

Risk prediction nomogram for major morbidity related to primary resection for esophageal squamous cancer

Xiao-long Liu, PhD^a, Rong-chun Wang, MS^b, Yi-yang Liu, MS^a, Hao Chen, MS, MS^a, Chen Qi, PhD^b, Li-wen Hu, PhD^b, Jun Yi, PhD^{b,*}, Wei Wang, PhD^{c,*}

Abstract

Background and Objectives: Postoperative major complications after esophageal cancer resection vary and may significantly impact long-term outcomes. This study aimed to build an individualized nomogram to predict post-esophagectomy major morbidity.

Methods: This retrospective study included 599 consecutive patients treated at a single center between January 2017 and April 2019. Of them, 420 and 179 were assigned to the model development and validation cohorts, respectively. Major morbidity predictors were identified using multiple logistic regression. Model discrimination and calibration were evaluated by validation. Regarding clinical usefulness, we examined the net benefit using decision curve analysis.

Results: The mean age was 64 years; 79% of the patients were male. The most common comorbidities were hypertension, diabetes mellitus, and stroke history. The 30-day postoperative major morbidity rate was 24%. Multivariate logistic regression analysis showed that age, smoking history, coronary heart disease, dysphagia, body mass index, operation time, and tumor size were independent risk factors for surgery-associated major morbidity. Areas under the receiver-operating characteristic curves of the development and validation groups were 0.775 (95% confidence interval, 0.721–0.829) and 0.792 (95% confidence interval, 0.709–0.874), respectively. In the validation cohort, the nomogram showed good calibration. Decision curve analysis demonstrated that the prediction nomogram was clinically useful.

Conclusion: Morbidity models and nomograms incorporating clinical and surgical data can be used to predict operative risk for esophagectomy and provide appropriate resources for the postoperative management of high-risk patients.

Abbreviations: ASA = American Society of Anesthesiologists, AUC = area under the curve, BMI = body mass index, CHD = coronary heart disease, COPD = chronic obstructive pulmonary disease, DCA = decision curve analysis, DM = diabetes mellitus, MIE = conventional minimally invasive esophagectomy.

Keywords: esophageal squamous cancer, major morbidity, nomogram, risk prediction

Editor: Wen-Wei Sung.

X-IL and R-cW contributed equally to this work.

The authors report no conflicts of interest.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

^a Department of Cardiothoracic Surgery, Jingling Hospital, Jingling School of Clinical Medicine, Nanjing Medical University, ^b Department of Cardiothoracic Surgery, Jingling Hospital, Medical School of Nanjing University, ^c Department of Thoracic Surgery, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China.

^{*} Correspondence: Jun Yi, Department of Cardiothoracic Surgery, Jingling Hospital, Medical School of Nanjing University, Nanjing 210029, China (e-mail: Dryijun@126.com), Wei Wang, Department of Thoracic Surgery, the First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, China (e-mail: wangwei15261883958@163.com).

Copyright © 2021 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Liu XI, Wang Rc, Liu Yy, Chen H, Qi C, Hu Lw, Yi J, Wang W. Risk prediction nomogram for major morbidity related to primary resection for esophageal squamous cancer. Medicine 2021;100:31(e26189).

Received: 18 June 2020 / Received in final form: 28 February 2021 / Accepted: 14 May 2021

http://dx.doi.org/10.1097/MD.000000000026189

1. Introduction

Although treatment paradigms for esophageal cancer have changed significantly over the past decade, esophagectomy remains the mainstay treatment for most patients with esophageal cancer selected to undergo curative treatment.^[1-4] However, the associated postoperative mortality and morbidity rates are 1% to 6% and 19% to 60%, respectively, although outcomes at experienced high-volume centers tend to be better.^[5-7] Complications can range from minor complications (atelectasis) to severe complications (sepsis). Some studies have confirmed that anastomotic leakage and other related complications in cervical anastomosis are relatively high after esophagectomy. Such high complications occur because of surgery involving a wide range of areas including the abdomen, chest, and neck as well as decreased oxygen supply and increased tension from the gastric tube. However, some surgeons prefer neck anastomosis because it involves a lower rate of serious postoperative complications than intrathoracic anastomosis.^[8,9]

