Total Gastrectomy Risk Model

Data From 20,011 Japanese Patients in a Nationwide Internet-Based Database

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Objective: To construct a risk model for total gastrectomy outcomes using a nationwide Internet-based database.

Background: Total gastrectomy is a very common procedure in Japan. This procedure is among the most invasive gastrointestinal procedures and is known to carry substantial surgical risks.

Methods: The National Clinical Database was used to retrieve records on more than 1,200,000 surgical cases from 3500 hospitals in 2011. After data cleanup, 20,011 records from 1623 hospitals were analyzed for procedures performed between January 1, 2011, and December 31, 2011.

Results: The average patient age was 68.9 years; 73.7% were male. The overall morbidity was 26.2%, with a 30-day mortality rate of 0.9%, in-hospital mortality rate of 2.2%, and overall operative mortality rate of 2.3%. The odds ratios for 30-day mortality were as follows: ASA (American Society of Anesthesiologists) grade 4 or 5, 9.4; preoperative dialysis requirement, 3.9; and platelet count less than 50,000 per microliter, 3.1. The odds ratios for operative mortality were as follows: ASA grade 4 or 5, 5.2; disseminated cancer, 3.5; and alkaline phosphatase level of more than 600 IU/L, 3.1. The C-index of 30-day mortality and operative mortality was 0.811 (95% confidence interval [CI], 0.744–0.879) and 0.824 (95% CI, 0.781–0.866), respectively.

Conclusions: We have performed the first reported risk stratification study for total gastrectomy, using a nationwide Internet-based database. The total gastrectomy outcomes in the nationwide population were satisfactory. The risk models that we have created will help improve the quality of surgical practice.

Keywords: National Clinical Database, risk factors of mortality, total gastrectomy, 30-day mortality, risk model

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Gastric cancer is currently the fourth most common malignancy worldwide[1] and is among the most prevalent types of cancer in Eastern Asia, including Japan, Korea, and China.[2] Surgical resection is often the only curative treatment, although some early gastric cancers limited to the mucosa may be treated endoscopically.[3] Total gastrectomy is usually indicated for tumors located in the upper third of the stomach or advanced gastric cancer extending to the cardia.

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Total gastrectomy is among the most invasive gastrointestinal procedures and is known to carry substantial surgical risks. Patients with gastric cancer frequently have anemia, malnutrition, or organ dysfunction due to tumor extension.[4] Major complications of total gastrectomy can be fatal; these complications include esophagojejunal anastomotic leakage, duodenal stump leakage, and pancreatic fistula related to suprapancreatic lymphadenectomy.[5] In addition, the proportion of patients with gastric cancer who are elderly is increasing.[6] Although all of these factors may affect mortality, and several additional factors influence the incidence of gastric cancer itself, there are few studies that have used a large patient cohort to describe a risk model of mortality for total gastrectomy.

The National Clinical Database (NCD), which commenced patient registration in January 2011, is a nationwide project that is linked to the surgical board certification system in Japan. In this study, we focused on the NCD division of gastrointestinal surgery that uses patient variables and definitions almost identical to those used by the American College of Surgeons National Surgical Quality Improvement Program.[7] Using this database, we created a risk model of mortality for Japanese patients undergoing total gastrectomy.

METHODS

Data Collection

In 2011, the NCD collected data on more than 1,200,000 surgical cases from 3500 hospitals. In the gastroenterological surgery section, the database registered all surgical cases that fell into this category; in addition, it required detailed input items for the 8 procedures, including total gastrectomy, that were determined to represent the performance of surgery in each specialty. Patients who declined to have their records entered in the NCD were excluded from our analysis. Records with missing data on patient age, sex, or status, 30 days after surgery were also excluded. A total of 20,011 patients who underwent total gastrectomy at 1623 institutions between January 1, 2011, and December 31, 2011, were eligible for analysis.

