiovasc Interv* 2014;7:80–87.
20. Tsai TT, Patel UD, Chang TI, Kennedy KF, Masoudi FA, Matheny ME, Kosiborod M, Amin AP, Messenger JC, Rumsfeld JS, Spertus JA. Contemporary incidence, predictors, and outcomes of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the NCDR Cath-PCI Registry. *JACC Cardiovasc Interv* 2014;7:1–9.
21. Gurm HS, Seth M, Kooiman J, Share D. A novel tool for reliable and accurate prediction of renal complications in patients undergoing percutaneous coronary intervention. *J Am Coll Cardiol* 2013;61: 2242–2248.
22. Tsai TT, Patel UD, Chang TI, Kennedy KF, Masoudi FA, Matheny ME, Kosiborod M, Amin AP, Weintraub WS, Curtis JP, Messenger JC, Rumsfeld JS, Spertus JA. Validated contemporary risk model of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the National Cardiovascular Data Registry Cath-PCI Registry. *J Am Heart Assoc* 2014;3:e001380.
23. Amin AP, Salisbury AC, McCullough PA, Gosch K, Spertus JA, Venkitachalam L, Stolker JM, Parikh CR, Masoudi FA, Jones PG, Kosiborod M. Trends in the incidence of acute kidney injury in patients hospitalized with acute myocardial infarction. *Arch Intern Med* 2012;172:246–253.
24. Abe M, Morimoto T, Akao M, Furukawa Y, Nakagawa Y, Shizuta S, Ehara N, Taniguchi R, Doi T, Nishiyama K, Ozasa N, Saito N, Hoshino K, Mitsuoka H, Toma M, Tamura T, Haruna Y, Kita T, Kimura T. Relation of contrast-induced nephropathy to long-term mortality after percutaneous coronary intervention. *Am J Cardiol* 2014;114:362–368.
25. McCullough PA, Sandberg KR. Epidemiology of contrast-induced nephropathy. *Rev Cardiovasc Med* 2003;4 suppl 5:S3–S9.

Japan's vision for health care in 2035

Over the past half century Japan has made remarkable achievements in good population health at low cost, with increased equity.[1] However, a demographic shift towards rapid ageing, the growth of non-communicable diseases (NCDs), and advances in medical technology have led to great changes in health-care needs. In the *Lancet* 2011 Series on Japan: Universal Health Care at 50 Years, three major challenges to Japan's health system were identified: sustainability, governance, and responsiveness.[2] In that Series, several reforms were proposed to assure the sustainability and equity of Japan's health accomplishments: implementation of human-security, value-based reforms; redefinition of the roles of central and local governments; improvements in the quality of health care; and a commitment to global health.[2]

Since the publication of the *Lancet* Series on Japan, reform has begun. Central government has begun to transfer the authority and responsibility for health funding allocation and efficiency decisions to prefectural governments, aiming towards 2025 when most of the baby boomers are projected to be aged 75 years or older.[3] Japan's Prime Minister Shinzo Abe has made a strong commitment to eliminate budget deficits by 2020 to ensure fiscal sustainability. Professional societies have collaborated to establish quality improvement initiatives, such as the National Clinical Databases.[4] To consolidate fragmented health-care research and institutions, the Japan Agency for Medical Research and Development was established.[5] However, many issues remain. Although there is general agreement about the need for structural reform, no one has been willing to take the political risks to break the policy inertia and transform Japan's health system with a long-term vision.

Within this context, the Japan Vision: Health Care 2035 Advisory Panel was established, under the leadership of the current Minister of Health, Labour and Welfare Yasuhisa Shiozaki, to develop a long-term health-care policy vision to meet the needs of the next two decades, with a focus on the year 2035. The Health Care 2035 Advisory Panel's report, *Japan Vision: Health Care 2035*,[6] which was published on June 9, confirms Japan's shared core values, since structural reform inevitably represents the values that a nation intends to achieve. We expanded and deepened the basic commitment to universal health coverage and equity in human security, which was proposed in the *Lancet* Japan Series.[2,7]

Three core principles underlie the *Japan Vision: Health Care 2035* report.[6] The first is fairness. The report underlines that Japan needs a health-care system built for all that does not create or support health disparities resulting from differences in age, employment status, or family situation. The second core principle is the need for solidarity built on individual autonomy. A health-care system is needed that supports individuals to actively participate in their community and encourages proactive approaches to health care. The third principle is shared prosperity for Japan and the world in a health-care system that leverages Japan's health-care ingenuity to resolve global health issues

On the basis of these principles, we developed three visions for health care in 2035: lean health care to implement value-based health care; better life design to empower personal and social healthy choices; and global health leadership to take a leading part in global health security and wellbeing. The figure shows the relations between the panel's guiding principles, the visions for health care in 2035, and the foundations that need to be established to support this vision.