Most studies that aimed to improve esophageal cancer surgery outcomes focused on long-term survival as the main outcome. However, postoperative major morbidity is an undesirable but critical outcome for both clinicians and patients with esophageal cancer. If adjuvant treatment is required, the timely initiation of chemotherapy or radiotherapy is delayed, which tends to impair overall survival.^[10,11] This might be related to postoperative weight loss and worsened nutritional status, which could, along with preexisting comorbidities, lead to a performance status decline and worse overall survival rate.^[12] Thus, it is important to identify subgroups that are at a higher risk of major morbidity after esophageal cancer surgery.

Some studies have suggested prediction models using the identified risk factors to predict the occurrence of postoperative complications in general, cardiac, and hepatocellular cancer surgery.^[13-16] Several studies have used nomograms to predict mortality and morbidity; however, they focused on clinical factors for complications after esophagectomy, which did not result in reliable risk models^[17,18] except for the prediction of pulmonary complications.^[19] Other previous predictions focused only on preoperative indicators and mortality for complications after esophagectomy, and their external validation results were unreliable.^[20] Models that focus on the presence of unspecified complications cannot be used in esophageal surgery owing to the large variation in complications. Owing to the lack of an effective tool for estimating the individual risk of postoperative major morbidity in the field of esophageal cancer, we aimed to build and evaluate a morbidity risk prediction model for a population of Chinese patients with esophageal cancer treated with surgical resection.

2. Materials and methods

2.1. Patient selection

This retrospective cohort study was performed in a single large and comprehensive medical center at Jin Ling Hospital, Nanjing, China. Data were obtained from the database of consecutive patients with esophageal squamous cancer treated between January 2017 and April 2019. All patients underwent a standard diagnostic workup including endoscopy with histological biopsy, endoscopic ultrasonography, computed tomography of the chest and abdomen, and external ultrasonography of the neck. Positron emission tomography was not routinely performed during the study period. However, it was optionally used to rule out cases of suspected metastasis, and adjuvant therapy was chosen as needed. All other pathologic cases of adenocarcinoma or other cell types or with distant metastasis, secondary malignancies, or a follow-up period <1 month were excluded from the study (Fig. 1). The Institutional Ethics Committee approved the study and the procedures followed were in accordance with the principles of the Declaration of Helsinki.

2.2. Variables

Clinical variables selected for the analysis included age at the time of surgery, sex, presence of comorbidities (diabetes mellitus



Figure 1. Flowchart depicting consecutive patients and reasons for exclusion from the present study.

[DM], hypertension, chronic obstructive pulmonary disease [COPD], coronary heart disease [CHD], stroke history), dysphagia symptoms, body mass index (BMI), drinking and smoking history of >20 years, and American Society of Anesthesiologists (ASA) score.^[21] Surgical data included operation time, number of lymph node dissections, anastomosis position (cervical or intrathoracic), type of surgery (open operation, conventional minimally invasive esophagectomy [MIE], and robot-assisted MIE), tumor length, and tumor location (upper, middle, lower). The other variables added were T- stage and N-stage from the American Joint Committee on Cancer 8th edition cancer staging system. Neoadjuvant chemoradiotherapy has been recommended for cT3-T4 or cN+ patients since the end of the last decade. It was performed with a taxaneand platinum-based double regimen. Two preoperative cycles were routinely recommended. Radiation was delivered by threedimensional conformal radiotherapy or intensity-modulated radiotherapy. The total radiation dose was at least 50 Gy delivered in conventional fractions. Meanwhile, preoperative laboratory values including white blood cell count and albumin and carcinoembryonic antigen levels were collected.