The NCD constructed software for an Internet-based data collection system, and the data managers of participating hospitals were responsible for forwarding their data to the NCD office. The NCD ensures traceability of its data by maintaining continuity in the staff who approve data, the staff of the departments in charge of annual cases, and the data-entry personnel. It also validates data consistency via random inspections by participating institutions. All variables, definitions, and inclusion criteria for the NCD are accessible to participating institutions on its Web site (http://www.ncd.or.jp); the database administrators also provide e-learning systems to teach participants how to input consistent data. The administrators answer all inquiries regarding data entry, answering approximately 80,000 inquiries in 2011, and Frequently Asked Questions are displayed on the Web site.

Endpoint

The primary outcome measure of this study was 30-day mortality and overall operative mortality. The calculation of operative mortality included all patients who died during the index hospitalization, including hospital stays up to 90 days, and any patient who died after hospital discharge within 30 days of the operation date.

Statistical Analysis

Data were randomly assigned to 2 subsets, with 80% allocated for model development and 20% for validation testing. The development data set comprised 16,036 records, and the validation data set comprised 3975 records. The 2 sets of logistic models, 30-day mortality and operative mortality, were constructed for the development data set using a stepwise selection of predictors, with the P value for inclusion set at 0.05. A goodness-of-fit test was performed to assess how well the model could discriminate between survivors and deceased patients. Model calibration, the degree to which the observed outcomes were similar to the predicted outcomes, was examined by comparing the observed with the predicted average within each of the 10 equal-sized subgroups, arranged in increasing order of patient risk.

RESULTS

Study Population Risk Profile

The total gastrectomy patient population represented in the NCD had an average age of 68.9 years; 73.7% of the population was male. The mean body mass index of the study population was 22.4 kg/m^2. Only 2.0% required emergency surgery. Furthermore, 4.6% of the patients needed assistance in activities of daily life. Weight loss of more than 10% was observed in 8.7% of patients. American Society of Anesthesiologists (ASA) scores of grade 3 and grade 4/5 were seen in 8.9% and 0.6% of patients, respectively. Preoperative comorbidities included diabetes mellitus in 8.9% of patients, preoperative respiratory distress in 2.4% of patients, disseminated cancer in 3.7% of patients, and ascites in 2.0% of patients. An abbreviated demographic and risk profile of the study population is shown in Table 1.

Morbidity

The overall morbidity in the total gastrectomy NCD population was 26.2%; grade II or higher complications, as defined by the Clavien-Dindo Classification of Surgical Complications system,[8] were observed in 18.3% of patients. Surgical complications included surgical site infection in 8.4% of patients, anastomotic leakage in 4.4% of patients, and pancreatic fistula (grades B, C) in 2.6% of patients. Nonsurgical complications included pneumonia in 3.6% of patients, renal failure in 1.3% of patients, central nervous system events in 0.7% of patients, and cardiac events in 0.6% of patients. The postoperative morbidities are presented in Table 2.

TABLE 1. Key Descriptive Data

Variables	N = 20,011
Age, mean, yr	68.9
Males, %	73.7
Body mass index, mean, kg/m^2	22.4
Status (emergent), %	2.0
ADL (any assistance), %	4.6
Weight loss, >10%, %	8.7
ASA score, %	
Grade 3	8.9
Grade 4 or 5	0.6
Diabetes, %	15.7
Previous cardiac surgery, %	1.1
Preoperative respiratory distress, %	2.4
Preoperative dialysis, %	0.5
Cerebrovascular accident, %	2.2
Disseminated cancer, %	3.7
Ascites, %	2.0

ADL indicates activities of daily life.

Outcomes

Total gastrectomy outcomes are presented in Table 3. The 30-day mortality was 0.9%, the in-hospital mortality was 2.2%, and the overall operative mortality was 2.3%.

