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Ⅲ．研究成果の刊行物・別刷

ORIGINAL ARTICLE

A Risk Model for Esophagectomy Using Data of 5354 Patients Included in a Japanese Nationwide Web-Based Database

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Objective: This study aimed to create a risk model of mortality associated with esophagectomy using a Japanese nationwide database.

Methods: A total of 5354 patients who underwent esophagectomy in 713 hospitals in 2011 were evaluated. Variables and definitions were virtually identical to those adopted by the American College of Surgeons National Surgical Quality Improvement Program.

Results: The mean patient age was 65.9 years, and 84.3% patients were male. The overall morbidity rate was 41.9%. Thirty-day and operative mortality rates after esophagectomy were 1.2% and 3.4%, respectively. Overall morbidity was significantly higher in the minimally invasive esophagectomy group than in the open esophagectomy group (44.3% vs 40.8%, $P = 0.016$). The odds ratios for 30-day mortality in patients who required preoperative assistance in activities of daily living (ADL), those with a history of smoking within 1 year before surgery, and those with weight loss more than 10% within 6 months before surgery were 4.2, 2.6, and 2.4, respectively. The odds ratios for operative mortality in patients who required preoperative assistance in ADL, those with metastasis/relapse, male patients, and those with chronic obstructive pulmonary disease were 4.7, 4.5, 2.3, and 2.1, respectively.

Conclusions: This study was the first, as per our knowledge, to perform risk stratification for esophagectomy using a Japanese nationwide database. The 30-day and operative mortality rates were relatively lower than those in previous reports. The risk models developed in this study may contribute toward improvements in quality control of procedures and creation of a novel scoring system.

Keywords: 30-day mortality, esophageal cancer, esophagectomy, minimally invasive esophagectomy, operative mortality, thoracoscopic surgery

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Esophageal cancer is the sixth leading cause of cancer-related mortality worldwide because of the high malignant potential and poor prognosis.[1] The postoperative 5-year survival rate in patients with American Joint Committee on Cancer stage I esophageal cancer is approximately 90%, and it decreases to 45% in patients with stage II disease, 20% in those with stage III disease, and 10% in those with stage IV disease.[2]

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Although the efficacy of chemoradiotherapy for esophageal cancer has been reported,[3–5] esophagectomy remains the mainstay of potential curative treatment for esophageal cancer. The recent improvement in long-term survival after esophagectomy can be attributed to advancements in surgical techniques for extended lymph node dissection and perioperative management.[6] However, esophagectomy is a highly invasive procedure with several serious postoperative complications, including pneumonia, anastomotic leaks, and sepsis, which may result in multiorgan failure.[7,8] A significant increase in morbidity and mortality after invasive procedures has been reported.[9–11]

Although several factors have been identified as predictors of morbidity and mortality after esophagectomy,[12–14] few have employed a large patient cohort to describe a risk model of mortality associated with esophagectomy.

Patient registration for the National Clinical Database (NCD) commenced in January 2011. It is a nationwide project that is linked to the surgical board certification system in Japan. In this study, we focused on the gastrointestinal surgery division of the NCD, which uses patient variables and definitions that are almost identical to those used by the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP).[15] Using this database, we developed a risk model of mortality associated with esophagectomy in Japan and focused on the comparison of minimally invasive esophagectomy (MIE) with open esophagectomy (OE).

PATIENTS AND METHODS

Data Collection

The NCD is a nationwide project in cooperation with the board certification system for surgery in Japan, and it collected data for more than 1,200,000 surgical cases from more than 3500 hospitals in 2011. The NCD, a Web-based data management system, continuously involves individuals who approve data, those in charge of annual case reporting from various departments, and data entry personnel, thereby assuring data traceability. Furthermore, it consecutively validates data consistency through inspections of randomly chosen institutions. Patients who refused publication of their treatment information were excluded from this study. Records with missing data or status at 30 days after surgery were also excluded. Essentially, only patients with complete data were registered in the NCD. All patients who underwent esophagectomy and were registered in the NCD were included in this study. Therefore, we have no detailed data on patients excluded because of missing data or insufficient follow-up. According to the inclusion criteria, only patients who underwent partial or total esophagectomy with reconstruction using any other organs such as the stomach, jejunum, or colon were included in this study. Therefore, 5354 patients who underwent esophagectomy in 713 hospitals from January 1, 2011, to December 31, 2011, were eligible for inclusion.

The NCD program focused on 30-day outcomes (whether or not a patient was discharged after initial admission) via direct ascertainment of the 30-day time point. Outcomes of esophagectomy include rigorously defined morbidities (ie, wound, respiratory,

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urinary tract, central nervous system, cardiac, and others) and mortality. The gastroenterological surgery section registers all surgical cases in the department and requires detailed input for the following items: esophagectomy, partial/total gastrectomy, right hemicolectomy, low anterior resection, hepatectomy, pancreatoduodenectomy, surgery for acute generalized peritonitis, and those cases that represent surgical procedures in each specialty. All variables, definitions, and inclusion criteria for the NCD were accessible online by the participating institutions (http://www.ncd.or.jp/), and the NCD supports an E-learning system so that participants can enter consistent data. In this study, preoperative patient variables such as clinical factors and laboratory data were almost identical to those used by the ACS NSQIP.[15] In particular, the NCD variables that were clinically suitable for esophagectomy and avoided multicollinearity for statistical analysis were chosen to create risk models of mortality following esophagectomy. The definitions of patient variables were also almost identical to those used by the ACS NSQIP.[15] Notably, the Web site is monitored and posts replies to all inquiries regarding data entry (approximately 80,000 inquiries in 2011), and it regularly posts some information under the Frequently Asked Questions tab.

Before esophagectomy, patients were generally assessed via esophagography, esophagoscopy, computed tomography, ultrasonography, endoscopic ultrasonography, and positron emission tomography in each institution. Clinical staging was performed preoperatively according to the TNM classification as proposed by the Union for International Cancer Control. Furthermore, patients' tolerance to the esophagectomy was routinely evaluated by the cardiac stress tests with electrocardiogram or echocardiogram, pulmonary function tests, blood gas analysis, and preoperative laboratory tests to assess general conditions including liver and renal functions, nutritional status, and comorbidities.

Endpoints

The primary outcome measures of this study were 30-day and operative mortalities. Operative mortality included all patients who had died within the index hospitalization period, regardless of the length of hospital stay (up to 90 days), any patient who had died after hospital discharge (up to 30 days after surgery), as well as all 30-day mortalities.

Statistical Analysis

Univariate analysis was performed using the Fisher exact test, unpaired Student *t* test, and the Mann-Whitney *U* test. To develop the risk model, data were randomly assigned to 2 subsets that were split 80/20 for model development and validation testing, respectively. The development data set included 4261 records and the validation data set included 1093 records. The 2 sets of logistic models (30-day and operative mortality) were constructed for the development data set using a stepwise selection of predictors with a P value of 0.05 for inclusion. A goodness-of-fit test was performed to assess the ability of the model to discriminate between survivors and deceased patients.

RESULTS

Risk Profile for the Study Population

The average age of the NCD esophagectomy patient population ($n = 5354$) was 65.9 years, and 4511 patients (84.3%) were males (Tables 1 and 2). Of the 5354 patients, only 0.8% required emergency esophagectomy. Preoperative risk and laboratory profiles for the study population are shown in Tables 1 and 2. Assistance in activities of daily living (ADL) before surgery was required in 2.0% patients, and weight loss of more than 10% during 6 months before surgery was observed in 9.2% patients. An American Society of Anesthesiologist (ASA) physical status of grade 3 or higher was observed in 7.3% patients. Histories of smoking within 1 year before surgery, preoperative habitual alcohol use, respiratory distress within 1 month before surgery, and preoperative chronic obstructive pulmonary disease (COPD) were recorded for 41.7%, 58.2%, 2.2%, and 6.1% patients, respectively. Other preoperative comorbidities included hypertension (30.5%), diabetes mellitus (12.7%), cerebrovascular disease (2.9%), and disseminated cancer (1.4%).

TABLE 1. Patient Clinical Parameters and Laboratory Data

	Total (n = 5354)
Age, median (25th–75th percentile), yrs	67.0 (61–72)
Sex	
Male	4511 (84.3%)
Female	843 (15.7%)
BMI, median (25th–75th percentile), kg/m^2	21.1 (18.8–23.1)
Length of hospital stay, median (25th–75th percentile), d	32.0 (23–49)
Length of ICU stay, median (25th–75th percentile), d	3.0 (2–5)
Preoperative blood tests, median (25th–75th percentile)	
WBC/mL	5600 (4430–6990)
Hemoglobin, g/dL	12.6 (11.2–13.9)
Platelet (×10,000/mL)	22.5 (18.3–27.9)
Albumin, g/dL	4.0 (3.7–4.3)
Total bilirubin, mg/dL	0.6 (0.4–0.8)
AST, U/L	20 (17–25)
ALT, U/L	16 (12–23)
ALP, U/L	221 (181–270)
Creatinine, mg/dL	0.8 (0.68–0.92)
Blood urea nitrogen, mg/dL	15 (12–19)
Sodium, mEq/L	140 (139–142)
CRP, mg/dL	0.14 (0.06–0.48)
PT-INR	1.0 (0.94–1.05)
APTT, sec	29.7 (26.6–31.8)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BMI, body mass index; CRP, C-reactive protein; ICU, intensive care unit; PT-INR, prothrombin time-international normalized ratio; WBC, white blood cells.