2.3. Definition of complications

The Clavien–Dindo modified classification^[22] of complications was used to define morbidity. Major morbidity was defined as an event greater or equal to grade III that occurred up to 30 days after surgery, both during the hospital stay or after discharge. The same 30-day period was used when mortality was reported.

2.4. Statistical analysis

Quantitative data are presented through adequate measures of central tendency and dispersion (mean and standard deviation or median and interguartile range). Categorical variables are presented as frequencies and proportions. Variable factor analysis was performed using univariate and multivariate logistic regression analyses. Variables showing statistical significance in the univariate analysis were included in the multivariate logistic regression analysis, and the forward stepwise method was used to select the variables that were eventually included in the model. Logistic regression models were built to identify independent predictors of morbidity. For model building, a group of seven variables was initially included into the model, including age, smoking history, BMI, dysphagia, CHD, operation time, and tumor size. The assumption of linearity was assessed for all continuous variables. No imputation method was used for the missing data. A nomogram was constructed with coefficients from the final models, and their attributable points are shown in Table 1. For the model performance assessment, its capacity to discriminate between events and nonevents was assessed through receiver-operating characteristic curves and the c-statistic, which represents the area under the curve (AUC). Calibration was performed to investigate the goodness of fit of the prediction model. Finally, to evaluate the performance of the prediction models, we introduced a newly developed analysis technique (decision curve analysis), which is based on the principle that the relative harm of false positives and false negatives can be expressed in terms of a probability threshold, where n is the total number of patients in the study and Pt is the given threshold probability. All statistical analyses were conducted using Empower(R) (www.empowerstats.com; X&Y Solutions, Inc.,

Table 1

Univariate and multivariate logistic regression models in the development group.

| | Univariate analysis OR (95% Cl) <i>P</i> | Multivariate analysis OR (95% Cl) <i>P</i> |
|-------------------|---|---|
| Age | 1.04 (1.01–1.07) .0077 | 1.05 (1.01-1.08) .0087 |
| Smoking | 2.57 (1.63-4.06) <.0001 | 2.45 (1.47-4.09) .0006 |
| Dinking | 1.37 (0.88–2.14) .1638 | |
| Sex | 1.75 (0.94–3.27) .0793 | |
| DM | 0.85 (0.36-2.04) .7236 | |
| HTN | 1.26 (0.79–2.02) .3348 | |
| COPD | 3.04 (0.75-12.37) .1207 | |
| CHD | 5.94 (2.14-16.50) .0006 | 4.94 (1.58–15.49) .0061 |
| Stroke | 1.27 (0.54–2.99) .5878 | |
| Dysphagia | 5.08 (2.64–9.76) <.0001 | 5.82 (2.81-12.03) <.0001 |
| BMI | 0.90 (0.84–0.97) .0038 | 0.90 (0.83-0.98) .0111 |
| Operation time | 1.50 (1.22–1.83) <.0001 | 1.48 (1.18–1.85) .0006 |
| Tumor size | 1.23 (1.08–1.41) .0023 | 1.23 (1.06–1.43) .0074 |
| Location | | |
| Upper | 1.0 | |
| Middle | 2.25 (0.64-7.91) .2069 | |
| Lower | 1.54 (0.42–5.57) .5133 | |
| ASA | | |
| 1 | 1.0 | |
| 2 | 0.57 (0.33-0.99) .0449 | |
| 3 | 2.12 (0.92-4.89) .0766 | |
| 4 | 0.54 (0.06-4.70) .5773 | |
| Type of operation | | |
| Open operation | 1.0 | |
| MIE | 1.95 (1.20–3.18) .0072 | |
| RAMIE | 2.79 (1.42-5.49) .0029 | |
| Anastomosis | | |
| Cervical | 1.0 | |
| Intrathoracic | 0.67 (0.40–1.11) .1225 | |
| Lymph no. | 1.02 (1.00–1.05) .0323 | |
| Tstage | | |
| TIS | 1.0 | |
| T1 | 0.87 (0.26-3.00) .8317 | |
| T2 | 0.70 (0.21-2.39) .5689 | |
| T3 | 1.30 (0.40–4.19) .6655 | |
| T4 | 1.12 (0.20-6.43) .8947 | |
| Nstage | | |
| NO | 1.0 | |
| N1 | 1.16 (0.69–1.94) .5743 | |
| N2 | 1.28 (0.66-2.49) .4700 | |
| N3 | 2.43 (0.53–11.16) .2543 | |
| NC | 0.91 (0.47-1.76) .7693 | |