These principles combine to form a new model for health care in Japan. One of the most striking changes in perspective in our vision is the position of health care itself. In Japan, health care had been regarded as just one part of the social security system and there has always

For the ***Lancet*** **Series on Japan: Universal Health Care at 50 Years** see http://www.thelancet.com/series/japan

For **Japan Agency for Medical Research and Development** see http://www.amed.go.jp/en/

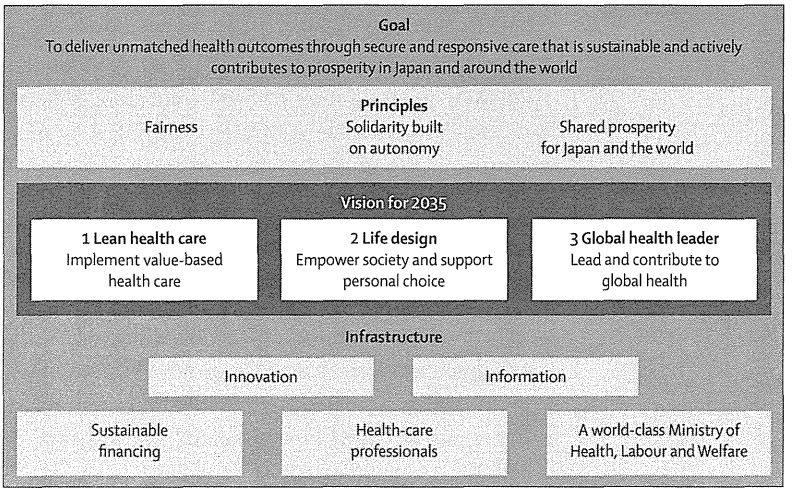


Figure: **Overview of Japan Vision: Health Care 2035**

been pressure to reduce health-care costs.[8] We believe, however, that health care can become a new social system that transcends sectors in the next two decades and has its own investment value in an ageing country.

This new model promotes value-based health care that could lead to better health outcomes, lower costs, and fewer adverse events. To accomplish this vision a nationwide system to undertake scientific and comprehensive assessment of values of current and future health-care interventions needs to be established. The responsibilities of a future health system will need to incorporate not only the integration of long-term care with prevention and management of chronic illness,[9] but also living conditions, employment, and other major social determinants of health.[10] The *Japan Vision: Health Care 2035* report also recognises the interconnectedness of the health sector with civil society, the private sector, and the broader community, so that promoting and preserving health is seen as the active responsibility of the whole community.

This revitalisation of health care as a socioeconomic driver within Japan is not the limit of our vision for the role of health in society. Japan can leverage its experience in developing a low-cost, equitable health system to support other countries in a grand convergence towards the year 2035 as they face challenges similar to those faced by Japan.[11] Through an active role in global health, Japan can create a virtuous cycle in which improvements in health lead to economic growth. In an interconnected world, these improvements will, in turn, secure Japan's own economic prosperity and ensure its own health and human security.

The Japan Vision: Health Care 2035 Advisory Panel has been offered an opportunity to present a vision that is relevant for the future of health not only in Japan, but also in many other countries confronted by rapid ageing, growth of NCDs, and concerns about fiscal sustainability.[6] We have identified a model in health that we believe offers a vision for global health. In addition to improving cost-effectiveness and enhancing resources for health care, this vision offers ways to cope with rapid population ageing amidst a falling birth rate. Success in Japan might also offer a way to rethink our approach to economic growth, living standards, the environment, and the protection of human health and wellbeing at a global level. We hope to initiate a debate around this vision for a healthier world.

*Hiroaki Miyata, Satoshi Ezoe, Manami Hori, Machiko Inoue, Kazumasa Oguro, Toshihisa Okamoto, Kensuke Onishi, Kohei Onozaki, Takeshi Sakakibara, Kazuhisa Takeuchi, Yasuharu Tokuda, Yuji Yamamoto, Mayuka Yamazaki, *Kenji Shibuya, for the Health Care 2035 Advisory Panel*

