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Ⅲ. 研究成果の刊行物・別刷

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, thorascopic surgery

(*Ann Surg* 2014;260:259–266)

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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Disclosure: This study was supported by a research grant from Ministry of Health, Labour and Welfare, Japan (M.G.). The other authors declare no conflicts of interest regarding this research.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.annalsurgery.com).

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ISSN: 0003-4932/14/26002-0259

DOI: 10.1097/SLA.0000000000000644

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,

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%

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.

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%).

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

TABLE 2. Preoperative Variables and Mortality

| Variables | Entire Study Population (n = 5354) | | 30-d Mortality (n = 63) | | | Operative Mortality (n = 181) | | |
|---------------------------|---------------------------------------|------|----------------------------|------|--------|----------------------------------|------|--------|
| | 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:

$$\text{Predicted mortality} = e^{(\beta_0 + \sum \beta_i X_i)} / 1 + e^{(\beta_0 + \sum \beta_i X_i)}.$$

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

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

| Variables | Entire Study Population (n = 5354) | | OE (n = 3603) | | MIE (n = 1751) | | P |
|------------------------------|---------------------------------------|------|---------------|------|----------------|------|--------|
| | n | % | n | % | n | % | |
| 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 |

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

| | (n = 5354) | | OE (n = 3603) | | MIE (n = 1751) | | P |
|---------------------------------|------------|------|---------------|------|----------------|------|--------|
| | n | % | n | % | n | % | |
| 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 ($\times 10,000/\text{mL}$) | 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).

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 ($\times 10,000/\text{mL}$) | 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 institutes 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.

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.

ACKNOWLEDGMENTS

The authors thank all the data managers and hospitals for participating in the NCD project and for their great efforts in entering data. They also thank Hideki Hashimoto, MD, and Noboru Motomura, MD, for providing direction toward development of the NCD and the working members of the Japanese Society of Gastroenterological Surgery database committee (Masayuki Watanabe, MD, Satoru Imura, MD, Fumihiko Miura, MD, Ichiro Hirai, MD, Yoshio Takesue, MD, Hiroyuki Suzuki, MD, Megumi Ishiguro, MD, Hiroyuki Konno, MD, Makoto Gega, MD, and Akihiko Horiguchi, MD).

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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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Manuscript received February 9, 2014; revised manuscript received June 16, 2014, accepted June 18, 2014.

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.

SEE PAGE 1010

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.

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 non-acute 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