ASA = the American Society of Anesthesiology, BMI = body mass index, CHD = coronary heart disease, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, HTN = hypertension, MIE = Conventional minimally invasive esophagectomy, NC = neoadjuvant chemoradiotherapy, RAMIE = robot-assisted minimally invasive esophagectomy.

Boston, MA) and R software (version 3.4.3; www.r-project.org). The significance level was set at 0.05, and all tests were 2-sided.

3. Results

3.1. Patient demographics

In this study, 599 consecutive patients were enrolled, including 420 in the development group and 179 in the validation group. There were 477 men and 122 women (median age, 65 years; range, 59–69 years). A total of 42 patients had DM, 189 had hypertension, and 240 had a history of smoking and drinking. A total of 13, 34, and 22 patients had COPD, stroke history, and

CHD, respectively. More than half of the patients had a primary tumor located in the middle esophagus and an anastomosis site in the cervical region. The median tumor size was 3.0 (range, 2.0–4.5) cm, median operation time was 3.80 (range, 2.90–4.55) hours, median BMI was 23.00 (range, 21.00–25.00) kg/m², and median number of harvested lymph nodes was 20.00 (range, 14.00–27.00) (Table 2). Most of the patients were staged as T2–3, with <50% having a node-positive disease. Neoadjuvant radiochemotherapy was administered to 13% of the patients. Comparison of the baseline data indicated no differences in the general characteristics of patients in the development and validation groups.

3.2. Morbidity outcome

A total of 218 patients had complications. The overall 30-day morbidity rate was 36.3%. The most common morbidities were pneumonia and wound site infection. The number of Clavien I (atelectasis, vocal cord paresis or paralysis) was 41(6.8%); the number of Clavien II (pneumonia, chyle leakage, pulmonary embolus) was 29 (4.8%); major morbidity occurred in 24.6% of subjects and half of the events were classified as Clavien III. The number of Clavien III was 72 (12%), the Anastomotic leak number was 48 (8%), reoperation due to thoracic duct injury was 14 (2.3%); the number of Clavien IV was 50 (8.3%), requiring artificial ventilation was 28 (4.8%), heart failure was 8 (1.3%), renal insufficiency was 3 (0.5%), combination of at least 2 complications was 11 (1.8%); the number of Clavien V (30- day postoperative death) was 26 (4.3%) (Table 3).

3.3. Nomogram development

Univariate analysis of the development group showed that the statistically significant risk factors were age, smoking history, CHD, BMI, ASA, dysphagia, type of operation, operation time, tumor size, and number of lymph nodes (P < 0.05). Statistically significant variables on univariate analysis were included in the multivariate logistic regression analysis. Age, smoking history, CHD, BMI, operation time, tumor size, and dysphagia were independent risk factors for esophagectomy with morbidity (Table 2) (P < 0.05). Based on the logistic multivariate regression analysis, 7 independent risk factors were included in the prediction model. We then established an individualized nomogram prediction model of surgery-associated major morbidity (Fig. 2). Based on the nomogram, we can obtain the points corresponding to each prediction indicator. The sum of the points is recorded as the total score, and the predicted risk corresponding to the total score is the probability of surgeryassociated morbidity.