Department of Health Policy and Management, School of Medicine, Keio University, Tokyo, Japan (HM); Cancer Control and Health Promotion Division, Health Service Bureau, Ministry of Health, Labour and Welfare, Tokyo, Japan (SE); Course of Human Welfare Environment, Department of Human Development, School of Humanities and Culture, Tokai University, Kanagawa, Japan (MH); Department of Family and Community Medicine, Hamamatsu University School of Medicine, Shizuoka, Japan (MI); Faculty of Economics, Hosei University, Tokyo, Japan (KOg); Office of Drug-Induced Damages, General Affairs Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, Tokyo, Japan (TO); Asia Pacific Alliance for Disaster Management, Tokyo, Japan (KOni); Health and Global Policy Institute, Tokyo, Japan (KOno); General Affairs Division, Heath Insurance Bureau, Ministry of Health, Labour and Welfare, Tokyo, Japan (TS); Welfare Manpower Promotion Office, Welfare Promotion Division, Social Welfare and War Victims' Relief Bureau, Ministry of Health, Labour and Welfare, Tokyo, Japan (KT); Japan Community Healthcare Organization, Tokyo, Japan (YT); Sony Computer Science Laboratories, Inc, Tokyo, Japan (YY); Harvard Business School Japan Research Center, Tokyo, Japan (MY); and Department of Global Health Policy, Graduate School of Medicine, The University of Tokyo, Tokyo 113-0033, Japan (KS)

shibuyak@m.u-tokyo.ac.jp

We are all members of the Health Care 2035 Advisory Panel. We declare no competing interests.

1 Reich MR, Ikegami N, Shibuya K, Takemi K. 50 years of pursuing a healthy society in Japan. *Lancet* 2011; **378:** 1051–53.

2 Shibuya K, Hashimoto H, Ikegami N, et al. Future of Japan's system of good health at low cost with equity: beyond universal coverage. *Lancet* 2011; **378:** 1265–73.

3 Ministry of Health, Labour and Welfare. Act on comprehensive promotion of healthcare and long-term care. Tokyo, Japan: Ministry of Health, Labour and Welfare, 2014 (in Japanese). http://www.mhlw.go.jp/file/05-Shingikai-10801000-Iseikyoku-Soumuka/0000052614_1.pdf (accessed June 14, 2015).

4 Takeuchi H, Miyata H, Gotoh M, et al. A risk model for esophagectomy using data of 5354 patients included in a Japanese nationwide web-based database. *Ann Surg* 2014; **260:** 259–66.

5 Nature. Japan. *Nature* 2015; **519:** 556–57.

6 Health Care 2035 Advisory Panel. Japan Vision: Health Care 2035. Tokyo, Japan: Ministry of Health, Labour and Welfare, 2015. http://www.mhlw.go.jp/seisakunitsuite/bunya/hokabunya/shakaihoshou/hokeniryou2035/ (accessed June 14, 2015).

7 Anand S. Human security and universal health insurance. *Lancet* 2012; **379:** 9–10.

8 Hashimoto H, Ikegami N, Shibuya K, et al. Cost containment and quality of care in Japan: is there a trade-off? *Lancet* 2011; **378:** 1174–82.

9 Integrated Community Care System. Policy brief: long-term care and welfare policy for the elderly. Tokyo, Japan: Ministry of Health, Labour and Welfare, 2014 (in Japanese). http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/hukushi_kaigo/kaigo_koureisha/chiiki-houkatsu/ (accessed June 14, 2015).

10 Commission on Social Determinants of Health. Closing the gap in a generation: health equity through action on the social determinants of health. Final Report of the Commission on Social Determinants of Health. Geneva: World Health Organization, 2008.

11 Jamison DT, Summers LH, Alleyne G, et al. Global health 2035: a world converging within a generation. *Lancet* 2013; **382:** 1898–955.

PLOS | ONE

RESEARCH ARTICLE

Angiographic Lesion Complexity Score and In-Hospital Outcomes after Percutaneous Coronary Intervention

Ayaka Endo[1,2], Akio Kawamura[2], Hiroaki Miyata[3], Shigetaka Noma[4], Masahiro Suzuki[5], Takashi Koyama[6], Shiro Ishikawa[7], Susumu Nakagawa[1], Shunsuke Takagi[8], Yohei Numasawa[9], Keiichi Fukuda[2], Shun Kohsaka[2]*, JCD-KICS Investigators[¶]

1 Department of Cardiology, Saiseikai Central Hospital, Tokyo, Japan, **2** Department of Cardiology, Keio University School of Medicine, Tokyo, Japan, **3** University of Tokyo, Healthcare Quality Assessment, Tokyo, Japan, **4** Department of Cardiology, Saiseikai Utsunomiya Hospital, Tochigi, Japan, **5** Department of Cardiology, National Hospital Organization, Saitama National Hospital, Saitama, Japan, **6** Department of Cardiology, Kyosai Tachikawa Hospital, Tokyo, Japan, **7** Department of Cardiology, Saitama City Hospital, Saitama, Japan, **8** Department of Cardiology, Hiratsuka City Hospital, Kanagawa, Japan, **9** Department of Cardiology, Ashikaga Red Cross Hospital, Tochigi, Japan