In the NCD, 5159 patients (96.4%) were diagnosed with esophageal cancer, 89 (1.7%) with gastric cancer involving the distal esophagus, and 21 (0.4%) with other malignancies such as head and neck cancer involving the proximal esophagus. Eighteen patients (0.3%) were diagnosed with benign tumors or gastrointestinal stromal tumors and 78 (1.3%) with benign diseases such as achalasia and corrosive esophageal injury.

Morbidity and Outcomes After Esophagectomy

The mean operative time and blood loss in the 5354 patients in the NCD esophagectomy population were 473 ± 160 minutes and 568 ± 570 mL (mean ± SD), respectively. Although we could not obtain the percentage of patients who underwent transhiatal or transthoracic approaches accurately in this study, only 232 (4.3%) of the 5354 patients underwent laparotomy (using the transhiatal approach) without thoracotomy. A total of 1751 (32.7%) patients underwent total (thoracoscopic and laparoscopic approaches) or hybrid (thoracoscopic or laparoscopic approach) MIE in the current study. Of these patients, 1436 (82.0%) underwent surgery using the thoracoscopic approach.

The overall morbidity rate in the NCD esophagectomy population was 41.9% (2244/5354). Surgical complications included surgical site infection (14.8%), anastomotic leakage (13.3%), and wound dehiscence (2.2%). Nonsurgical complications included incidences of pneumonia (15.4%), renal failure (2.4%), central nervous

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TABLE 2. Preoperative Variables and Mortality

	Entire Study Population (n = 5354)		30-d Mortality (n = 63)			Operative Mortality (n = 181)		
Variables	**n**	**%**	**n**	**%**	***P***	**n**	**%**	***P***
Male	4511	84.3	57	1.3	0.222	164	3.6	0.016
Emergency operation	43	0.8	3	7.0	0.014	6	14	0.003
ADL, any assistance	105	2.0	6	5.7	0.001	21	20.0	<0.001
Weight loss, >10%	494	9.2	15	3.0	<0.001	40	8.1	<0.001
Smoking within 1 year	2230	41.7	36	1.6	0.014	80	3.6	0.491
Habitual alcohol use	3118	58.2	40	1.3	0.442	108	3.5	0.702
Respiratory distress	118	2.2	7	5.9	<0.001	21	17.8	<0.001
COPD	328	6.1	7	2.1	0.107	24	7.3	<0.001
Pneumonia	64	1.2	3	4.7	0.039	9	14.1	<0.001
Hypertension	1633	30.5	25	1.5	0.129	62	3.8	0.286
Congestive heart failure	15	0.3	2	13.3	0.013	4	26.7	0.001
Myocardial infarction	9	0.2	0	0.0	1.00	0	0.0	1.00
Angina	44	0.8	1	2.3	0.407	3	6.8	0.185
Preoperative dialysis	13	0.2	1	7.7	0.143	2	15.4	0.069
Diabetes mellitus	681	12.7	10	1.5	0.445	31	4.6	0.087
Cerebrovascular disease	157	2.9	5	3.2	0.037	13	8.3	0.002
ASA physical status								
Grade 3–5	390	7.3	12	3.1	0.002	27	6.9	<0.001
Grade 4–5	8	0.1	1	12.9	0.09	3	37.5	0.002
Grade 5	2	0.04	1	50.0	0.023	2	100	0.001
Preoperative chemotherapy	1005	18.8	9	0.9	0.420	29	2.9	0.384
Preoperative radiotherapy	263	4.9	2	0.8	0.769	7	2.7	0.603
Disseminated cancer	76	1.4	3	3.9	0.060	5	6.6	0.113

system events (1.7%), cardiac events (1.2%), and septic shock (1.8%; Table 3). The reoperation rate after esophagectomy was 8.8%. In the NCD study population, the 30-day and operative mortality rates after esophagectomy were 1.2% (63/5354) and 3.4% (181/5354), respectively. Most postoperative complications were implicated in the increased 30-day and operative mortality rates (Table 3).

Comparison of OE and MIE

We compared MIE (n = 1751) with OE (n = 3603) outcomes using the NCD (Tables 4 and 5). The preoperative ASA physical status was better, rate of preoperative chemotherapy was higher, and rate of preoperative radiotherapy was lower in the MIE group than in the OE group. The operative time was significantly longer in the MIE group than in the OE group ($P < 0.001$), whereas blood loss was markedly lesser in the MIE group than in the OE group ($P < 0.001$). Notably, overall morbidity was significantly higher in the MIE group than in the OE group (44.3% vs 40.8%, $P = 0.016$). In particular, the incidence of anastomotic leakage was significantly higher in the MIE group than in the OE group (14.9% vs 12.5%, $P = 0.016$). Moreover, the reoperation rate within 30 days was significantly higher in the MIE group than in the OE group (8.0% vs 5.6%, $P = 0.001$). However, there were no marked differences in 30-day or operative mortality rates between the OE and MIE groups.

Model Results

Univariate analysis revealed that some preoperative risk factors were significantly increased in the 30-day and operative mortality groups, including preoperative requirement of assistance in ADL (any assistance); weight loss of more than 10% within 6 months before surgery; history of smoking within 1 year before surgery; history of respiratory distress within 1 month before surgery; history of COPD, congestive heart failure, or cerebrovascular disease before surgery; and ASA physical status classification (Table 2). Preoperative chemotherapy and radiotherapy were not correlated with increased mortality.

Risk models of 30-day and operative mortality were developed. The final logistic models with odds ratio (OR) and 95% confidence intervals (CIs) are presented in Tables 6 and 7. Preoperative assistance in ADL was the most significant factor in both models (30-day mortality: OR = 4.203; 95% CI: 1.649–10.715; operative mortality: OR = 4.707; 95% CI: 2.545–8.707). In addition, the following overlapping variables between the 2 models were observed: weight loss of more than 10% within 6 months before surgery (30-day mortality: OR = 2.427; 95% CI: 1.228–4.799; operative mortality: OR = 1.983; 95% CI: 1.267–3.104) and age group (30-day mortality: OR = 1.506; 95% CI: 1.228–1.847; operative mortality: OR = 1.355; 95% CI: 1.202–1.528).

A history of smoking within 1 year before surgery (OR = 2.578; 95% CI: 1.404–4.733) was an independent variable in the 30-day mortality group (Table 6). Male sex (OR = 2.263; 95% CI: 1.236–4.144), history of COPD before surgery (OR = 2.100; 95% CI: 1.242–3.550), and presence of metastatic/relapsed cancer (OR = 4.459; 95% CI: 1.827–10.882) were identified as independent variables in the operative mortality group (Table 7). In addition, there were several independent variables in the preoperative laboratory data, such as white blood cell and platelet counts; serum albumin, sodium, and blood urea nitrogen levels; and prothrombin time-international normalized ratio (PT-INR).

The scoring system for the mortality risk models according to the logistic regression equation was as follows:

$$\text{Predicted mortality} = e\left(\beta 0 + \sum \beta i Xi\right)/1 + e\left(\beta 0 + \sum \beta i Xi\right).$$

βi is the coefficient of the variable Xi in the logistic regression equation provided in Table 6 for 30-day mortality, and Table 7 for operative mortality. $Xi = 1$ if a categorical risk factor is present and 0 if it is absent. For age category, $Xi = 1$ if patient age is <59; 60–64 $Xi = 2$; 65–69 $Xi = 3$; 70–74 $Xi = 4$; and ≥75 $Xi = 5$.

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TABLE 3. Postoperative Complications and Mortality

	n = 5354		30-d Mortality (n = 63)			Operative Mortality (n = 181)		
	n	%	n	%	*P*	n	%	*P*
Surgery								
Operating time >6 h	4184	78.1	48	1.1	0.759	139	3.3	0.648
Bleeding 1000–2000 mL	579	10.8	9	1.6	0.41	42	7.3	<0.001
Bleeding > 2000 mL	134	2.5	7	5.2	0.001	13	9.7	0.001
Transfusion any	504	9.4	39	7.7	<0.001	93	18.5	<0.001
Transfusion over 5 U	188	3.5	24	12.8	<0.001	63	33.5	<0.001
Surgical complications								
Surgical site infection								
Superficial incision	414	7.7	11	2.7	0.008	31	7.5	<0.001
Deep incision	253	4.7	12	4.7	<0.001	26	10.3	<0.001
Organ space	495	9.2	18	3.6	<0.001	57	11.5	<0.001
Anastomotic leakage	711	13.3	20	2.8	<0.001	64	9.0	<0.001
Wound dehiscence	116	2.2	7	6.0	<0.001	17	14.7	<0.001
Nonsurgical complications								
Pneumonia	822	15.4	37	4.5	<0.001	113	13.7	<0.001
Unplanned intubation	450	8.4	42	9.3	<0.001	101	22.4	<0.001
Prolonged ventilation over 48 h	610	11.4	42	6.9	<0.001	110	18.0	<0.001
Pulmonary embolism	19	0.4	1	5.3	0.202	3	15.8	0.025
Renal failure	126	2.4	27	21.4	<0.001	64	50.8	<0.001
CNS events	91	1.7	20	22.0	<0.001	35	38.5	<0.001
Cardiac events	66	1.2	31	47.0	<0.001	43	65.2	<0.001
Septic shock	99	1.8	25	25.3	<0.001	54	54.5	<0.001
Readmission within 30 d	98	1.8	0	0.0	0.631	1	1.0	0.263
Reoperation any	470	8.8	15	3.2	<0.001	47	10.0	<0.001
Reoperation within 30 d	343	6.4	12	2.5	0.001	39	11.4	<0.001

CNS indicates central nervous system.