3.4. Nomogram validation

The validation of the model was based on discrimination and calibration. We drew the receiver-operating characteristic curves of predicted probability and calculated the AUC values for the development and validation groups. The AUC values for morbidity risk in the development and validation groups were 0.775 (95% confidence interval [CI], 0.721–0.829) and 0.792 (95% CI, 0.709–0.874) (Fig. 3A and B), respectively. The 95% CI of the calibration belt for the development and validation groups crossed the diagonal bisector line (Fig. 4A and B). Therefore, the predicted probability of the model was consistent

Table 2

| Baseline | characteristics | of the | development | group and | validation |
|----------|-----------------|--------|-------------|-----------|------------|
| group (n | =599). | | | | |

| 0 | De | velopment | N | alidation | |
|--|----------------|--------------------------------|----------------|--------------------------------|----------------------|
| Group | | (n = 420) | | (n = 179) | Р |
| Age (median, Q1–Q3) BMI, kg/m ² (Median, Q1–Q3) Smoking history | 64.00 23.00 | (59.00–69.00) (21.00–25.00) | 65.00 23.00 | (60.00–70.00) (21.00–25.00) | .264 .746 .835 |
| No Yes | 219 201 | (52.14%) (47.86%) | 95 84 | (53.07%) (46.93%) | |
| Dinking history | 201 | (11.0070) | 01 | (10.0070) | .659 |
| No | 250 | (59.52%) | 110 | (61.45%) | |
| Yes | 170 | (40.48%) | 69 | (38.55%) | |
| Sex | 00 | (10.05%) | 40 | (00.400/) | .219 |
| Female | 240 | (19.05%) | 42 | (23.46%) | |
| DM | 540 | (00.95%) | 107 | (70.3470) | 588 |
| No | 389 | (92.62%) | 168 | (93.85%) | .000 |
| Yes | 31 | (7.38%) | 11 | (6.15%) | |
| HTN | | | | | .289 |
| No | 293 | (69.76%) | 117 | (65.36%) | |
| Yes | 127 | (30.24%) | 62 | (34.64%) | 105 |
| No | 412 | (98.10%) | 174 | (97.21%) | .490 |
| Yes | 8 | (1.90%) | 5 | (2.79%) | |
| CHD | - | (| - | () | .938 |
| No | 403 | (95.95%) | 172 | (96.09%) | |
| Yes | 17 | (4.05%) | 7 | (3.91%) | |
| Stroke history | 000 | (00 570() | | (05 500()) | .349 |
| N0 Voc | 393 | (93.57%) | 1/1 | (95.53%) | |
| Dvsnhagia | 21 | (0.43%) | 0 | (4.47.70) | 188 |
| No | 377 | (89.76%) | 154 | (86.03%) | .100 |
| Yes | 43 | (10.24%) | 25 | (13.97%) | |
| Tumor location | | | | | .224 |
| Upper | 20 | (4.76%) | 15 | (8.38%) | |
| Middle | 250 | (59.52%) | 103 | (57.54%) | |
| LOWER | 150 | (35.71%) | 61 | (34.08%) | 030 |
| 1 | 274 | (65.24%) | 121 | (67 60%) | .902 |
| 2 | 115 | (27.38%) | 45 | (25.14%) | |
| 3 | 25 | (5.95%) | 11 | (6.15%) | |
| 4 | 6 | (1.43%) | 2 | (1.12%) | |
| Operation time, h | 3.90 | (2.90-4.60) | 3.60 | (2.80-4.50) | .761 |
| lumor size, cm | 3.50 | (2.30 - 4.50) | 3.00 | (2.20 - 4.35) | ./20 |
| Lymph 10. | 20.00 | (14.00-20.00) | 21.00 | (15.00-27.50) | .301 278 |
| Onen operation | 200 | (47 62%) | 81 | (45.25%) | .270 |
| MIE | 170 | (40.48%) | 68 | (37.99%) | |
| RAMIE | 50 | (11.90%) | 30 | (16.76%) | |
| Anastomosis | | | | | .269 |
| Cervical | 296 | (70.48%) | 118 | (65.92%) | |
| Intratnoracic | 124 | (29.52%) | 61 | (34.08%) | 600 |
| TIS | 16 | (3.81%) | 8 | (4.47%) | .023 |
| T1 | 93 | (22.14%) | 33 | (18.44%) | |
| T2 | 111 | (26.43%) | 50 | (27.93%) | |
| T3 | 189 | (45.00%) | 86 | (48.04%) | |
| T4 | 11 | (2.62%) | 2 | (1.12%) | |
| Nstage | 050 | | 104 | (50.100/) | .936 |
| NU NH | 250 | (59.52%) | 104 | (58.10%) | |
| N2 | 53 | (20.19%) | 49 24 | (27.37%) | |
| N3 | 7 | (1.67%) | 2 | (1.12%) | |
| NC | | | _ | , | .935 |
| No | 365 | (86.90%) | 156 | (87.15%) | |
| Yes | 55 | (13.10%) | 23 | (12.85%) | |

