TAVIの使用成績調査とNCDの連携

使用成績調査における臨床データベース事業の連携

- ***使用成績調査の転換期***
  - 科学的な安全対策への転換が求められている
  - 従来の調査方法だけではなく，様々な研究デザインを用いた調査や産官学連携への期待

- ***臨床データベース事業との連携による新しい試み***
  - 臨床学会・臨床現場を主体とした臨床データベース事業
  - 専門家として，術前のリスク評価や治療成績等のモニタリングを行うことによる，医療の質向上の取り組み
  - 質の高いデータ収集（調査項目の精査，登録率・入力精度の高いデータの蓄積）
  - 利益相反やデータの管理体制に関する透明性の確保

経カテーテル大動脈弁治療（TAVI）用生体弁「サピエンXT」
（エドワーズライフサイエンス社，2013年6月21日承認）

TAVR企業

薬事法上の
使用成績調査の実施
（600症例）

経カテーテル的大動脈弁置換術
（TAVR）関連学会協議会

厚生労働省指導の下，
TAVR実施施設基準を策定

TAVR実施施設の認定
TAVR実施症例の全例登録
（JACVSD登録の義務付け）

TAVI Registry

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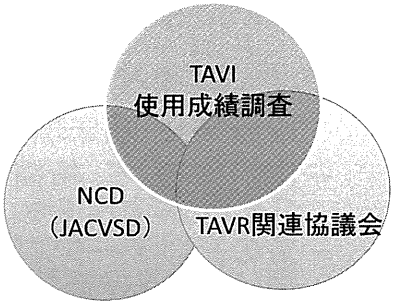
- NCDとTAVI調査で共通する項目は，1度のみの入力で済むよう，システムを設計
  - まずTAVI症例として，TAVI調査項目を優先して入力
    （症例の承認も，NCDとは異なる単位で設定）
    - ➢ 秋以降に，NCDシステム（JACVSD）とのデータ連携
    - ➢ 連携後に，NCD症例登録システムから
      必要な情報を追加入力

医療現場での入力負荷を軽減



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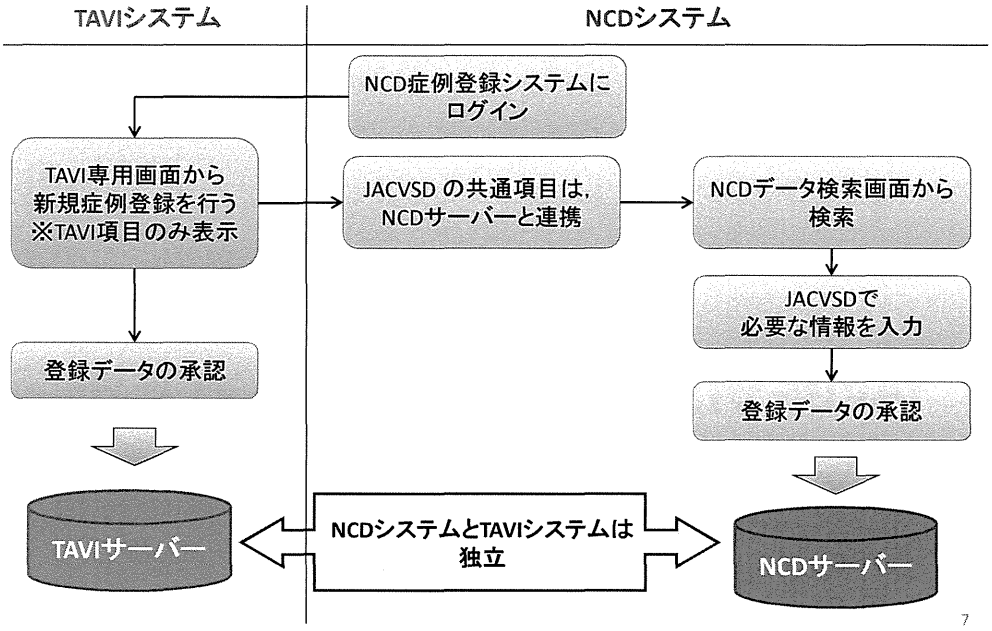
NCD/TAVIシステムの連携



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NCD Registry事業の今後の可能性

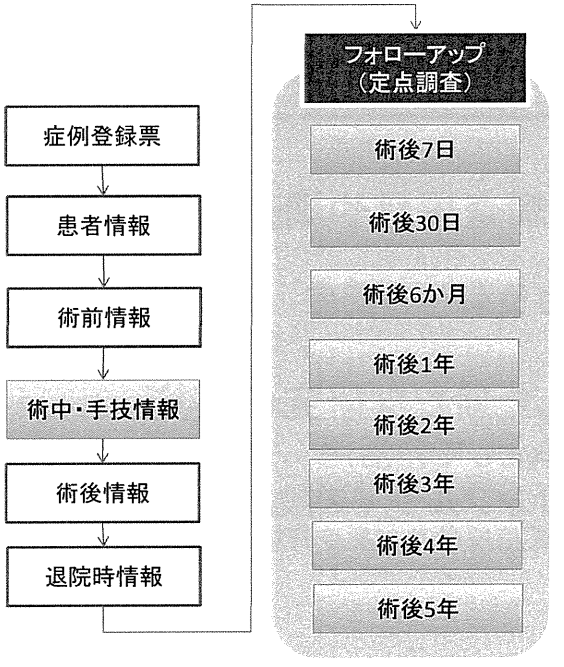
- Registryデータの連携による Real world での実態把握
- 研究目的に応じた、調査項目や調査対象症例の柔軟な設計
  - スピード・コスト・入力負荷への配慮
- Registryをベースにした新たな研究の実施
  - 研究のプラットホームとしての活用
  - 研究計画段階でのサンプルサイズ設計や、研究の実施可能性の検討*（対象施設数や対象症例数の検討）*