TABLE 4. Comparison of Preoperative Variables Between OE and MIE

	Entire Study Population (n = 5354)		OE (n = 3603)		MIE (n = 1751)		
Variables	n	%	n	%	n	%	*P*
Age, mean, yrs	65.9	—	66.1	—	65.7	—	0.15
BMI, mean, kg/m^2	21.1	—	21.1	—	21.2	—	0.29
Male	4511	84.3	3064	85.0	1447	82.6	0.025
Emergency operation	43	0.8	35	0.9	8	0.5	0.050
ADL, any assistance	105	2.0	80	2.2	25	1.4	0.058
Weight loss, >10%	494	9.2	355	9.9	139	7.9	0.023
Smoking within a year	2230	41.7	1487	41.3	743	42.4	0.425
Habitual alcohol use	3118	58.2	2067	57.4	1051	60.0	0.067
Respiratory distress	118	2.2	93	2.6	25	1.4	0.007
COPD	328	6.1	205	5.7	123	7.0	0.060
Pneumonia	64	1.2	45	1.2	19	1.1	0.69
Hypertension	1633	30.5	1098	30.5	535	30.6	0.95
Congestive heart failure	15	0.3	11	0.3	4	0.2	0.79
Myocardial infarction	9	0.2	6	0.2	3	0.2	1.00
Angina	44	0.8	29	0.8	15	0.9	0.87
Preoperative dialysis	13	0.2	10	0.3	3	0.2	0.57
Diabetes mellitus	681	12.7	477	13.2	204	11.7	0.11
Cerebrovascular disease	157	2.9	107	3.0	50	2.9	0.86
ASA physical status							
Grade 3–5	390	7.3	297	8.2	93	5.3	<0.001
Grade 4–5	8	0.1	7	0.2	1	0.1	0.29
Grade 5	2	0.04	2	0.1	0	0.0	1.00
Preoperative chemotherapy	1005	18.8	646	17.9	359	20.5	0.025
Preoperative radiotherapy	263	4.9	201	5.6	62	3.5	0.001
Disseminated cancer	76	1.4	62	1.7	14	0.8	0.007

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TABLE 5. Comparison of Postoperative Complications and Mortality Between OE and MIE

	(n = 5354)		OE (n = 3603)		MIE (n = 1751)		
	n	%	n	%	n	%	*P*
Surgery							
Operating time, mean, min	473	—	450	—	523	—	<0.001
Bleeding, mean, mL	568	—	618	—	466	—	<0.001
Operating time > 6 h	4184	78.1	2640	73.3	1544	88.2	<0.001
Bleeding 1000–2000 mL	579	10.8	455	12.6	124	7.1	<0.001
Bleeding > 2000 mL	134	2.5	100	2.8	34	1.9	0.076
Transfusion any	504	9.4	364	10.1	140	8.0	0.014
Transfusion > 5 U	188	3.5	134	3.7	54	3.1	0.27
Overall morbidity	2244	41.9	1469	40.8	775	44.3	0.016
30-d mortality	63	1.2	46	1.3	17	1.0	0.42
Operative mortality	181	3.4	129	3.6	52	3.0	0.26
Surgical complications							
Surgical site infection							
Superficial incision	414	7.7	277	7.7	137	7.8	0.87
Deep incision	253	4.7	174	4.8	79	4.5	0.63
Organ space	495	9.2	323	9.0	172	9.8	0.32
Anastomotic leakage	711	13.3	450	12.5	261	14.9	0.016
Wound dehiscence	116	2.2	80	2.2	36	2.1	0.76
Nonsurgical complications							
Pneumonia	822	15.4	560	15.5	262	15.0	0.60
Unplanned intubation	450	8.4	305	8.5	145	8.3	0.83
Prolonged ventilation over 48 h	610	11.4	426	11.8	184	10.5	0.17
Pulmonary embolism	19	0.4	11	0.3	8	0.5	0.46
Renal failure	126	2.4	93	2.6	33	1.9	0.12
CNS events	91	1.7	65	1.8	26	1.5	0.43
Cardiac events	66	1.2	48	1.3	18	1.0	0.43
Septic shock	99	1.8	72	2.0	27	1.5	0.28
Readmission within 30 d	98	1.8	70	1.9	28	1.6	0.45
Reoperation any	470	8.8	299	8.3	171	9.8	0.080
Reoperation within 30 d	343	6.4	203	5.6	140	8.0	0.001

CNS indicates central nervous system.

TABLE 6. Risk Model for 30-Day Mortality

Variables	β Coefficient	OR	95% CI		*P*
Age category	0.409	1.506	1.228	1.847	<0.001
Smoking within 1 yr	0.947	2.578	1.404	4.733	0.002
ADL (any assistance)	1.436	4.203	1.649	10.715	0.003
Weight loss > 10%	0.887	2.427	1.228	4.799	0.011
Platelet > 40 (×10,000/mL)	0.919	2.507	1.128	5.570	0.024
Sodium level < 135 mEq/L	1.278	3.591	1.699	7.591	0.001
PT-INR > 1.1	0.702	2.019	1.044	3.903	0.037
WBC < 4000/mL	1.018	2.767	1.439	5.320	0.002
WBC > 12000/mL	1.295	3.650	1.180	11.288	0.025
Intercept (β_0)	−7.165				<0.001

Age category (<59, 60–64, 65–69, 70–74, and ≥75 years).

Model Performance

To evaluate model performance, both the C-index (measure of model discrimination), which was the area under the receiver operating characteristics (ROC) curve, and the model calibration across risk groups were evaluated. The C-index of 30-day and operative mortality was 0.791 (95% CI: 0.725–0.858; $P < 0.001$) and 0.776 (95% CI: 0.737–0.814; $P < 0.001$), respectively, in the development data set and 0.767 (95% CI: 0.654–0.880; $P = 0.001$) and 0.742 (95% CI: 0.666–0.819; $P < 0.001$), respectively, in the validation data set. The ROC curves of model performance in the validation data set are shown in Figure 1 (Supplemental Digital Content, available at http://links.lww.com/SLA/A543).

To clarify the influence of the choice of OE or MIE on the risk models established in this study, we applied the risk models to the OE and MIE groups. The C-indices of 30-day and operative mortality were 0.770 (95% CI: 0.697–0.844; $P < 0.001$) and 0.778 (95% CI: 0.736–0.820; $P < 0.001$), respectively, in the OE group (n = 3603) and 0.824 (95% CI: 0.742–0.906; $P = 0.001$) and 0.746 (95% CI: 0.689–0.804; $P < 0.001$), respectively, in the MIE group (n = 1751) (Figures 2 and 3; Supplemental Digital Content, available at http://links.lww.com/SLA/A543). Moreover, the calibration of the models demonstrated a favorable correlation between the predicted mortality rate and the matched observed mortality rate among the patient risk subgroups (data not shown).

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TABLE 7. Risk Model for Operative Mortality

Variables	β Coefficient	OR	95% CI		P
Age category	0.304	1.355	1.202	1.528	<0.001
Sex (male)	0.817	2.263	1.236	4.144	0.008
ADL (any assistance)	1.549	4.707	2.545	8.707	<0.001
COPD	0.742	2.100	1.242	3.550	0.006
Weight loss > 10%	0.685	1.983	1.267	3.104	0.003
Cancer metastasis/relapse	1.495	4.459	1.827	10.882	0.001
Platelet < 12 (×10,000/mL)	0.684	1.981	1.014	3.870	0.045
Albumin < 3.5 g/dL	0.800	2.225	1.500	3.299	<0.001
Blood urea nitrogen < 8 mg/dL	0.938	2.555	1.251	5.218	0.010
Sodium < 138 mEq/L	0.726	2.068	1.404	3.044	<0.001
PT-INR > 1.25	1.098	2.999	1.569	5.734	0.001
WBC < 4500 /mL	0.584	1.794	1.233	2.611	0.002
Intercept (β_0)	−6.014				<0.001

Age category (<59, 60–64, 65–69, 70–74, and ≥75 years).

DISCUSSION

In this study, a total of 5354 patients who underwent esophagectomy in 713 institutes throughout Japan were analyzed using the NCD study population data. Although perioperative management has gradually improved, the morbidity and mortality rates after esophagectomy are the highest among all types of solid tumor surgeries in Japan.[6,16] However, until now, there were no confirmed data regarding morbidity and mortality after esophagectomy based on a nationwide survey in Japan.

To the best of our knowledge, this is the first report that used the nationwide database in Japan to convincingly demonstrate the incidence of preoperative comorbidities and postoperative complications and rate of mortality among patients who underwent esophagectomy. Furthermore, we attempted to develop a risk model of mortality using preoperative variables of patients undergoing esophagectomy. In this study, the overall morbidity rate in the NCD esophagectomy population was 41.9%. Various postoperative complications included pneumonia (15.4%), anastomotic leakage (13.3%), and septic shock (1.8%). The 30-day mortality rate was 1.2% and the operative mortality rate was 3.4%. Most postoperative complications were implicated in the increased 30-day and operative mortality rates.