Model Results

Risk models for 30-day mortality and operative mortality were developed; the final logistic models with the odds ratios and 95% confidence intervals are presented in Tables 4 and 5. The ASA score (grade 4 or 5) was the most significant factor in both models. In addition, there were 11 variables that appeared in both models: a preoperative dialysis requirement; a total bilirubin level of more than 2 mg/dL; the presence of disseminated cancer; an alkaline phosphatase level of more than 600 IU/L; an aspartate aminotransferase level of more than 35 IU/L; a prothrombin time–international normalized ratio of more than 1.25; any assistance needed for preoperative activities of daily living; the presence of ascites; a serum albumin level of less than 3.5 g/dL; and the patient's age category (see Tables 4 and 5 for the definition of age category).

Model Performance

To assess the performance of the models, both the C-index and the model calibration across risk groups were evaluated. The receiver operating characteristic curves of both models are shown in Figure 1. The C-index, a measure of model discrimination represented by the area under the receiver operating characteristic curve, was 0.811 for 30-day mortality (95% confidence interval, 0.744–0.879) (Fig. 1A) and 0.824 for overall operative mortality (95% confidence interval, 0.781–0.866) (Fig. 1B). Figure 2 demonstrates the calibration of the models or how well the rates for the predicted event matched those of observed event among patient risk subgroups. (Figure 2A, 30-day mortality risk model; and Figure 2B, operative mortality risk model)

DISCUSSION

Although mortality due to gastric cancer has been steadily decreasing in recent years,[9] the incidence of this cancer in Japan is still the highest of all solid tumors,[10] probably due to the high incidence of *Helicobacter pylori* infection in the Japanese population.[11] Gastric cancer is one of the most commonly encountered diseases in Japanese surgical units; Japanese surgeons are therefore very familiar with gastric cancer surgery, which explains why our study cases were collected from such a large number of institutes.

Although numerous studies have reported the morbidity and mortality rates for gastrectomy in general, few have described these rates for total gastrectomy alone. Moreover, it is still unknown whether total gastrectomy should be considered a more invasive procedure than distal gastrectomy. A randomized controlled trial comparing D1 subtotal gastrectomy with D3 total gastrectomy for cancers located in the gastric antrum revealed that significantly more abdominal abscesses are observed in patients undergoing total gastrectomy; this is attributed to the extended lymphadenectomy involved in the latter procedure.[12] In contrast, an Italian study demonstrated that postoperative morbidity rates are comparable between subtotal gastrectomy and total gastrectomy,[13] although postoperative quality of life is significantly better after subtotal gastrectomy.[14] Both studies

TABLE 2. Morbidities in the NCD Total Gastrectomy Population

Complications	Test Set (n = 16,036)	Validation Set (n = 3975)	Overall Incidence (N = 20,011)
Overall complications	4216 (26.3)	1033 (26.0)	5249 (26.2)
Grade II or higher*	2965 (18.5)	708 (17.8)	3668 (18.3)
Surgical complications			
Surgical site infection	1355 (8.4)	331 (8.3)	1686 (8.4)
Superficial incisional	503 (3.1)	128 (3.2)	631 (3.2)
Deep incisional	244 (1.5)	66 (1.7)	310 (1.5)
Organ space	1024 (6.4)	251 (6.3)	1275 (6.4)
Anastomotic leak	711 (4.4)	170 (4.3)	881 (4.4)
Pancreatic fistula (grade B, C)	419 (2.6)	110 (2.8)	529 (2.6)
Bile leak	81 (0.5)	15 (0.4)	96 (0.5)
Wound dehiscence	161 (1.0)	37 (0.9)	198 (1.0)
Nonsurgical complications			
Pneumonia	589 (3.7)	137 (3.4)	726 (3.6)
Unplanned intubation	282 (1.8)	57 (1.4)	339 (1.7)
Prolonged ventilation >48 h	308 (1.9)	70 (1.8)	378 (1.9)
Pulmonary embolism	25 (0.2)	3 (0.1)	28 (0.1)
Renal failure	213 (1.3)	46 (1.2)	259 (1.3)
CNS events	121 (0.8)	28 (0.7)	149 (0.7)
Cardiac events	90 (0.6)	23 (0.6)	113 (0.6)
Sepsis	138 (0.9)	24 (0.6)	162 (0.8)

The values given are number (percentage).
*Clavien-Dindo classification.
CNS indicates central nervous system.