ASA = the American Society of Anesthesiology, BMI = body mass index, CHD = coronary heart disease, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, HTN = hypertension, MIE = Conventional minimally invasive esophagectomy, NC = Neoadjuvant chemoradiotherapy, RAMIE = Robot-assisted minimally invasive esophagectomy.

% 36.3

6.8
4.8
24.6
12
8
2.3
8.3
4.8
1.3
0.5
1.8
4.3

| Overall and major complications after esphogectomy. | | | | |
|---|--|-----|--|--|
| Complication category | Complications | No. | | |
| Overall morbidity | I–V | 218 | | |
| | Clavien I | | | |
| | Atelectasis, vocal cord paresis or paralysis Clavien II | 41 | | |
| | Pneumonia, chyle leakage, pulmonary embolus | 29 | | |
| Major morbidity | III–V | 148 | | |
| | Clavien III | 72 | | |
| | Anastomotic leak | 48 | | |
| | Reoperation due to thoracic duct injury | 14 | | |
| | Clavien IV | 50 | | |
| | Requiring artificial ventilation | 28 | | |
| | Heart failure | 8 | | |
| | Renal insufficiency | 3 | | |
| | Combination of at least 2 complications | 11 | | |
| | Clavien V (30-day postoperative death) | 26 | | |

Table 3

with the actual probability, which suggested that the prediction model had strong concordant performance and the calibration of the prediction model in both groups was perfect. benefit of the validation group was better than that of the development group between the threshold probabilities.

4. Discussion

3.5. Decision curve analysis

Figure 5A and B illustrates the decision curves for models to predict the diagnosis of risk factors in patients after esophagectomy. The model was useful for threshold probabilities, and the net

In the present study, a nomogram for predicting major morbidity after esophagectomy was constructed and validated internally. The factors incorporated in the model were age, smoking history, CHD, BMI, tumor size, dysphagia, and operation time. In terms







Figure 3. Receiver-operating characteristic curves for validating the discrimination power of the nomogram. Development group (A) and validation group (B) (area under the curve = 0.775 vs 0.792).

of model performance, the constructed model showed good discrimination and calibration.

Postoperative complication rates are associated with a high morbidity rate of 19% to 60%.^[5] Nonetheless, the results have improved over time, and the postoperative mortality rate was <5% in the Japanese database.^[6,7] Esophagectomy procedures are usually complex and extensive; therefore, the postoperative morbidity rate is high. Models that focus on the presence of unspecified complications cannot be used in esophageal surgery because of the large variation in complications.^[23] The 30-day postoperative major morbidity rate in our study was 24%, which

is similar to the previously reported rate. Postoperative morbidity adversely affects patients with esophageal cancer for several reasons, including escalating health care costs and increasing stress for patients and their families. Furthermore, if adjuvant treatment is required, the timely initiation of chemotherapy or radiotherapy is delayed, which is associated with impaired overall survival. Thus, identifying patients at a potential risk of postoperative morbidity is critical.