In this study, we could not calculate the percentage of patients with squamous cell carcinoma or adenocarcinoma. Furthermore, we could not determine the clinical and pathological stage of esophageal cancer because of the lack of data in the NCD. However, in our previous report, which was a comprehensive survey of esophageal cancer cases in 214 institutions in Japan (2004),[17] 92.7% patients who underwent esophagectomy were diagnosed with squamous cell carcinoma whereas 4.0% were diagnosed with adenocarcinoma. Also, in our previous report,[17] 23.3% patients who underwent esophagectomy were diagnosed with cStage I disease, 31.4% with cStage II disease, and 35.8% with cStage III disease (Union for International Cancer Control-TNM, 5th ed). After surgery, 22.6% patients who underwent esophagectomy were diagnosed with pStage I disease, 37.9% with pStage II disease, and 35.3% with pStage III disease. In general, patients with high-grade dysplasia, carcinoma in situ, and T1a (up to lamina propria) tumors are treated via endoscopic resection procedures such as endoscopic mucosal resection and/or endoscopic submucosal dissection in Japan.[18] The proportion of patients with each histological type and each clinical and pathological stage in the current study was thought to be similar to that in our previous report.[17]

Regarding postesophagectomy reconstruction, the NCD did not clarify the percentage of individual reconstruction procedures. However, in our previous report,[17] 83.5% esophagectomy patients underwent gastric pull-up reconstruction, 3.6% underwent colonic interposition, and 4.2% underwent jejunal interposition. The proportion of patients who underwent each reconstruction procedure in the current study was considered to be almost similar to that in our previous report.[17] Therefore, we have to consider the possibility that colonic or jejunal interposition may have influenced the data for postoperative complications in this study.

Similar to this study, only 6.0% patients underwent laparotomy using the transhiatal approach in our previous survey.[17] The specific characteristics of thoracic esophageal squamous cell carcinoma, which is much more common than esophageal adenocarcinoma in Japan, include multidirectional lymphatic flow from the primary lesion and widespread and random patterns of lymph node metastasis from the cervical region to the abdomen.[2,19] On the basis of these clinical observations, transthoracic extended radical esophagectomy with 3-field lymph node dissection is recognized as a standard procedure in Japan.[2,20] The transhiatal approach is not as common in Japan because most patients with esophageal squamous cell carcinoma, which primarily occurs in the middle thoracic esophagus, are increasingly treated via thoracoscopic approach as opposed to the transhiatal approach.

However, transthoracic esophagectomy with 3-field lymph node dissection is one of the most invasive gastrointestinal surgeries.[9–11] In fact, the overall morbidity rate in our study seemed relatively high, but it was virtually identical to those in reports from the United Kingdom (overall medical morbidity, 39%; reintervention rate because of surgical morbidity, 18%)[21] and the United States (overall morbidity, 50%).[22] In particular, postoperative pneumonia and anastomotic leakage were major problems that could not be ignored in this study, and most postoperative complications were related to increased mortality. However, a recent systematic review of short-term clinical outcomes after esophagectomy demonstrated that the incidence of pneumonia was reportedly 1.5% to 38.9% whereas that of anastomotic leaks was 0% to 35%.[23] Therefore, the morbidity rates for pneumonia (15.4%) and anastomotic leakage (13.3%) in this study may be within average ranges.

Our results also demonstrated that 30-day mortality was relatively lower in Japan (1.2%) than in the United Kingdom (4.3%),[21] United States (3.0%),[22] and other large national databases.[24] The systematic review also indicated that the 30-day mortality rate after esophagectomy was 0% to 11.1% whereas the operative mortality rate was 0% to 15.4%.[23] These results suggest that not only prevention of postoperative complications but also appropriate management is crucial to minimize mortality after esophagectomy.

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Reportedly, MIE procedures such as thoracoscopic esophagectomy are increasingly performed worldwide.[25,26] In this study, we compared the outcomes of MIE with OE using the NCD and found that although there were no significant differences in 30-day or operative mortality rates between the OE and MIE groups, the incidence of anastomotic leakage and the rate of reoperation within 30 days because of surgical complications were significantly higher in the MIE group than in the OE group. However, the patient clinical background were markedly different between the 2 groups in the current study; therefore, in future studies, it is necessary to adjust the preoperative biases to objectively compare MIE and OE groups using other statistical methods such as propensity score matching. Nevertheless, our results were compatible with those from a previous study conducted in the United Kingdom by Mamidanna et al,[21] who reported the comparison of MIE with OE in the largest series of patients and confirmed the safety of MIE, even though MIE was associated with higher reoperation rates because of surgical complications and there were no marked benefits in operative mortality.

In this study, several patient and perioperative factors, including preoperative requirement of assistance in ADL; weight loss of more than 10% within 6 months before surgery; history of smoking within 1 year before surgery; history of respiratory distress within 1 month before surgery; history of COPD; congestive heart failure; and cerebrovascular disease before surgery; and ASA physical status were related to increased mortality as per univariate analysis. These results were relatively consistent with those of a previous analysis using the ACS NSQIP esophagectomy database.[22] It is likely that the preoperative requirement of assistance in ADL was because of various reasons such as comorbidities, advanced-stage esophageal cancer, and patient age.

The risk models developed in our study indicated that preoperative requirement of assistance in ADL, weight loss of more than 10% within 6 months before surgery, and age group were significant factors in both the 30-day and operative mortality models. History of smoking within 1 year before surgery, male sex, history of preoperative COPD, and abnormal preoperative laboratory test results were also identified as independent variables in the 30-day and operative mortality groups. Furthermore, presence of metastatic or relapsed cancer was significantly correlated with operative mortality. It is likely that preoperative poor general condition, as indicated by preoperative requirement of assistance in ADL, weight loss, and advanced age, were significantly correlated with mortality after esophagectomy. In addition, current smoking status and COPD are established strong predictors of pulmonary complications after esophagectomy.[22,27] Our results were compatible with those of previous analyses using large nationwide databases.[21,22] In contrast, presence of metastatic or relapsed esophageal cancer may be related to not only shorter cancer-specific survival but also high morbidity and mortality rates that have been reported in association with surgery for noncurative esophageal cancer.[6,28]

Several independent variables in the preoperative laboratory data, such as white blood cell and platelet counts; serum albumin, sodium, and blood urea nitrogen levels; and PT-INR have not been reported in previous risk models of mortality following esophagectomy.[14,21,22,24] However, abnormal laboratory test results are generally associated with poor overall health. A white blood cell (WBC) count of more than 12,000/mL and a platelet count of more than 400,000/mL may be linked to the possibility of preoperative infection and/or chronic inflammation. On the other hand, a WBC count of less than 4000/mL and a platelet count of less than 120,000/mL could be largely affected by preoperative chemo/radiotherapy. Hypoalbuminemia, which is a marker of malnutrition, is reportedly correlated with postoperative complications and mortality after esophagectomy.[29] Other abnormal laboratory data such as low sodium and blood urea nitrogen levels and extended PT-INR may result from various comorbidities, but severe liver dysfunction or liver cirrhosis because of excess alcohol use may be responsible for the abnormal laboratory test results in patients with esophageal squamous cell carcinoma.[1] Reportedly, esophagectomy in patients with cirrhosis carries a high risk of mortality and morbidity.[30] The preoperative abnormal laboratory data identified in our study can serve as novel markers for esophagectomy.

The C-indices of the 30-day and operative mortality models in the validation data set were 0.767 and 0.742, respectively. These results suggest that our risk models may be reliable and feasible in clinical practice. Although the usefulness of several scoring systems such as the Physiological and Operative Severity Score for enumeration of Mortality and Morbidity (POSSUM) in predicting the risk of esophagectomy has been reported,[31,32] these scoring systems seem to be unsuitable for prospective esophagectomy patients because the POSSUM model frequently overpredicts mortality after esophagectomy.[31,32] Therefore, we developed a novel scoring system suitable for patients with esophagectomy through these risk models, which will be evaluated in future studies.

Limitations

The use of the national database, derived from all types of patients and hospitals, would be expected to contribute to improvements in quality control of surgical procedures. However, the outcomes obtained in this study were influenced by hospital volume, training status and compliance, surgical specialization, resource utilization, and procedure-specific variables, which may change in the future.[33] However, variables pertaining to the risk of mortality in this study should be evaluated in a future study using these basic risk models. The NCD did not include information regarding clinical staging of esophageal cancer and preoperative clearance based on several clinical evaluations or the exclusion criteria of each institution. Furthermore, we could not obtain information regarding patients who avoided esophagectomy based on preoperative evaluations, and the NCD did not contain information regarding patients with prior operative histories.

We recognize that 2-field lymphadenectomy using the Ivor Lewis procedure or transhiatal esophagectomy is more commonly performed for esophageal adenocarcinoma in Western countries. Because differences in pathology may result in differences in surgical procedures, it remains unclear whether the mortality risk models developed in this study are applicable to assess patients in western countries.

Our results demonstrated favorable C-indices for 30-day and operative mortalities in the OE and MIE groups, suggesting that our risk models may not be markedly influenced by the choice of OE or MIE. However, the safety and benefits of MIE compared with those of conventional OE should be evaluated in more depth in the next study using this nationwide database.

The NCD commenced in January 2011 and has continued until 2013. To improve the contents of the NCD, we have decided to add the information of the TNM staging to the latest NCD, and we also plan to revise the NCD to add several important data for further studies.

CONCLUSIONS

We reported the first risk stratification esophagectomy study, as per our knowledge, based on a Japanese nationwide Web-based database. The 30-day and operative mortality rates in this study population were 1.2% and 3.4%, respectively, which were very satisfactory. We also developed risk models pertaining to esophagectomy, which should contribute to improvements in procedural quality control and creation of a novel scoring system suitable for esophagectomy.

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Appropriateness Ratings of Percutaneous Coronary Intervention in Japan and Its Association With the Trend of Noninvasive Testing

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate the appropriateness of percutaneous coronary intervention (PCI) in Japan and clarify the association between trends of pre-procedural noninvasive testing and changes in appropriateness ratings.

BACKGROUND Although PCI appropriateness criteria are widely used for quality-of-care improvement, they have not been validated internationally. Furthermore, the correlation of appropriateness ratings with implementation of newly developed noninvasive testing is unclear.