¶ Membership of the JCD-KICS Investigators is listed in the Acknowledgments.
* kohsaka@cpnet.med.keio.ac.jp

OPEN ACCESS

Citation: Endo A, Kawamura A, Miyata H, Noma S, Suzuki M, Koyama T, et al. (2015) Angiographic Lesion Complexity Score and In-Hospital Outcomes after Percutaneous Coronary Intervention. PLoS ONE 10(6): e0127217. doi:10.1371/journal.pone.0127217

Editor: Tohru Minamino, Niigata University Graduate School of Medical and Dental Sciences, JAPAN

Received: June 11, 2014

Accepted: April 13, 2015

Published: June 29, 2015

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: The authors have no support or funding to report.

Competing Interests: The authors have declared that no competing interests exist.

Abstract

Objective

We devised a percutaneous coronary intervention (PCI) scoring system based on angiographic lesion complexity and assessed its association with in-hospital complications.

Background

Although PCI is finding increasing application in patients with coronary artery disease, lesion complexity can lead to in-hospital complications.

Methods

Data from 3692 PCI patients were scored based on lesion complexity, defined by bifurcation, chronic total occlusion, type C, and left main lesion, along with acute thrombus in the presence of ST-segment elevation myocardial infarction (1 point assigned for each variable).

Results

The patients' mean age was 67.5 +/- 10.8 years; 79.8% were male. About half of the patients (50.3%) presented with an acute coronary syndrome, and 2218 (60.1%) underwent PCI for at least one complex lesion. The patients in the higher-risk score groups were older ($p < 0.001$) and had present or previous heart failure ($p = 0.02$ and $p = 0.01$, respectively). Higher-risk score groups had significantly higher in-hospital event rates for death, heart failure, and cardiogenic shock (from 0 to 4 risk score; 1.7%, 4.5%, 6.3%, 7.1%, 40%, $p < 0.001$); bleeding with a hemoglobin decrease of >3.0 g/dL (3.1%, 11.0%, 13.1%, 10.3%, 28.6%, $p < 0.001$);

and postoperative myocardial infarction (1.5%, 3.1%, 3.8%, 3.8%, 10%, p = 0.004), respectively. The association with adverse outcomes persisted after adjustment for known clinical predictors (odds ratio 1.72, p < 0.001).

Conclusion

The complexity score was cumulatively associated with in-hospital mortality and complication rate and could be used for event prediction in PCI patients.

Introduction

Percutaneous coronary intervention (PCI) is a reliable and effective therapeutic option for patients with coronary artery disease (CAD) and has become one of the most widely applied treatments in present-day cardiology. However, although periprocedural complications have declined over time, the risk of complications for patients with complex lesions in coronary vessels remains high. The definition of complex lesions includes vessel bifurcation, the presence of thrombus, involvement of the left main trunk, and the increasing number of "difficult" lesions that are now treated (e.g., those that are heavily calcified or diffuse, lesions in vessels with excessive tortuosity, or chronic total occlusive lesions) [1–9]. Therefore, it is important to evaluate the risk of complications in patients undergoing PCI for complex lesions.

No simple and user-friendly risk scoring system based on angiographic information has yet been established. The SYNTAX Score was devised to evaluate the angiographic characteristics that make a lesion suitable for either PCI or coronary artery bypass grafting (CABG), but it is not exactly a comprehensive bedside risk prediction tool [9–10]. Clinicians need a risk scoring system that will help predict short-term (i.e., in-hospital) outcomes, allowing informed clinical decisions to be made. The identification and quantification of the clinical factors associated with the complication risk would also facilitate observational research into the comparative effectiveness of therapeutic approaches. Further, at the policy-making level, predicted risk estimates can help "level the playing field" of provider outcome metrics, helping to adjust for potential differences in cases treated.

Based on the above considerations, we devised a modern PCI scoring system based on simple criteria of angiographic lesion complexity. Utilizing data from a multicenter Japanese registry, we assessed its association with in-hospital mortality and complications, as a means of facilitating more precise risk prediction.