Several prediction models for postoperative morbidity have been introduced in general surgery, cardiac surgery, gastric cancer, and hepatocellular carcinoma populations.^[13] However,



Figure 4. Calibration plots of the nomogram for the probability of morbidity in the development group (A) and validation group (B).



the aforementioned models could not be reliably used in esophageal cancer, and the predisposing risk factors for postoperative morbidity after esophagectomy for cancer did not result in reliable predictive models.^[24] Lagarde et al developed a nomogram to predict the occurrence and severity of complications in patients undergoing esophagectomy.^[25] The nomogram provides a graphical representation of the predictive strength of specific predictors and enables clinicians to calculate an overall risk score for individual patients that reflects their personal risk. Although Grotenhuis et al validated the nomogram, the validation population was closely related to the derivation population, indicating the need for further validation in a different surgical population. Meanwhile, the duration of enrolled consecutive series ultimately exceeded >10 years. However, the duration of the present study was only 2 years and it included only patients with pathologically proven esophageal squamous cell carcinoma. An interesting feature of our constructed nomogram is the incorporation of dysphagia. In the previously suggested models for morbidity and mortality, dysphagia was not analyzed as a potential predictor of postoperative morbidity. Patients with esophageal cancer frequently experience dysphagia to a degree that a reduction in food intake is apparent at the initial diagnosis. Malnutrition is associated with an increased risk of postoperative complications in patients undergoing esophagectomy.^[26-28]

In the present study, ASA scores and type of operation, which were reported as predictors of postoperative morbidity in other studies, did not show a significant prognostic value. COPD was not a significant risk factor; however, smoking history was a risk factor. This finding may be explained by the fact that COPD diagnostic criteria are relatively strict considering a low ratio (<0.70) of the forced expiratory volume in 1 second. Therefore, the diagnostic COPD number was lower, and some smokers did not have airflow obstruction. In a previous longitudinal study, Woodruff et al found that respiratory symptoms were common in present or former smokers despite forced expiratory volume in 1 second: forced vital capacity and forced vital capacity values being generally normal.^[29] A previous study selected smoking history as a risk factor, which could adequately cover the complications associated with lung disease.^[30] This is consistent with a study

reporting that smoking is a risk factor for postoperative morbidity, whereas preoperative smoking cessation for >90 days is ideal to reduce morbidities after esophagectomy.^[31]

Other studies reported that preoperative prediction of complications in individual patients remains difficult, most likely because of the complexity of the mechanisms causing these complications. However, these studies did not include operation time, tumor size, and cancer stage as risk factors. Our study findings are consistent with a study that demonstrated that MIE, minimally invasive Ivor Lewis and transhiatal esophagectomy in particular, is safe and equivalent to the open esophagectomy technique with respect to overall morbidity and mortality.^[32] Despite improvements in postoperative cancer surgery care, operative time remains an important and often overlooked predictor of complications. It was recently reported to be associated with morbidity after transhiatal and Ivor Lewis esophagectomies^[33] and an independent predictor of major morbidity in a Korean series along with pulmonary and cardiovascular comorbidities.^[34] The impact of operative time is likely to be experienced mostly among patients with worse performance status and in low-volume institutions, where mortality rates are historically higher.^[5] Our study demonstrated that operation time is correlated with major morbidity.

Our study presented and validated a user-friendly nomogram that generates a simple graphical quantification of postoperative morbidity probability. It incorporates both preoperative clinical parameters and surgical data to enhance the prediction of surgical outcomes in clinical practice and provide objective parameters for selecting specific populations, which is in line with the current trend toward personalized medicine and alternative treatment approaches. The quality of surgical care can be audited among both physicians and patients by comparing the expected rate of postoperative morbidity with the actual rate. In addition, to develop a reliable model, all clinical predictors should be tested for inclusion. The number of enrolled patients in the present study was sufficiently large to test candidate predictors. We performed decision curve analysis to assess the performance of the diagnostic models. The model was useful between threshold probabilities, and the net benefit of the validation group was better than that of the development group.