METHODS We assigned an appropriateness rating to 11,258 consecutive PCIs registered in the Japanese Cardiovascular Database according to appropriateness use criteria developed in 2009 (AUC/2009) and the 2012 revised version (AUC/2012). Trends of pre-procedural noninvasive testing and appropriateness ratings were plotted; logistic regression was performed to identify inappropriate PCI predictors.

RESULTS In nonacute settings, 15% of PCIs were rated inappropriate under AUC/2009, and this percent increased to 30.7% under AUC/2012 criteria. This was mostly because of the focused update of AUC, in which the patients were newly classified as inappropriate if they lacked proximal left anterior descending lesions and did not undergo pre-procedural noninvasive testing. However, these cases were simply not rated under AUC/2009. The amount of inappropriate PCIs increased over 5 years, proportional to the increase in coronary computed tomography angiography use. Use of coronary computed tomography angiography was independently associated with inappropriate PCIs (odds ratio: 1.33; $p = 0.027$).

CONCLUSIONS In a multicenter, Japanese PCI registry, approximately one-sixth of nonacute PCIs were rated as inappropriate under AUC/2009, increasing to approximately one-third under the revised AUC/2012. This significant gap may reflect a needed shift in appropriateness recognition of methods for noninvasive pre-procedural evaluation of coronary artery disease. (J Am Coll Cardiol Intv 2014;7:1000–9) © 2014 by the American College of Cardiology Foundation.

The advent of percutaneous coronary intervention (PCI) has significantly changed the treatment strategy for patients with coronary artery disease (CAD). However, although PCI has a significant benefit for reducing mortality and recurrent myocardial infarction among patients presenting

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with acute coronary syndrome (1), its survival benefit has not been clearly established for patients with stable CAD (2). Because the patients who undergo PCI are exposed to the risks of periprocedural complications such as bleeding or procedure-related myocardial infarction, the appropriate indications of PCI are of significant importance.

To promote the appropriate and judicious implementation of PCI, the American College of Cardiology Foundation and 6 other societies published joint appropriateness use criteria (AUC) for PCI in 2009 (AUC/2009) (3). These AUC have been applied to real-world clinical practice along with various registry data, and studies have demonstrated a strong possibility of PCI overuse in real-world practice in Western countries (4–6). However, reports on AUC application to patients outside of North America are sparse.

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In Japan, the number of PCI procedures has been increasing. More than 200,000 procedures in >800 hospitals were performed in 2012; this number is disproportionately large compared with the number of coronary artery bypass grafting (CABG) procedures. The number of PCI procedures is estimated to be >14 times greater than CABG procedures (7). Consequently, whereas the proportion of elective PCIs accounts for < 40% in the United States, as many as three-fourths of PCIs are performed in nonacute settings in Japan (7,8), and a greater number of patients with multivessel diseases are treated with PCI in Japan than in the United States (9). Furthermore, the pre-procedural evaluation is also quite different between the 2 countries: the performance of coronary CT angiography (CTA) is increasing remarkably in Japan, whereas the stress testing remains the main modality in the United States. These unique characteristics in Japan underscore the need for a proper evaluation of PCI appropriateness.

The purpose of our study was to evaluate the appropriateness of PCI indications in Japan on the basis of U.S. criteria and to compare the rate and characteristics of inappropriate PCIs between both countries. At present, 2 versions of AUC have been published in the United States. The original AUC/2009 was updated in 2012 (AUC/2012), emphasizing the importance of performing noninvasive stress testing before elective PCIs (10). The use of coronary CTA as a pre-procedural test is increasing in Japan and may have significantly altered appropriateness ratings. Although the risk of adverse cardiovascular events could be stratified by the extent of anatomic lesions on the basis of coronary CTA, computed tomography (CT)-based PCIs are rarely recognized as appropriate indications under current AUC. Therefore, in addition to reviewing the overall rating of PCI appropriateness, we sought to clarify its association with the trend in performing various noninvasive diagnostic tests.

ABBREVIATIONS AND ACRONYMS

AUC = appropriateness use criteria

CABG = coronary artery bypass grafting

CAD = coronary artery disease

CTA = computed tomography angiography

CT = computed tomography

FFR = fractional flow reserve

JCD = Japan Cardiovascular Database

PCI = percutaneous coronary intervention

PLAD = proximal left anterior descending artery

METHODS

DATA SOURCE. The Japan Cardiovascular Database (JCD) is an ongoing, prospective multicenter registry designed to collect clinical background and outcome data on consecutive PCI patients (11). In this registry, 16 teaching hospitals within the metropolitan Tokyo area participated and registered all PCI procedures performed during the study period, including failure cases, using an Internet-based interface. Approximately 200 variables were collected for each patient; clinical variables and in-hospital outcomes for JCD were defined in accordance with the National Cardiovascular Data Registry version 4.1. This registry, sponsored by the American College of Cardiology (12,13), is the largest national clinical registry program for diagnostic cardiac catheterization and PCI, with >1,500 centers currently participating across the United States. Additionally, in the JCD-PCI registry, the subgroup of patients who underwent an intracoronary infusion of acetylcholine to induce coronary vasospasm was also registered because vasospastic angina accounts for a significant portion of patients with CAD and acute coronary syndromes in Japan (14). Clinical research coordinators specifically trained in registering PCI procedures confirmed the proper registration of each patient. In addition, data reported on the Internet-based system were checked, and investigators visited each hospital quarterly to audit the database for completeness and consistency.

STUDY POPULATION. A total of 11,258 consecutive patients who underwent PCI procedures between September 2008 and March 2013 for acute and nonacute indications were registered in the database. A total of 1,208 patients were excluded because they underwent serial PCIs during the same hospitalization, there were insufficient baseline data, or they only underwent the acetylcholine challenge test. The remaining 10,050 patients were included in our study (**Figure 1**).

DEVELOPMENT OF AUC/2009 AND ITS RATING ASSIGNMENTS. AUC/2009 was developed by a collaboration of 6 American professional organizations

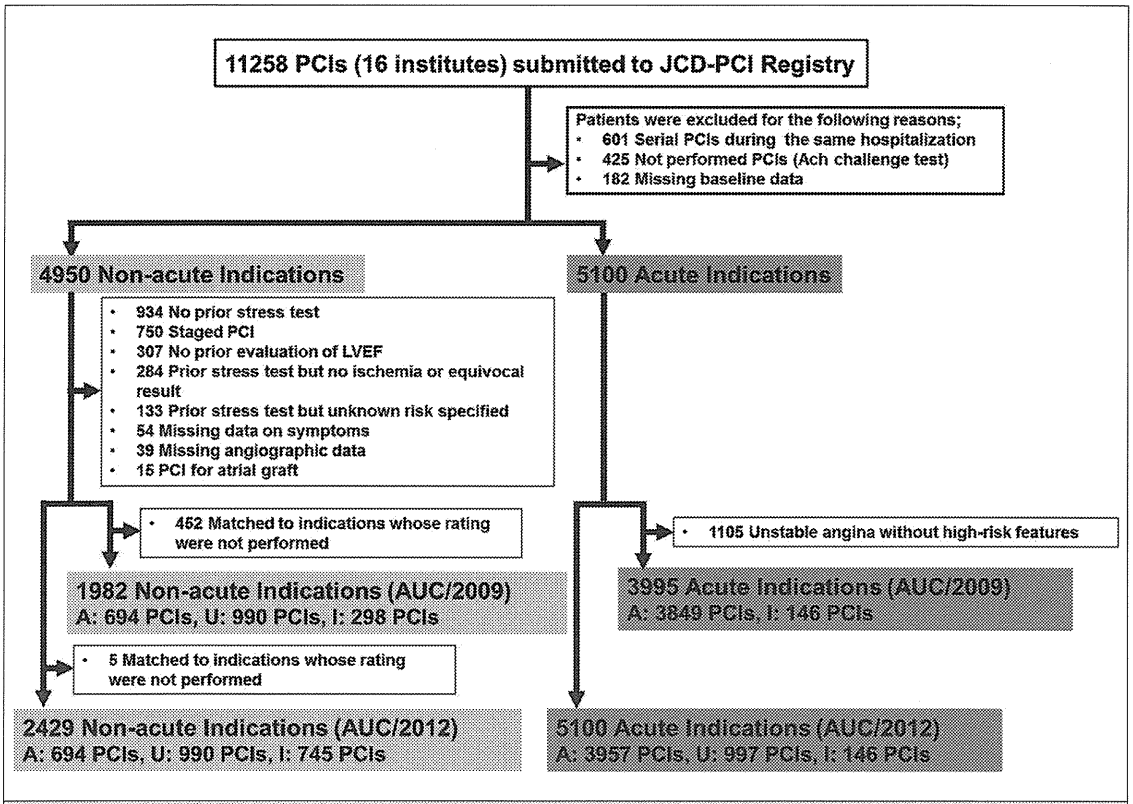

FIGURE 1 Study Cohort Creation

Patients registered in JCD-PCI Registry were divided into 2 groups (nonacute and acute indications). Each group was rated under AUC/2009 and AUC/2012. A = appropriate; Ach = acetylcholine; AUC = appropriateness use criteria; I = inappropriate; JCD-PCI = Japan Cardiovascular Database-Percutaneous Coronary Intervention; LVEF = left ventricular ejection fraction; U = uncertain.

(the American College of Cardiology Foundation, the Society for Cardiovascular Angiography and Intervention, the Society of Thoracic Surgeons, the American Association for Thoracic Surgery, the American Heart Association, and the American Society of Nuclear Radiology) in 2009. The methodology to develop the AUC for coronary revascularization was previously described (3).