TABLE 3. Outcome Rates in the NCD Total Gastrectomy Population

Outcomes	Test Set (n = 16,036)	Validation Set (n = 3975)	Overall Incidence (N = 20,011)
30-d mortality	153 (1.0)	34 (0.9)	187 (0.9)
In-hospital mortality	358 (2.2)	89 (2.2)	447 (2.2)
Operative mortality	367 (2.3)	90 (2.3)	457 (2.3)
Reoperation within 30 d	542 (3.4)	122 (3.1)	664 (3.3)
Readmission within 30 d	311 (1.9)	86 (2.2)	397 (2.0)

The values given are number (percentage).

TABLE 4. Risk Model of 30-Day Mortality

Variables	Status	Hazard Ratio	95% Confidence Interval
ASA score	Grade 4 or 5	9.383	4.85–18.152
Preoperative dialysis	Present	3.906	1.546–9.867
Platelet count	<50,000/μL	3.064	1.256–7.473
Total bilirubin	>2.0 mg/dL	2.919	1.189–7.17
Disseminated cancer	Present	2.641	1.603–4.35
Alkaline phosphatase	>600 IU/L	2.457	1.153–5.232
Previous cardiac surgery	Present	2.346	0.997–5.518
Aspartate aminotransferase	>35 IU/L	2.340	1.549–3.537
Diabetes	Insulin use	2.182	1.116–4.266
PT-INR	>1.25	2.182	1.318–3.613
Preoperative ADL	Any assistance	2.086	1.329–3.272
Ascites	Present	2.018	1.11–3.669
Preoperative transfusion	Present	1.936	1.208–3.102
Blood urea nitrogen	>25 mg/dL	1.886	1.201–2.961
Albumin	<3.5 g/dL	1.714	1.167–2.517
Alkaline phosphatase	>340	1.682	1.032–2.739
Hemoglobin	Male, <13.5 g/dL; female, <12.5 g/dL	1.659	1.03–2.675
Age category		1.194	1.067–1.337

Age category is defined as follows: category 1, <60 years; category 2, ≤60 to <65 years; category 3, ≤65 to <70 years; category 4, ≤70 to <75 years; category 5, ≤75 years.
ADL indicates activities of daily living; PT-INR, prothrombin time–international normalized ratio.

TABLE 5. Risk Model of Operative Mortality

Variables	Status	Hazard Ratio	95% Confidence Interval
ASA score	Grade 4 or 5	5.248	2.735–10.07
Disseminated cancer	Present	3.458	2.514–4.757
Alkaline phosphatase	>600 IU/L	3.116	1.812–5.356
Total bilirubin	>2.0 mg/dL	2.751	1.355–5.587
Preoperative dialysis	Present	2.583	1.146–5.819
Pancreaticosplenectomy	Present	2.219	1.177–4.185
White blood cell count	>11,000/μL	2.037	1.368–3.033
Preoperative ADL	Any assistance	2.015	1.469–2.764
PT-INR	>1.25	1.880	1.292–2.737
Cerebrovascular accident	Present	1.858	1.136–3.037
ASA score	Grade 3	1.819	1.37–2.417
Ascites	Present	1.752	1.133–2.71
Respiratory distress	Present	1.719	1.139–2.594
Aspartate aminotransferase	>35 IU/L	1.685	1.252–2.266
Status	Emergent	1.656	1.031–2.662
White blood cell count	<3500/μL	1.629	1.172–2.265
Weight loss	>10%	1.584	1.185–2.119
Sodium	<138 mEq/L	1.429	1.104–1.85
Albumin	<3.5 g/dL	1.411	1.045–1.905
Albumin	<3.0 g/dL	1.353	0.974–1.88
Hematocrit	<30%	1.339	1.025–1.75
Age category		1.294	1.199–1.396

Age category is defined as follows: category 1, <60 years; category 2, ≤60 to <65 years; category 3, ≤65 to <70 years; category 4, ≤70 to <75 years; category 5, ≤75 years.