Methods

Study design

The Japan Cardiovascular Database (JCD) is a large, ongoing, prospective multicenter cohort study designed to collect clinical background and outcome data on PCI patients. Data consisting of approximately 200 variables were collected for each patient. Participating hospitals were instructed to record data from consecutive hospital visits for PCI and to record them in an Internet-based database system. This system performs checks to ensure that the reported data are complete and internally consistent. PCI with any commercially available coronary device could be included. The decision to perform PCI was made according to the investigators' clinical assessment of their patients. The study did not mandate specific interventional or surgical techniques, such as vascular access, or use of specific stents or closure devices. Although the

size of the sheath and guiding catheter were not protocol-mandated in this cohort, the commonly used size was 6-Fr to 8-Fr when a transfemoral approach was used and 6-Fr for transradial interventions. The majority of clinical variables in the JCD were defined according to the National Cardiovascular Data Registry (NCDR), which was sponsored by the American College of Cardiology (ACC) to conduct comparative research in order to determine the factors leading to disparities in PCI management. The NCDR is a large PCI registry system with over 1,000,000 entries for ischemic heart disease and over 500,000 entries for PCI, collected from more than 500 institutions in the US [11].

The study was approved by the institutional review board of Keio University School of Medicine. The patient record was anonymized and de-identified prior to analysis. Major teaching hospitals within the metropolitan Tokyo area were selected for the pilot phase of this study, and the study protocol was approved by the institutional review board at each site. The written consent was obtained by the study participants. Patients were enrolled at the event; all the consecutive PCI procedures during the study period, including failure cases, were registered. Patients aged <18 years were excluded.

The present study was funded by the Kakenhi (Grant-in-Aid for Scientific Research) (No. 21790751). The JCD Steering Committee was responsible for overall study guidance, including the study protocol, data analysis, and interpretation of the results. The Department of Healthcare Quality Assessment of Tokyo University managed the database independently. Keio University School of Medicine Interhospital Cardiology Study Group managed the participating sites and provided a monthly on-site monitoring service to assure data accuracy and completeness throughout the study. During the planning, implementation and reporting of this study, there were no issues such as conflict of interest, conflict of responsibility, or intellectual property rights.

Information disclosure

Before the launch of the JCD, information about the objectives of the present study, its social significance, and an abstract were provided for clinical trial registration with the University Hospital Medical Information Network, which is recognized by the International Committee of Medical Journal Editors as an "acceptable registry" according to a statement issued in September 2004 (UMIN R000004736).

Definition of lesion complexity risk score and clinical outcomes

A complex lesion was defined as a treated lesion possessing at least one of the following high-risk angiographic lesion characteristics: bifurcation, chronic total occlusion (CTO), Type C, unprotected left main trunk (UPLMT), and thrombus formation. The size of the main or side branch vessel had to be at least 1.5 mm in diameter, as assessed by diagnostic angiogram, and significant stenosis was defined as a reduction of at least 50% in luminal diameter, by visual assessment. Bifurcation lesions were defined as a division of a vessel into at least two branches, with the plaque extending from at least one of the limbs to the branching point. A CTO lesion was defined as a 100% occluded lesion with complete interruption of antegrade flow (TIMI flow grade 0) that had been present for at least 3 months. Type C lesions were as defined by the American Heart Association/American College of Cardiology (AHA/ACC). UPLMT lesions were left main trunk lesions without patent coronary artery bypass grafts in the left anterior descending artery or the left circumflex artery. Thrombotic lesions were defined as the presence of new ST-segment elevation myocardial infarction (STEMI) as clinical presentation, with cardiac biomarkers exceeding the upper limit of normal, according to the individual hospital's laboratory parameters. The operator determined the presence of these characteristics at the time

of the coronary angiography. Patients were stratified both by absolute complex lesion status (yes/no), and by the total number of the five complex lesion criteria that were present (score 0: no complex lesion, score 1: one complex lesion, score 2: two complex lesions, score 3: three complex lesions, score 4: four complex lesions, and score 5: all complex lesions).