We used an algorithm to map PCIs in the JCD-PCI registry to AUC/2009 and rate the procedures as appropriate, uncertain, or inappropriate. This algorithm, which was validated in a previous study (6), enabled the mapping to be performed in an efficient manner. All the definitions in our study were identical to those in AUC/2009. We optimized our mapping algorithm to maximize the use of existing data and minimize the influence of missing data. For example, certain nonacute indications can be assigned the appropriateness rating independent of noninvasive risk results (e.g., 3-vessel CAD with abnormal left ventricular systolic function). In these scenarios, an appropriateness classification could be provided even when noninvasive risk testing was not performed or results were not available.

Among the 10,050 patients, a rating could not be determined for 2,968 nonacute and 1,105 acute PCIs, leaving a total of 1,982 nonacute and 3,995 acute PCIs that could be rated (Figure 1). Among the acute indications, unstable angina without high-risk features was the main cause of rating failure. In the nonacute settings, mapping failure was mainly due to one of the following: no previous stress test performed, staged PCI, previous stress test with no ischemia or equivocal result, previous evaluation of left ventricular systolic function, and matched to indications that were not rated.

REVISED AUC/2012 AND ITS RATING ASSIGNMENTS. AUC/2009 was updated in 2012 (AUC/2012) (10). In the revised AUC/2012 version, unstable angina without high-risk features, which was an excluded clinical scenario in AUC/2009, was successfully mapped and divided into 2 indications according to the Thrombolysis In Myocardial Infarction score. In AUC/2009,

the clinical scenario of an asymptomatic patient without previous bypass surgery and with 1- or 2-vessel disease not involving the proximal left anterior descending artery (PLAD) who underwent no noninvasive testing was not evaluated because it was thought to be uncommon. However, in the revised AUC/2012, this clinical scenario was determined to be inappropriate. Accordingly, successfully mapped procedures increased, and 2,429 nonacute and 5,100 acute PCIs were rated (Figure 1).

STATISTICAL ANALYSIS. The proportion of PCIs classified as appropriate, uncertain, or inappropriate was determined, after stratification by acute versus nonacute indications on the basis of AUC/2009 and AUC/2012. Baseline characteristics and clinical variables of patients were compared by appropriateness categories. Differences were evaluated using the chi-square or Fisher exact test for categorical variables and the Student unpaired *t* test for continuous variables. Cochran-Armitage analysis was used to evaluate the trends of the proportion of inappropriate PCIs and of the implementation of various tests. Multivariate logistic regression analysis was performed to examine the relationship between the implementation of coronary CTA and inappropriate PCI, adjusting for potential confounders. The covariates included in the model were symptomatic status (symptomatic vs. asymptomatic), extent of ischemic burden (low risk vs. intermediate or high risk), antianginal medication (optimal vs. suboptimal medication), angiographic characteristics (left main trunk, triple-vessel disease, chronic total occlusion, or PLAD), and the time period when the PCI was performed (divided into 8 categories: September 2008 to June 2009, July 2009 to December 2009, January 2010 to June 2010, July 2010 to December 2010, January 2011 to June 2011, July 2011 to December 2011, January 2012 to June 2012, and July 2012 to March 2013). Data were analyzed using SPSS, version 20 (SPSS Inc., Chicago, Illinois). All p values were 2-sided, and significance was defined as $p < 0.05$ for all analyses.

RESULTS

PATIENT CHARACTERISTICS. Table 1 summarizes the clinical characteristics of patients who underwent PCIs in acute and nonacute settings. The mean age was 67.9 ± 10.9 years; 79.4% were male. Coronary risk factors, including a history of myocardial infarction and PCI, hypertension, hypercholesterolemia, and diabetes mellitus, were common; however, the prevalence of a history of CABG was lower than that in previous reports (4).

TABLE 1 Baseline Characteristics of Acute and Nonacute PCIs

	Total (N = 10,050)	Acute (n = 5100)	Nonacute (n = 4950)
Demographics			
Male	7,978 (79.4)	3,972 (77.9)	4,006 (80.9)
Age, yrs	67.9 ± 10.9	67.5 ± 11.8	68.2 ± 9.7
Clinical factors			
Hypertension	7,462 (74.3)	3,588 (70.4)	3,874 (78.3)
Hypercholesterolemia	6,681 (66.6)	3,109 (61.1)	3,572 (72.2)
Diabetes mellitus	4,229 (42.1)	1,901 (37.4)	2,328 (47.0)
Current and past smoking	3,517 (35.1)	2,022 (39.8)	1,495 (30.3)
History of MI	2,501 (24.9)	799 (15.7)	1,702 (34.4)
Previous PCI	3,613 (36.0)	990 (19.4)	2,623 (53.0)
Previous CABG	532 (5.3)	195 (3.8)	337 (6.8)
Hemodialysis	430 (4.3)	181 (3.6)	249 (5.0)
Cerebrovascular disease	909 (9.1)	454 (8.9)	455 (9.2)
Peripheral arterial disease	817 (8.1)	292 (5.7)	525 (10.6)
Chronic lung disease	309 (3.1)	153 (3.0)	156 (3.2)

Values are n (%) or mean ± SD.

CABG = coronary artery bypass grafting; MI = myocardial infarction; PCI = percutaneous coronary intervention.

ACUTE INDICATIONS. Among the patients with acute indications for PCI, ST-segment elevation myocardial infarction was found in 49.3%, whereas cardiogenic shock was found in 16.9%. All clinical indications for appropriate and inappropriate PCIs in the acute settings are outlined in Table 2. Overall, most acute indications (96.3%) were categorized as appropriate under AUC/2009 (Figure 2, Online Table 1), whereas all inappropriate procedures were categorized as hemodynamic and electrically stable patients, with

TABLE 2 All the Clinical Scenarios in the Acute Setting

AUC/2009 Indication No.	Indication	n (%)
Appropriate PCI		
1	STEMI, ≤12 h from onset of symptoms Revascularization of the culprit artery	1,397 (35.0)
9	UA/NSTEMI and high-risk features of short-term risk if death or nonfatal MI Revascularization of the presumed culprit artery	1,361 (34.1)
11	Patients with acute myocardial infarction (STEMI or NSTEMI) Evidence of cardiogenic shock Revascularization of ≥1 coronary arteries	755 (18.9)
2	STEMI, onset of symptoms within the previous 12–24 h Severe HF, persistent ischemic symptoms, or hemodynamic or electrical instability present	336 (8.4)
Inappropriate PCI		
3	STEMI, >12 h from symptom onset Asymptomatic; no hemodynamic instability and no electrical instability	146 (3.7)

AUC = appropriateness use criteria; HF = heart failure; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina.

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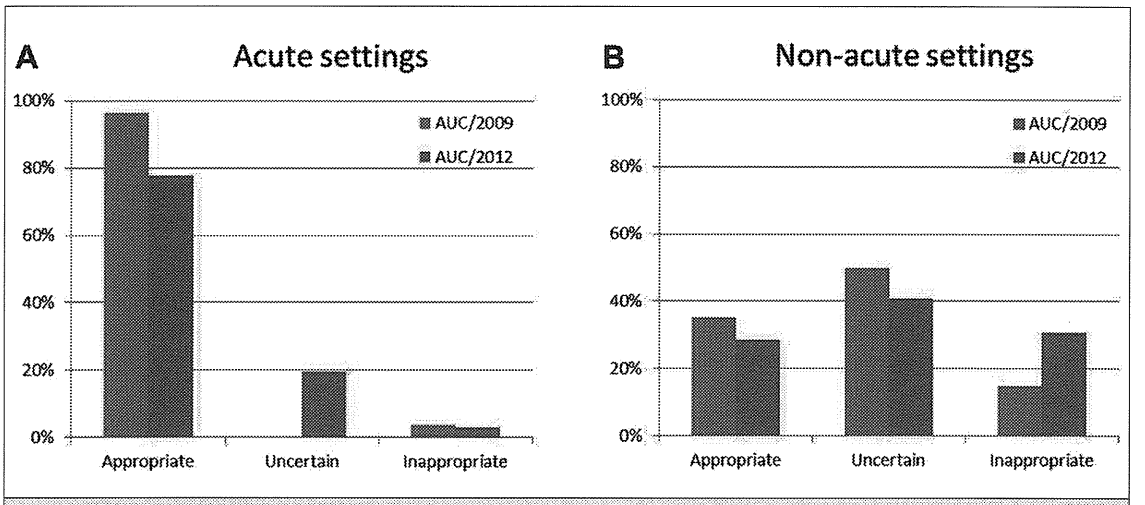

FIGURE 2 Appropriate Ratings Under Each Criterion

Appropriate ratings under each criterion in acute **(A)** settings and nonacute **(B)** settings. AUC = appropriateness use criteria.

PCI performed >12 h after symptom onset after ST-segment elevation myocardial infarction.

On the basis of AUC/2012, almost all cases of unstable angina without high-risk features (997 [90.2%]) were classified as uncertain, whereas 108 (9.8%) were considered appropriate. Overall, nearly 80% of acute procedures were categorized as appropriate (3,957 [77.6%]), whereas 997 (19.5%) were categorized uncertain and 146 (2.9%) were inappropriate (**Figure 2**, Online Table 1). All clinical indications for acute PCIs assessed by AUC/2012 are shown in Online Table 2.