ADL indicates activities of daily living; PT-INR, prothrombin time–international normalized ratio.

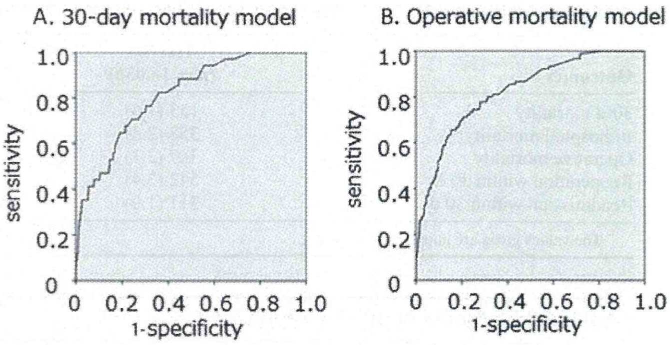

FIGURE 1. Receiver operating characteristic curves of each model. The C-index, a measure of model discrimination represented by the area under the receiver operating characteristic curve, was (A) 0.811 for 30-day mortality (95% CI, 0.744–0.879) and (B) 0.824 for overall operative mortality (95% CI, 0.781–0.866). CI indicates confidence interval.

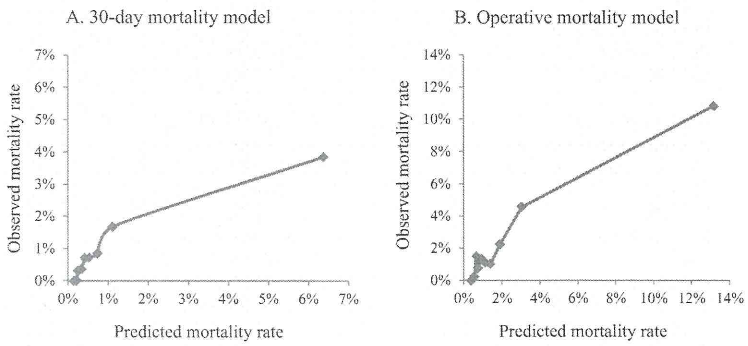

FIGURE 2. The calibration of (A) 30-day mortality model, and (B) operative mortality model.

report that mortality is similar between subtotal gastrectomy and total gastrectomy.[12,13] These results suggest that morbidity experienced after gastrectomy may depend on the extent of lymphadenectomy rather than the extent of gastrectomy. Several randomized controlled trials performed in Western countries have demonstrated that morbidity is significantly higher after D2 or greater lymphadenectomy than after D1 dissection.[15–17]

Although the operative outcomes for gastrectomy have been reported from several high-volume centers,[18] the nationwide outcomes in Japan remain unknown. The advent of the NCD enables the analysis of these nationwide outcomes for several operative procedures, including total gastrectomy. In addition, the database allows researchers to determine interinstitutional differences in the outcomes and factors affecting these differences. Most importantly, development of a risk model using this database is expected to contribute to improved quality control for several procedures.