The primary outcome was all-cause in-hospital mortality and secondary outcomes included all in-hospital complications. In-hospital complications collected in the data system included in-hospital death from any cause after PCI; the combined cardiac events included in-hospital cardiac death (in-hospital death, heart failure or cardiogenic shock) [12], periprocedural myocardial infarction (defined as an increase in serum creatine kinase to above normal levels, associated with positive isoenzymes, routinely measured for all patients on the day after the PCI procedure), bleeding with a hemoglobin decrease of more than 3.0 g/dL or blood transfusion, contrast nephropathy, and persistent coronary flow reduction (TIMI flow less than grade 3). Contrast nephropathy was defined, according to the established definition in the literature, as an increase in serum Cr level $\geq$0.5 mg/dL or $\geq$25% above baseline values at 30 days after administration of contrast media, in the absence of any other identifiable major kidney insult. Major bleeding was defined as: 1) bleeding requiring a blood transfusion; 2) a decrease in the Hb level by $\geq$3.0 g/dL due to bleeding from any site, including the percutaneous entry site, retroperitoneum, gastrointestinal tract, genitourinary tract, and other/unknown sites; and 3) the need for intervention/surgery at the bleeding site to reverse/stop or correct the bleeding (such as surgical closure/exploration of the arteriotomy site, balloon angioplasty to seal an arterial tear, or endoscopy with cautery of a gastrointestinal bleed). The latter definition is equivalent to Bleeding Academic Research Consortium Type 3 bleeding.

Statistical analysis

Patients were stratified by the complexity score (0–5) of the target lesion(s), as described above. Descriptive statistics were calculated on the basis of clinical characteristics and treatment information for the registered patients. Statistical analysis was performed using SPSS version 15 (SPSS, Chicago, IL, USA). When continuous variables were assumed to show a normal distribution, the data were expressed as mean ± SD. When normality was not assumed, the data were expressed as median and interquartile range. Categorical data were summarized in terms of frequency and proportion. The 95% confidence intervals of the mean, median, and proportion values were also calculated. The baseline clinical characteristics of patients were compared using chi-square tests for categorical variables and analysis of variance for continuous variables. A two-tailed p-value <0.05 was considered statistically significant. Multivariate logistic regression analysis was performed to assess the association of increments in each lesion complexity score with in-hospital mortality and complications.

Results

Patients and baseline characteristics

Among the 3692 patients who underwent PCI procedures between September 1, 2008, and August 31, 2011, and were recorded in the JCD Registry, 2218 (60.1%) underwent revascularization of at least one complex lesion (Fig 1). Of the total of 3264 complex lesions, 894 (24.2%) were bifurcation, 266 (7.2%) were CTO, 1000 (27.1%) were type C, 270 (7.3%) were UPLMT, and 834 (22.6%) were STEMI. Thus, the most common types of complex lesion undergoing revascularization were type C, bifurcation, and STEMI lesions. The distribution of the study patients by complexity score is shown in Fig 1. In total, 1474 patients (39.9%) had no complex lesion attempted (score 0 group), 1375 patients (37.2%) had one complex lesion (score 1 group), 650 patients (17.6%) had 2 complex lesions (score 2 group), 183 patients (5.0%) had 3