NONACUTE INDICATIONS. In nonacute settings, 35.1% of PCIs were classified as appropriate, 49.9% as uncertain, and 15.0% as inappropriate under AUC/2009 (**Figure 2**, Online Table 1). Compared with procedures classified as appropriate or uncertain,

TABLE 3 Key Variables in Classifying Appropriateness for Nonacute PCIs in AUC/2009

		Procedural Appropriateness			
	Total (N = 1,982)	**Appropriate (n = 694)**	**Uncertain (n = 990)**	**Inappropriate (n = 298)**	**p Value**
Angina					<0.001
No symptoms	555 (32.2)	172 (24.8)	145 (14.6)	238 (79.9)	
CCS angina class					
I	377 (19.0)	67 (9.7)	283 (28.6)	27 (9.1)	
II	750 (37.8)	188 (27.1)	529 (53.4)	33 (11.1)	
III	239 (12.1)	214 (30.8)	25 (2.5)	0 (0)	
IV	38 (1.9)	30 (4.3)	8 (0.8)	0 (0)	
Unknown	23 (1.2)	23 (3.3)	0 (0)	0 (0)	
Noninvasive ischemia evaluation					<0.001
Low risk	228 (11.5)	19 (2.7)	82 (8.3)	127 (42.6)	
Intermediate risk	742 (37.4)	228 (32.9)	343 (34.6)	171 (57.4)	
High risk	195 (9.8)	156 (22.5)	39 (3.9)	0 (0)	
Maximal antianginal medications	117 (5.9)	70 (10.1)	45 (4.5)	2 (0.7)	<0.001
Angiographic characteristics					
Left main trunk	111 (5.6)	109 (15.7)	1 (0.1)	1 (0.3)	<0.001
3VD without left main trunk	345 (17.4)	290 (41.8)	46 (4.6)	9 (3.0)	<0.001
CTO without other coronary stenosis	77 (3.9)	15 (2.2)	44 (4.4)	18 (6.0)	0.007
Presence of proximal LAD stenosis	508 (25.6)	316 (45.5)	183 (18.5)	9 (3.0)	<0.001

Values are n (%).

CCS = Canadian Cardiovascular Society; CTO = chronic total occlusion; LAD = left anterior descending artery; 3VD = 3-vessel disease; all other abbreviations as in Table 2.

TABLE 4 Most Frequent Clinical Scenarios for Nonacute PCIs Classified as Inappropriate and Uncertain by AUC/2009

AUC/2009 Scenario No.	Indication: Anatomy	Previous CABG	Symptoms	Cardiac Risk (Noninvasive Tests)	Antianginal Medication	n (%)
Inappropriate PCIs						298
14a	1- or 2-vessel CAD, no proximal LAD involvement	No	Asymptomatic	Intermediate	None or minimal	146 (7.4)
12a	1- or 2-vessel CAD, no proximal LAD involvement	No	Asymptomatic	Low	None or minimal	60 (3.0)
12b	1- or 2-vessel CAD, no proximal LAD involvement	No	CCS class I or II	Low	None or minimal	57 (2.9)
56a	≥1 stenoses in non-CABG territory all bypass grafts patent	Yes	Asymptomatic	Intermediate	None or minimal	13 (0.7)
24a	CTO of 1 major coronary artery without other coronary stenoses	No	Asymptomatic	Intermediate	None or minimal	12 (0.6)
Uncertain PCIs						990
18b	1- or 2-vessel CAD, no proximal LAD involvement	No	CCS class I or II	Not available	Not available	524 (26.4)
14b	1- or 2-vessel CAD, no proximal LAD involvement	No	CCS class I or II	Intermediate	None or minimal	174 (8.8)
30b	1-vessel CAD involving the proximal LAD	No	CCS class I or II	Intermediate	None or minimal	49 (2.5)
36a	2-vessel CAD involving the proximal LAD	No	Asymptomatic	Intermediate	None or minimal	42 (2.1)
16a	1- or 2-vessel CAD, no proximal LAD involvement	No	Asymptomatic	High	None or minimal	29 (1.5)

CAD = coronary artery disease; all other abbreviations as in Tables 1 to 3.

inappropriate PCIs were more likely to be performed for patients who had no symptoms (appropriate, 24.8%; uncertain, 14.6%; inappropriate, 78.9%; $p < 0.001$), low-risk results from noninvasive testing (appropriate, 2.7%; uncertain, 8.3%; inappropriate, 42.6%; $p < 0.001$), or chronic total occlusion (appropriate, 2.2%; uncertain, 4.4%; inappropriate, 6.0%; $p < 0.007$) (Table 3). Overall, almost all of the inappropriate PCIs were confined to 5 scenarios, as summarized in Table 4. Frequently encountered scenarios included PCIs with suboptimal antianginal medications or involvement of single or multiple epicardial vessels other than the left main trunk or PLAD.

Under AUC/2012, asymptomatic patients with 1- or 2-vessel CAD with no PLAD involvement and without previous noninvasive testing (indication 18a in AUC/2009, indication 20a in AUC/2012) were rated as inappropriate (n = 447). When these scenarios were added, the percent of inappropriate PCIs increased from 15.0% to 30.7% (Figure 2, Online Table 1). Of these cases, as many as 120 (26.8%) were evaluated using coronary CTA before the procedures, and the results were positive in almost all the cases (noninterpretable, 4 cases; negative, 1 case). The most frequent clinical scenarios for nonacute PCIs classified as inappropriate and uncertain by AUC/2012 are summarized in Table 5.

ASSOCIATION BETWEEN TEMPORAL TRENDS OF NONINVASIVE TESTING AND THE RATE OF INAPPROPRIATE RATINGS. Figure 3 summarizes the use of several noninvasive tests such as the stress myocardial perfusion imaging and coronary CTA and fractional flow reserve (FFR). FFR is a pressure wire-based ischemic evaluation during coronary angiography. Figure 3 also demonstrates the temporal trends of the proportion of inappropriate PCIs. Among patients who underwent PCI, the proportion of patients evaluated with coronary CTA and FFR substantially increased (p for trend < 0.001), which coincided with a decrease in use of the stress myocardial perfusion imaging over the course of 5 years (p for trend < 0.001). Contemporaneously, the proportion of inappropriate PCIs increased (p for trend $= 0.003$) in parallel with the increase in coronary CTA use. Implementation of coronary CTA was associated with the rating of inappropriate PCI (odds ratio: 1.33; 95% confidence interval: 1.03 to 1.70; $p = 0.027$). Further, the time variables were not independently associated with the rating of inappropriate PCI (Online Table 3).

Figure 4 presents the change in the proportion of PCIs rated as inappropriate. Although the proportion of inappropriate PCIs accounted for 30.7% of all the elective procedures when the CT-based procedures were classified as inappropriate, this proportion decreased substantially (from 5.0% to 25.7%) when the CT-based procedures were classified as appropriate. Although the proportion of inappropriate PCIs tended to increase even when the CT-based procedures were classified as appropriate, the trend was not statistically significant (p for trend $= 0.09$).

DISCUSSION

In this contemporary, multicenter Japanese PCI registry, almost all acute PCIs were acceptable regardless of the criteria applied. However, approximately one-sixth of nonacute PCIs were rated as inappropriate under the original criteria. Under the updated AUC/

TABLE 5 Most Frequent Clinical Scenarios for Nonacute PCIs Classified as Inappropriate and Uncertain by AUC/2012

AUC/2012 Scenario No.	Indication: Anatomy	Previous CABG	Symptoms	Cardiac Risk	Antianginal Medication	n (%)
Inappropriate PCIs						745
20a	1- or 2-vessel CAD, no proximal LAD involvement	No	Asymptomatic	Not performed	Not available	447 (18.4)
16a	1- or 2-vessel CAD, no proximal LAD involvement	No	Asymptomatic	Intermediate	None or minimal	146 (6.0)
14a	1- or 2-vessel CAD, no proximal LAD involvement	No	Asymptomatic	Low	None or minimal	60 (2.5)
14b	1- or 2-vessel CAD, no proximal LAD involvement	No	CCS class I or II	Low	None or minimal	57 (2.3)
58a	≥1 stenoses in non-CABG territory, all bypass grafts patent	Yes	Asymptomatic	Intermediate	None or minimal	13 (0.6)
26a	CTO of 1 major coronary artery without other coronary stenoses	No	Asymptomatic	Intermediate	None or minimal	12 (0.5)
Uncertain PCIs						990
20b	1- or 2-vessel CAD, no proximal LAD involvement	No	CCS class I or II	Not available	Not available	524 (21.6)
16b	1- or 2-vessel CAD, no proximal LAD involvement	No	CCS class I or II	Intermediate	None or minimal	174 (7.2)
32b	1-vessel CAD involving the proximal LAD	No	CCS class I or II	Intermediate	None or minimal	49 (2.0)
38a	2-vessel CAD involving the proximal LAD	No	Asymptomatic	Intermediate	None or minimal	42 (1.7)
18a	1- or 2-vessel CAD, no proximal LAD involvement	No	Asymptomatic	High	None or minimal	29 (1.2)

Abbreviations as in Tables 1 to 4.

2012, the rate of inappropriate PCIs increased to nearly one-third because noninvasive stress testing was not performed before a large number of elective PCIs in Japan and was seemingly affected by the increasing trend of coronary CTA.

Under the original criteria (AUC/2009), the proportion of inappropriate procedures in our study was almost within the range reported in previous studies. Similar to our study, previous reports have shown that almost all coronary revascularization procedures performed in the acute setting were appropriate (4,6), whereas ratings in nonacute settings varied widely, from 11.6% to 17% depending on the study (4-6,15). Additionally, the characteristics of the nonacute procedures that we classified as inappropriate were also concordant with those reported in previous studies. Inappropriate PCIs were likely to be performed in patients who were either asymptomatic or mildly symptomatic (Canadian Cardiovascular Society class I or II), were receiving suboptimal antianginal medication, and had no PLAD coronary artery stenosis. In our study, the proportion and indications of inappropriate PCIs in Japan were similar to the results of previous studies from North America, which indicates that AUC/2009 may be useful for assessing the appropriateness of PCIs internationally. The same approach, including the education of physicians regarding procedural appropriateness, is needed to improve patient selection in nonacute settings globally.

