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

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

CNS indicates central nervous system.

TABLE 6. Risk Model for 30-Day Mortality

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

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

Model Performance

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

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

TABLE 7. Risk Model for Operative Mortality

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

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

DISCUSSION

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

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

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

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

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

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

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

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 Horiguch, MD).

REFERENCES

1. Jemal A, Bray F, Center M, et al. Global cancer statics. *CA Cancer J Clin.* 2011;61:69–90.
2. Ando N, Ozawa S, Kitagawa Y, et al. Improvement in the results of surgical treatment of advanced squamous esophageal carcinoma during 15 consecutive years. *Ann Surg.* 2000;232:225–232.
3. Herskovic A, Martz K, al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med.* 1992;326:1593–1598.
4. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85–01). Radiation Therapy Oncology Group. *JAMA.* 1999;281:1623–1627.
5. Shitara K, Muro K. Chemoradiotherapy for treatment of esophageal cancer in Japan: current status and perspectives. *Gastrointest Cancer Res.* 2009;3:66–72.
6. Takeuchi H, Saikawa Y, Oyama T, et al. Factors influencing the long-term survival in patients with esophageal cancer who underwent esophagectomy after chemoradiotherapy. *World J Surg.* 2010;34:277–284.
7. Cascinelli N, Morabito A, Santinami M, et al. Immediate or delayed dissection of regional nodes in patients with melanoma of the trunk: a randomized trial. WHO Melanoma Programme. *Lancet.* 1998;351:793–796.
8. Eifel P, Axelson JA, Costa J, et al. National Institutes of Health Consensus Development Conference Statement: adjuvant therapy for breast cancer, November 1–3, 2000. *J Natl Cancer Inst.* 2001;93:979–989.
9. Fujita H, Kakegawa T, Yamana H, et al. Mortality and morbidity rates, postoperative course, quality of life, and prognosis after extended radical lymphadenectomy for esophageal cancer. Comparison of three-field lymphadenectomy with two-field lymphadenectomy. *Ann Surg.* 1995;222:654–662.
10. Kinugasa S, Tachibana M, Yoshimura H, et al. Postoperative pulmonary complications are associated with worse short- and long-term outcomes after extended esophagectomy. *J Surg Oncol.* 2004;88:71–77.
11. Fang WT, Chen WH, Chen Y, et al. Selective three-field lymphadenectomy for thoracic esophageal squamous carcinoma. *Dis Esophagus.* 2007;20:206–211.
12. Bartels H, Stein HJ, Siewert JR. Preoperative risk analysis and postoperative mortality of esophagectomy for resectable esophageal cancer. *Br J Surg.* 1998;85:840–844.
13. Bailey SH, Bull DA, Harpole DH, et al. Outcomes after esophagectomy: a ten-year prospective cohort. *Ann Thorac Surg.* 2003;75:217–222.
14. Wright CD, Kucharczuk JC, O'Brien SM, et al. Predictors of major morbidity and mortality after esophagectomy for esophageal cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database risk adjustment model. *J Thorac Cardiovasc Surg.* 2009;137:587–595.
15. Shiloach M, Frencher SK, Jr, Steeger JE, et al. Toward robust information: data quality and inter-rater reliability in the American College of Surgeons National Surgical Quality Improvement Program. *J Am Coll Surg.* 2010;210:6–16.
16. Tachimori Y, Kanamori N, Uemura N, et al. Salvage esophagectomy after high-dose chemoradiotherapy for esophageal squamous cell carcinoma. *J Thorac Cardiovasc Surg.* 2009;137:49–54.
17. Ozawa S, Tachimori Y, Baba H, et al. Comprehensive registry of esophageal cancer in Japan, 2004. *Esophagus.* 2012;9:75–98.
18. Oyama T, Tomori A, Hotta K, et al. Endoscopic submucosal dissection of early esophageal cancer. *Clin Gastroenterol Hepatol.* 2005;3:S67–S70.
19. Takeuchi H, Fujii H, Ando N, et al. Validation study of radio-guided sentinel lymph node navigation in esophageal cancer. *Ann Surg.* 2009;249:757–763.
20. Akiyama H, Tsurumaru M, Udagawa H, et al. Radical lymph node dissection for cancer of the thoracic esophagus. *Ann Surg.* 1994;220:360–373.
21. Mamidanna R, Bottle A, Aylin P, et al. Short-term outcomes following open versus minimally invasive esophagectomy for cancer in England. *Ann Surg.* 2012;255:197–203.
22. Dhungel B, Diggs BS, Hunter JG, et al. Patient and peri-operative predictors of morbidity and mortality after esophagectomy: American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP), 2005–2008. *J Gastrointest Surg.* 2010;14:1492–1501.
23. Blencowe NS, Strong S, McNair A, et al. Reporting of short-term clinical outcomes after esophagectomy. A systematic review. *Ann Surg.* 2012;255:658–666.
24. Stavron EP, Smith GS, Baker DF. Surgical outcomes associated with oesophagectomy in New South Wales: an investigation of hospital volume. *J Gastrointest Surg.* 2010;14:951–957.
25. Luketich JD, Schauer PR, Christie NA, et al. Minimally invasive esophagectomy. *Ann Thorac Surg.* 2000;70:906–911.
26. Takeuchi H, Kawakubo H, Kitagawa Y. Current status of minimally invasive esophagectomy for patients with esophageal cancer. *Gen Thorac Cardiovasc Surg.* 2013;61:513–521.
27. Ferguson MK, Celauro AD, Prachand V. Prediction of major pulmonary complications after esophagectomy. *Ann Thorac Surg.* 2011;91:1494–1501.
28. Lerut T, Moond J, Coosemans W, et al. Postoperative complications after transthoracic esophagectomy for cancer of the esophagus and gastroesophageal junction are correlated with early cancer recurrence. *Ann Surg.* 2009;250:798–807.
29. Marin FA, Lamônica-Garcia VC, Henry MA, et al. Grade of esophageal cancer and nutritional status impact on postsurgery outcomes. *Arq Gastroenterol.* 2010;47:348–353.
30. Mariette C. Is there a place for esogastric cancer surgery in cirrhotic patients? *Ann Surg Oncol.* 2008;15:680–682.
31. Lagarde SM, Maris AK, de Castro SM, et al. Evaluation of O-POSSUM in predicting in-hospital mortality after resection for oesophageal cancer. *Br J Surg.* 2007;94:1521–1526.
32. Lai F, Kwan TL, Yuen WC, et al. Evaluation of various POSSUM models for predicting mortality in patients undergoing elective oesophagectomy for carcinoma. *Br J Surg.* 2007;94:1172–1178.
33. Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. *N Engl J Med.* 2011;364:2128–2137.