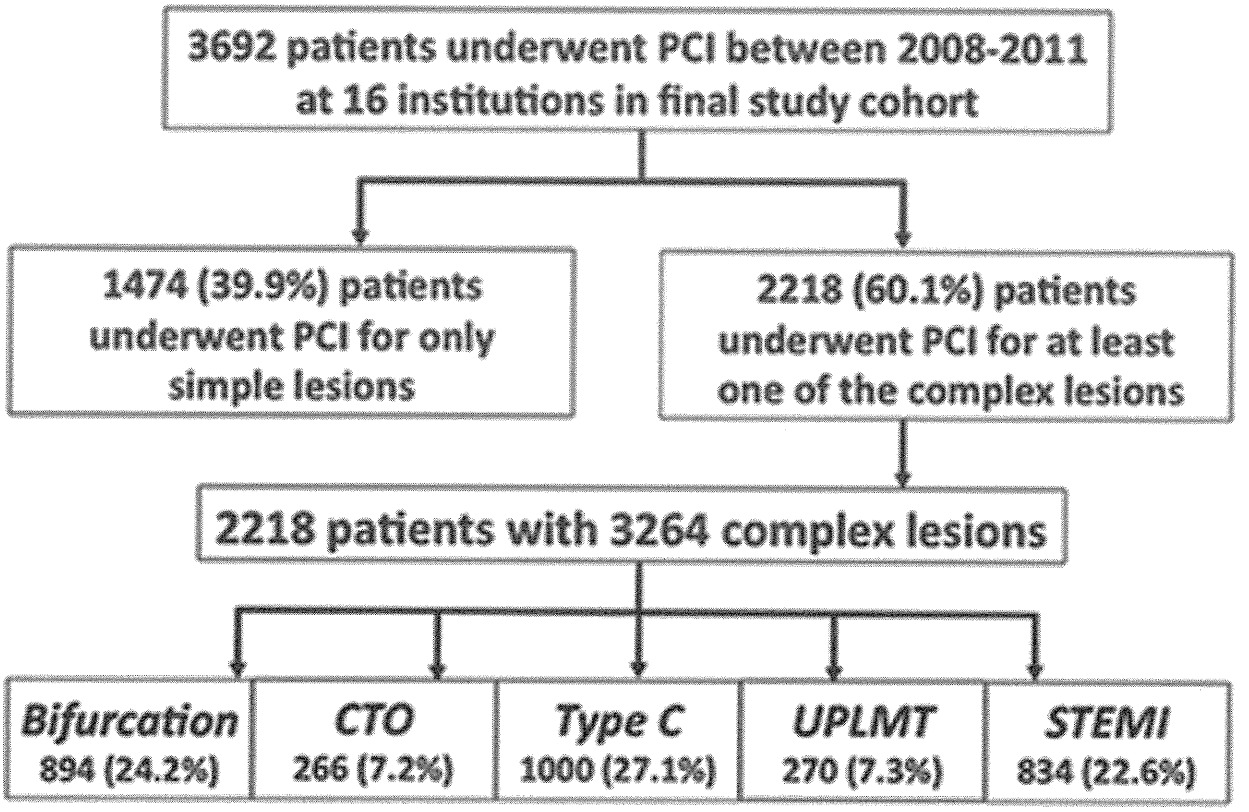


Fig 1. Flowchart showing the patients included in the present analysis. A total of 3692 patients were evaluated.

doi:10.1371/journal.pone.0127217.g001

complex lesions (score 3 group), and 10 patients (0.3%) had 4 complex lesions attempted (score 4 group). No patients had lesions with all types of complexity (score 5 group).

The clinical and angiographic characteristics of all the groups are shown in Table 1. The mean age of the entire cohort was 67.5 ± 10.8 years and 2935 (79.5%) were male. Overall, 1857 (50.3%) of the patients presented with acute coronary syndromes (ACS) and 1557 (42.2%) underwent non-elective procedures. The relationship between lesion complexity score and baseline variables had an inverted U-shape for male sex and a U-shape for age, especially for patients over 70 years old. Compared to patients in the score 0 group, patients in higher score groups had a lower left ventricular ejection fraction and were more likely to have a multi-vessel lesion in the left anterior descending artery. Patients in higher score groups also tended to present with ACS and heart failure, underwent more emergency PCI procedures, and were treated more frequently with a femoral artery approach, with intra-aortic balloon pump support, and with drug-eluting stents (DES).

Clinical outcomes

Details of in-hospital complications are shown in Table 2. Although 3265 (88.4%) procedures were completed successfully, 427 (11.6%) were associated with at least one complication. The rates of in-hospital mortality and complications were higher in the higher score groups compared with the lower score groups. Importantly, patients in higher score groups had significantly higher rates of in-hospital events, including death, heart failure and cardiogenic shock,

Table 1. Patient Demographics.