ABBREVIATIONS AND ACRONYMS

AUC = appropriateness use criteria

CABG = coronary artery bypass grafting

CAD = coronary artery disease

CTA = computed tomography angiography

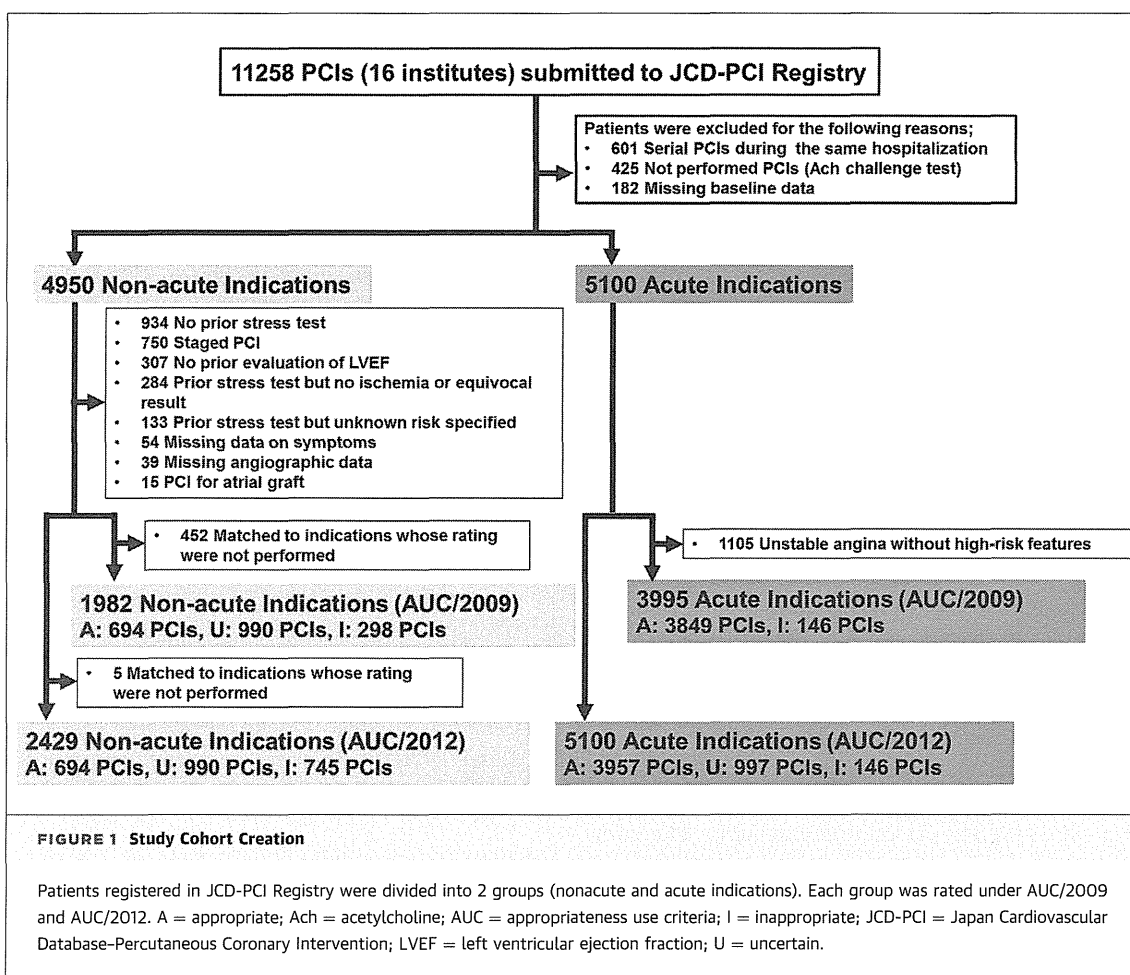
CT = computed tomography

FFR = fractional flow reserve

JCD = Japan Cardiovascular Database

PCI = percutaneous coronary intervention

PLAD = proximal left anterior descending artery



(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), anti-anginal 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.

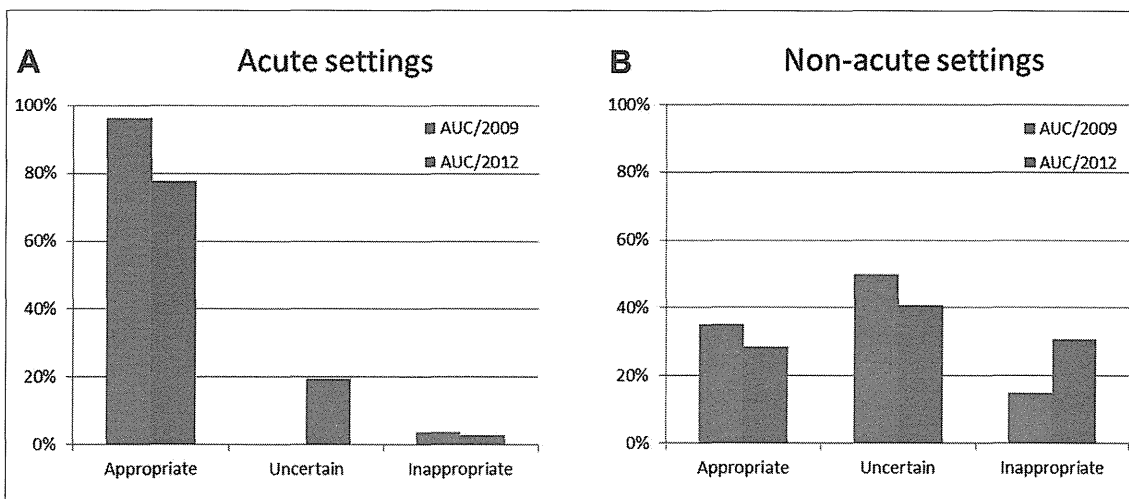


FIGURE 2 Appropriate Ratings Under Each Criterion

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,

| | Total (N = 1,982) | Procedural Appropriateness | | | p Value |
|-------------------------------------|----------------------|----------------------------|------------------------|----------------------------|---------|
| | | Appropriate (n = 694) | Uncertain (n = 990) | Inappropriate (n = 298) | |
| 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. | Anatomy | Indication | | | | n (%) |
|---------------------------|--|---------------|-------------------|----------------------------------|------------------------|------------|
| | | Previous CABG | Symptoms | Cardiac Risk (Noninvasive Tests) | Antianginal Medication | |
| 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/