Between the 2009 and 2012 criteria, the proportion of inappropriate procedures increased substantially from 15.0% to 30.7% in our registry, whereas Hannan et al. (5) reported that the percent of inappropriate PCIs using New York State's Cardiac Surgery Reporting System and the Percutaneous Coronary Interventions Reporting System would increase from 14.3% with AUC/2009 to 23.2% when AUC/2012 was applied. These increases were mainly explained by the following scenario: asymptomatic patients who did not undergo previous noninvasive testing, presence of 1- or 2-vessel CAD, and no PLAD involvement (indication 18a in AUC/2009, indication 20a in AUC/2012). In AUC/2009, this clinical scenario was not rated because the panel members thought that its likelihood was very low. However, these cases would appear to be particularly inappropriate for revascularization because there is no expectation of survival benefit and no possibility of improvement in quality of life. Accordingly, in the revised version AUC/2012, such cases were rated as inappropriate (10). Therefore, the greater increase in inappropriate procedures in our registry compared with the Hannan et al. (5) study is a reflection of the unwillingness to perform previous noninvasive stress testing in Japan.

Less frequent use of noninvasive stress testing may be due to the advent of coronary CTA, which has become recognized as a useful prognostic modality (16). In fact, approximately one-third of the patients in our registry who did not undergo noninvasive stress testing underwent coronary CTA. Furthermore, the proportion of inappropriate PCIs increased substantially in parallel with the increase in the use of coronary CTA. Because appropriateness criteria assign much value to functional information in reflection of a strong tilt toward physiological assessment of ischemia in the United States, coronary CTA, which

only provides anatomic information, is not recognized as one of the previous noninvasive tests under these criteria. In recent studies, the excellent negative predictive value and acceptable positive predictive value with diagnostic use of coronary CTA have been documented (17,18), and the analyses from the CONFIRM registry have demonstrated the prognostic value of coronary CTA. Those patients with nonobstructive or obstructive CAD detected by coronary CTA had an increased risk of long-term mortality compared with those without (16), which might indicate that the risk of adverse cardiovascular events could be stratified by the extent of anatomic lesions. Additionally, subanalysis of the COURAGE trial demonstrated that the anatomic burden of coronary disease, but not ischemic burden, predicted the risk of adverse cardiovascular events (19), which emphasized the importance of anatomic as well as ischemic assessment in patients with CAD. Because such a potential impact of anatomic assessment on adverse cardiovascular outcomes has been demonstrated, we can argue that CT-based procedures can be hypothetically graded as appropriate instead of inappropriate. In our analysis, the proportion of inappropriate PCI decreased by 5% when CT-based procedures were classified not as inappropriate but as appropriate. This proportion of inappropriate PCIs was similar to the findings of earlier reports assessed using revised 2012 criteria (5). This result might demonstrate that the appropriateness of PCIs in Japan was not properly assessed according to the current criteria because the recognition of CAD was totally different from that in the United States. Further studies are needed to evaluate the appropriateness of CT-guided PCIs, which may suggest that a revision of AUC is needed.

Although revascularization for patients who show no signs of functional ischemia is not the standard of care under current guidelines (20), ischemic evaluation is likely to be performed using FFR without a previous stress test, on the basis of the results of the FAME2 (Fractional Flow Reserve versus Angiography for Multi-vessel Evaluation II) study (21). Actually in our registry, the prevalence of PCIs using FFR substantially increased, which coincided with an increase in coronary CTA use. The number of inappropriate PCIs showed an increasing trend even when the CT-based procedures were excluded (or considered appropriate). This may due to the increase in the use of FFR. Because FFR enables the evaluation of the significance of CAD in the cardiac catheterization laboratory, pre-procedural tests might have been omitted in some of the patients. Among the patients mapped to scenario 20a under

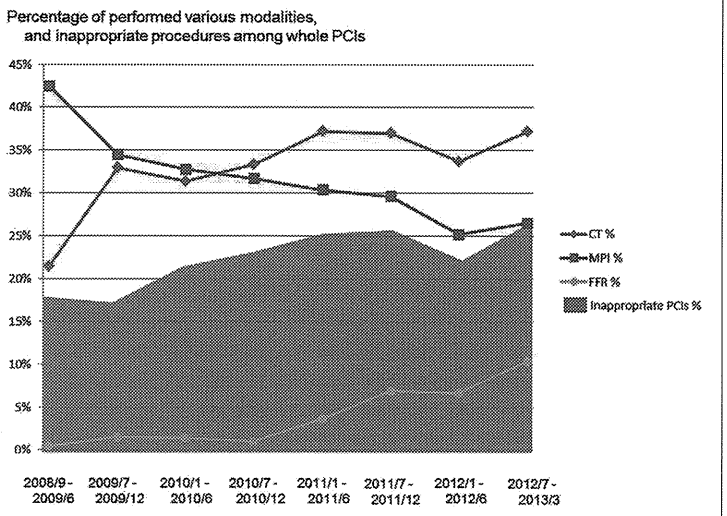

FIGURE 3 Association Between Temporal Trends of Noninvasive Testing and Frequency of Inappropriate Ratings

Gray area indicates the percentages of inappropriate procedures on the basis of original appropriateness criteria (AUC/2009). CT = computed tomography; FFR = functional flow reserve; MPI = myocardial perfusion imaging; PCI = percutaneous coronary intervention.

AUC/2012, almost one-tenth underwent FFR. This trend may indicate that methods for evaluating ischemia have been changing. However, in AUC/2009 or AUC/2012, ischemic evaluation by FFR is

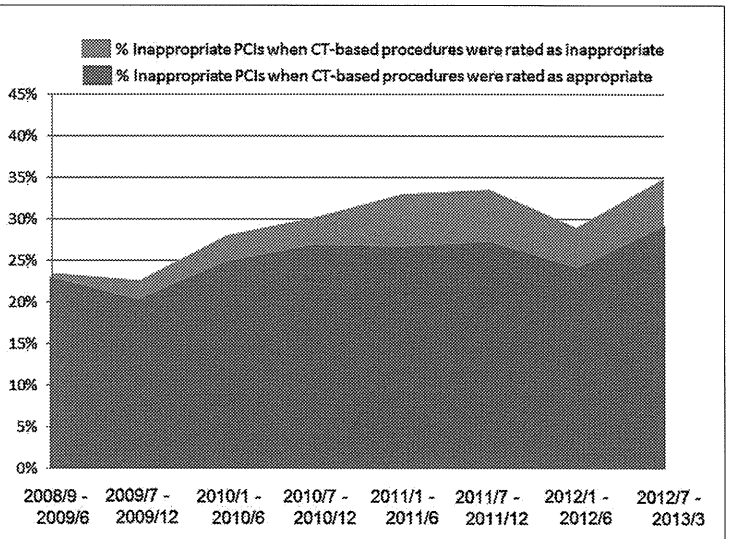

FIGURE 4 Change in the Proportion of PCIs Rated as Inappropriate When CT-Based Procedures Were Classified Not as Inappropriate but as Appropriate

Light brown indicates the trend of proportion of inappropriate PCIs when CT-based procedures were rated as inappropriate. **Dark brown** indicates the trend of proportion of inappropriate PCIs when CT-based procedures were rated as appropriate. Abbreviations as in Figure 3.

accepted only for 1- or 2-vessel CAD with borderline stenosis of 50% to 60%. The use of FFR in coronary artery stenosis >60% was not adjudicated, which was also mentioned in the previous study (4). In view of this, there is room for improvement in AUC/2009 or AUC/2012 to permit a more precise evaluation of appropriateness.

There are several reasons for the wide implementation of coronary CTA in Japan. First, high-technology medical equipment including CT and magnetic resonance imaging is widely available in Japan; the number of CT scanners per million people in Japan is estimated to be >7 times more than that in the United States (22). Second, there is universal health coverage in Japan, which makes it easier for patients to access medical resources. In 1961, Japan managed to extend social health insurance to the entire population and achieved universal health coverage (23). This health policy is equally applied to all healthcare facilities, and the provision of equal medical services is achieved across the entire nation. Further studies focused specifically on coronary CTA are needed to close this scientific gap in PCI indications.

STUDY LIMITATIONS. For a thorough understanding of our results, several limitations should be acknowledged. First, not all hospitals that perform PCI in Japan participate in our registry. Our registry, however, is multicenter and includes a relatively large number of procedures. We believe that this is one of the representative Japanese databases on PCI patients and that our results comprise the most complete assessment of practice patterns throughout Japan currently.

Second, the use of coronary CTA has become more widespread in Japan compared with the United States. In 2010, the percent of PCI patients evaluated with coronary CTA was >30% in Japan, whereas it was only 2.7% in the United States (8). Although there is a significant gap in the use of coronary CTA, the temporal trends of noninvasive testing, in which previous anatomic assessment has been increasing, are similar in both countries. This means that similar trends regarding appropriateness of PCIs will be highlighted in the near future in the United States.

CONCLUSIONS

In a multicenter Japanese PCI registry, approximately one-sixth of PCIs were rated as inappropriate under the AUC/2009 in nonacute settings, and the rate of inappropriate PCIs increased to approximately one-third on the basis of the revised AUC/2012. The significant changes in the inappropriate PCI rating between the 2009 and 2012 criteria may be due to the technological evolution of cardiovascular imaging, which continues to evolve in everyday cardiology practice. Further effort is needed to refine and correct the growing disconnection between the AUC and modern pre-PCI evaluation.

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APPENDIX For supplemental tables and information, please see the online version of this article.