	Score 0 (n = 1474)	Score 1(n = 1375)	Score 2 (n = 650)	Score 3 (n = 183)	Score 4 (n = 10)	P value
Demographics						
Age, yrs	68.42±10.16	66.62±11.10	66.58±11.22	69.43±10.32	72.40±10.95	<0.001
50–59 yrs, n (%)	248 (16.8)	291 (21.2)	132 (20.3)	29 (15.8)	0 (0.0)	0.011
60–69 yrs, n (%)	519 (35.2)	480 (34.9)	228 (35.1)	63 (34.4)	2 (20.0)	0.902
70–79 yrs, n (%)	601 (40.8)	452 (32.9)	217 (33.4)	68 (37.2)	5 (50.0)	<0.001
>80 yrs, n (%)	181 (12.3)	162 (11.8)	67 (10.3)	32 (17.5)	2 (20.0)	0.102
Male, n (%)	1136 (77.1)	1098 (79.9)	533 (82.0)	161 (88.0)	7 (70.0)	0.002
Height, (cm)	161.45±8.92	162.46±9.83	162.40±8.77	163.45±8.33	158.38±7.48	0.005
Weight, (kg)	63.51±12.03	64.86±13.75	63.85±12.78	63.59±12.69	60.73±9.13	0.064
Body mass index, (kg/m2)	24.24±3.35	25.38±26.58	24.13±3.75	23.71±3.23	24.86±2.53	0.316
Clinical history						
Obese (BMI >30), n (%)	75 (5.1)	100 (7.3)	40 (6.2)	9 (4.9)	1 (10.0)	0.155
Hypertension, n (%)	1139 (77.3)	958 (69.7)	446 (68.6)	124 (67.8)	7 (70.0)	<0.001
Hyperlipidemia, n (%)	1031 (69.9)	892 (64.9)	429 (66.0)	106 (57.9)	6 (60.0)	0.003
Diabetes, n (%)	626 (42.5)	554 (40.3)	267 (41.1)	67 (36.6)	5 (50.0)	0.5
Insulin-dependent diabetes, n (%)	139 (9.4)	138 (10.0)	63 (9.7)	12 (6.6)	2 (20.0)	0.469
Current smoking, n (%)	427 (29.0)	523 (38.0)	236 (36.3)	57 (31.1)	2 (20.0)	<0.001
Familiy history of CAD, n (%)	32 (2.2)	45 (3.3)	25 (3.8)	4 (2.2)	0 (0.0)	0.184
Use of antianginal agents, n (%)	350 (23.7)	249 (18.1)	130 (20.0)	32 (17.5)	2 (20.0)	0.004
COPD, n (%)	45 (3.1)	34 (2.5)	19 (2.9)	4 (2.2)	0 (0.0)	0.833
Cancer, n (%)	51 (3.5)	49 (3.6)	23 (3.5)	5 (2.7)	0 (0.0)	0.951
Preoperative Creatinine, (mg/dl)	1.22±1.63	1.18±1.53	1.24±1.72	1.12±1.21	1.03±0.24	0.879
GFR, (ml/min)	87.13±33.03	87.79±31.13	90.13±34.26	89.94±46.56	71.08±15.09	0.211
Hemodialysis, n (%)	57 (3.9)	44 (3.2)	26 (4.0)	4 (2.2)	1 (10.0)	0.48
LVEF, (%)	59.35±12.75	55.81±13.99	54.78±13.18	54.81±13.09	46.86±13.43	<0.001
Cerebro-vascular disease, n (%)	125 (8.5)	98 (7.1)	52 (8.0)	18 89.8)	1 (10.0)	0.595
Peripheral artery disease, n (%)	102 (6.9)	99 (7.2)	49 (7.5)	15 (8.2)	3 (30.0)	0.083
Prior MI, n (%)	417 (28.3)	299 (21.7)	153 (23.5)	37 (20.2)	4 (40.0)	<0.001
Prior PCI, n (%)	651 (44.2)	416 (30.3)	189 (29.1)	62 (33.9)	3 (30.0)	<0.001
Prior CABG, n (%)	98 (6.6)	68 (4.9)	32 (4.9)	7 (3.8)	0 (0.0)	0.167
Prior HF, n (%)	142 (9.6)	81 (5.9)	39 (6.0)	14 (7.7)	2 (20.0)	0.001
Admission presentation						
STEMI, n (%)	0 (0)	508 (36.9)	250 (38.5)	70 (38.3)	6 (60.0)	<0.001
non-STEMI, n (%)	150 (10.2)	82 (6.0)	45 (6.9)	9 (4.9)	1 (10.0)	<0.001
Unstable angina, n (%)	404 (27.4)	221 (16.1)	82 (12.6)	28 (15.3)	1 (10.0)	<0.001
CCS 3, n (%)	378 (25.6)	259 (18.8)	111 (17.1)	29 (15.8)	2 (20.0)	<0.001
CCS 4, n (%)	139 (9.4)	136 (9.9)	59 (9.1)	13 (7.1)	2 (20.0)	0.575
Stable angina, n (%)	501 (34.0)	314 (22.8)	135 (20.8)	38 (20.8)	1 (10.0)	<0.001
Silent ischemia, n (%)	375 (25.4)	223 (16.2)	127 (19.5)	35 (19.1)	1 (10.0)	<0.001
Heart Failure, n (%)	143 (9.7)	125 (9.1)	78 (12.0)	22 (12.0)	3 (30.0)	0.049
NYHA 3, n (%)	76 (5.2)	75 (5.5)	43 (6.6)	12 (6.6)	2 (20.0)	0.194
NYHA 4, n (%)	38 (2.6)	54 (3.9)	33 (5.1)	7 (3.8)	2 (20.0)	0.012
In-hospital presentation						
Staged PCI, n (%)	109 (7.4)	106 (7.7)	46 (7.1)	19 (10.4)	0 (0.0)	0.523
Silent ischemia, n (%)	251 (17.0)	152 (11.1)	101 (15.5)	26 (14.2)	1 (10.0)	<0.001
2 vessel disease, n (%)	623 (42.3)	593 (43.1)	308 (47.4)	106 (57.9)	8 (80.0)	<0.001
3 vessel disease, n (%)	324 (22.0)	339 (24.7)	174 (26.8)	58 (31.7)	4 (40.0)	0.01

(*Continued*)