8

TAVI症例登録システムの入力方法

9

TAVI症例　登録の流れ



有害事象

- A.デバイス関連
- B.出血関連
- C.循環器関連
- D.入院を要する
  その他の有害事象

以下は速やかに報告
－死亡
－弁血栓・弁移動・弁塞栓・弁抜去
－感染性心内膜炎
－大量出血（4単位以上の輸血を要した），
　入院を要した出血
－その他入院を要した有害事象

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TAVI Registryの症例登録について①

- 追跡調査（フォローアップ）の実施
  - 術後7日, 30日, 6か月, 1～5年（1年単位）

- 有害事象の調査

  本調査における有害事象の定義は以下です.

> デバイスとの因果関係がはっきりしないものを含め,
> サピエンXTを使用した患者に生じたあらゆる好ましくない,
> あるいは意図しない徴候, 症状.
> デバイスに不具合が確認されなかった場合であっても,
> TAVRの実施によって発生したと考えられる健康被害を含む.

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TAVI Registryの症例登録について②

- 有害事象の調査（続き）

調査対象となる有害事象

カテゴリー	有害事象の例
A. デバイス関連	大動脈弁血栓, 大動脈弁に対する再手術・インターベンション
B. 出血関連	大量出血, アクセス部位の出血
C. 循環器関連	心筋梗塞, 感染性心内膜炎, 脳梗塞
D. 入院を要するその他の有害事象	

※下記に該当する有害事象は, 随時、速やかに入力をお願いいたします.
－死亡
－弁血栓・弁移動・弁塞栓・弁抜去
－感染性心内膜炎
－大量出血（4単位以上の輸血を要した）・入院を要した出血
－その他入院を要した有害事象

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TAVI Registryの症例登録について③

- TAVIデータの承認・症例のロック

	NCD	TAVI Registry
承認の単位	患者情報から退院時情報まで全ての情報を，一度承認して完了	承認の単位を調査時期で分ける 例）患者情報～術中情報， 退院時情報，フォローアップ情報
症例のロック	毎年1月1日～12月31日の対象症例に対して，翌年4月上旬	TAVIの運用手順に従って実施

- 使用成績調査用として，新たな機能を追加
  - データ承認後のデータ修正履歴の表示
  - 医療機関へ，フォローアップの時期が近付いたら／フォローアップが未入力の場合に，通知する機能
  - 有害事象が入力されたら，医療機器メーカーへ自動で通知される機能

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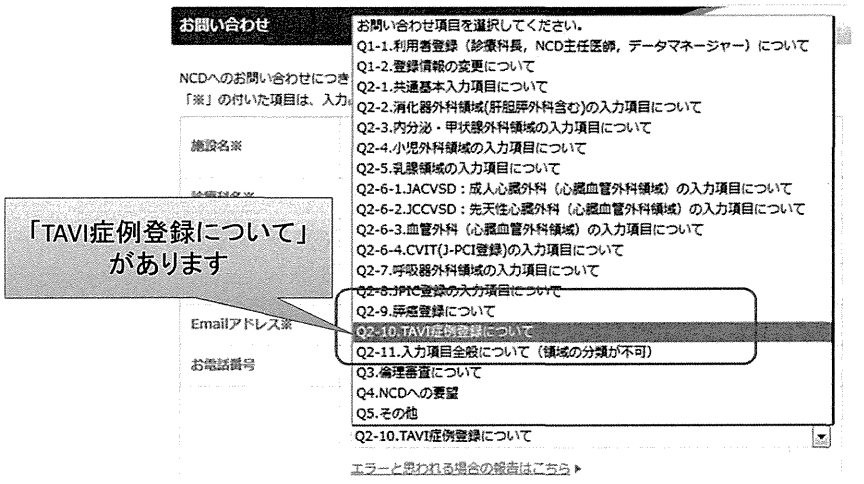
お問い合わせについて

当該データベースについて、入力方法やシステム等のご質問は、NCDにお問い合わせください。

※エドワーズライフサイエンス社は、データ入力・アカウント発行・システム全般等にかかるにご質問には対応しておりません。



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II. 学会等発表実績

学会等発表実績

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著者氏名	書籍タイトル	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
	なし						

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III.　研究成果の刊行物・別刷

ORIGINAL ARTICLE

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

Hiroya Takeuchi, MD, PhD, Hiroaki Miyata, PhD,†‡ Mitsukazu Gotoh, MD, PhD,†‡ Yuko Kitagawa, MD, PhD,† Hideo Baba, MD, PhD,† Wataru Kimura, MD, PhD,† Naohiro Tomita, MD, PhD,† Tohru Nakagoe, MD, PhD,† Mitsuo Shimada, MD, PhD,† Kenichi Sugihara, MD, PhD,§ and Masaki Mori, MD, PhD§*

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%).

TABLE 1. Patient Clinical Parameters and Laboratory Data

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

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

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

Morbidity and Outcomes After Esophagectomy

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

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

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:

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

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

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.