In this study, we observed an overall morbidity of 26.2% in NCD patients undergoing total gastrectomy. Morbidity in the aforementioned randomized trials ranged from 16.8% to 28% in the D1 groups and 33% to 46% in the D2 or greater groups.[15–17] The 30-day mortality and overall postoperative mortality rates in the NCD total gastrectomy population were 0.9% and 2.3%, respectively. Mortality rates in the other trials ranged from 1.8% to 6.5% in the D1 groups and 3.7% to 13% in the D2 or greater groups. According to a recent report conducted by the Japanese Gastric Cancer Association using a nationwide registry, D2 lymph node dissection is performed in 49.2% of patients and extended D1 dissection is performed in 20.9% of patients whereas D0 or D1 lymphadenectomy is performed in 27.2% of patients.[18] When we consider the fact that such a high percentage of patients undergo D2 lymph node dissection at many institutions, the morbidity and mortality rates for total gastrectomy are satisfactorily low in Japan.

According to our risk models, the most important variable affecting both 30-day and overall operative mortality rates is the ASA score. The ASA classification is among the most commonly used scoring systems, although it is subjective and prone to interobserver variability.[19] The ASA grade has the advantages of simplicity and of universal use[20] and is known to be an effective risk indicator when used either alone[21] or in combination with other parameters.[22,23] Other factors affecting mortality can be divided into 2 groups, with the first group including factors related to patients' general condition such as the need for preoperative dialysis and laboratory test abnormalities and the second group including variables related to tumor extension such as the presence of disseminated cancer and ascites. It is reasonable to presume that a poor preoperative general condition correlates with postoperative mortality. As an example of the impact of the second group of variables, peritoneal dissemination is a progression pattern distinctive for gastric cancer; curative resection is usually impossible in this situation, and palliative resection is often performed for symptom relief. High morbidity and mortality rates have been reported for noncurative gastric cancer surgery.[24]

In our risk model, body mass index was not a significant factor affecting the mortality. Overweight is a well-known risk of postoperative complications after gastrectomy. Tsujinaka et al[25] investigated influence of overweight on surgical complications after gastrectomy using data from Japan Clinical Oncology Group study 9501, which explored survival benefit of para-aortic D3 dissection over standard D2 dissection. They revealed that being overweight increased the risk for surgical complications in patients who underwent D2 dissection.[25] Kulig et al[26] conducted a multicenter study to evaluate the effects of overweight on surgical outcomes in a Western patient population and demonstrated that higher body mass index was associated with a higher rate of cardiopulmonary complications and intra-abdominal abscess. Despite the increase in postoperative complications in overweight patients, obesity did not affect the mortality in both studies, as observed in this study.

Preoperative treatment may also affect the occurrence of mortality after total gastrectomy. In the European countries, perioperative chemotherapy is the standard treatment approach for patients with resectable gastroesophagel cancer.[27] In contrast, postoperative chemotherapy using S-1 is the standard therapy for patients with stage II/III gastric cancer in Japan.[28] Only 4.3% and 0.1% of the NCD total gastrectomy population underwent neoadjuvant chemotherapy and radiotherapy, respectively, and therefore neoadjuvant therapy was not a significant factor affecting the mortality.

The C-indices of the models for 30-day mortality and operative mortality indicate that our models are reliable. Although the usefulness of several scoring systems, such as the Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM)[29] and the Estimation of Physiologic Ability and Surgical Stress (E-PASS),[30,31] in predicting the risks associated with gastrectomy has been reported, these systems are not specific to Japanese patients undergoing total gastrectomy. Using our risk model results, we may be able to create a novel scoring system suitable for total gastrectomy in Japanese patients.

It is unclear whether all total gastrectomy cases all over Japan are really enrolled in the NCD. Basically, the data manager in each participating hospital is responsible for the data enrollment. However, as the NCD is linked to the surgical board certification system, we assume that almost all cases are enrolled in this system. Indeed, the number of cases in this study is almost 5 times higher than that of the nationwide registry maintained by the Japan Gastric Cancer Association.[18]

CONCLUSIONS

We have reported the first risk stratification study on total gastrectomy in Japan by using a nationwide Internet-based database. The nationwide mortality rates after total gastrectomy are quite satisfactory. We have developed risk models for total gastrectomy that will contribute to improving the quality of this procedure.

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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, 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%).

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.

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.

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

	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.

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