Although we achieved good results, the present study had some limitations. First, this retrospective study may have underestimated the morbidity rate. Nonetheless, all included patients received postoperative care at our institution, and the data were extracted from the linked database in 2016 in our institution. Therefore, this point may minimize the ascertainment bias. Second, although we performed rigorous internal validation, the nomogram still requires external validation by other institutions to gain general acceptance. A nomogram for routine practical use should be developed in a general population rather than in a selected group of patients treated in specialized hospitals. The specific characteristics of the population (robot-assisted MIE, esophageal squamous cancer) would likely render the nomogram minimally valuable elsewhere. Third, surgeon-related factors, such as skill and experience, and gastric tube length were not analyzed in the present nomogram model.

In summary, predictive parameters for postoperative complications after primary resection for esophageal squamous cancer are age, smoking history, coronary heart disease, dysphagia, body mass index, operation time, and tumor size. The nomogram was constructed based on logistic regression model. The point value assigned to each factor was proportional to the odds ratio derived from the beta coefficients for each factor determined by the regression analysis. This nomogram incorporates seven variables. For each level of each prognostic variable, points were allocated according to the scale shown. The total score was determined by adding individual parameter points and was used to calculate the predicted probability of 30-day major morbidity. A total score of 262 was assigned a value of 0.5 and used to define the groups at high-risk of 30-day major morbidity after primary resection for esophageal squamous cancer. Patients at higher risk should be given nutritional support before surgery to increase their weight, shorten the operation time, strengthen monitoring after surgery, and promptly find problems and deal with them in time.

5. Conclusion

We developed and internally validated an individualized nomogram for predicting major morbidity after esophagectomy. Using this prediction model, we can accurately predict the risk of esophagectomy, which helps to improve the understanding of operative risk and screening of high-risk patients.

Acknowledgments

The authors thank Dr. Bin Yang for providing the design suggestions and statistical guidance. The authors are grateful to all the participants involved in the present study for their enthusiasm and commitment.

Author contributions

Conceptualization: xiaolong liu, Rong-chun Wang, Wei Wang. Data curation: Rong-chun Wang, Yi-yang Liu, Chen Qi.

- Funding acquisition: Chen Qi, Wei Wang.
- Investigation: Hao Chen, Chen Qi, Wei Wang.
- Methodology: xiaolong liu, Yi-yang Liu, Hao Chen, Chen Qi. Resources: xiaolong liu, Yi-yang Liu, Hao Chen, Chen Qi.
- Software: Chen Qi.
- Supervision: Li-wen Hu.
- Validation: Li-wen Hu.

Visualization: Li-wen Hu.

- Writing original draft: xiaolong liu.
- Writing review & editing: Jun Yi, Wei Wang.

References

- Lagergren J, Smyth E, Cunningham D, Lagergren P. Oesophageal cancer. Lancet 2017;390:2383–96.
- [2] Uzunoglu FG, Reeh M, Kutup A, Izbicki JR. Surgery of esophageal cancer. Langenbecks Arch Surg 2013;398:189–93.
- [3] Allum WH, Blazeby JM, Griffin SM, et al. Guidelines for the management of oesophageal and gastric cancer. Gut 2011;60:1449–72.
- [4] Van Daele E, Van de Putte D, Ceelen W, et al. Risk factors and consequences of anastomotic leakage after Ivor Lewis oesophagectomydagger. Interact Cardiovasc Thorac Surg 2016;22:32–7.
- [5] Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. N Engl J Med 2002;346:1128–37.
- [6] Takeuchi H, Miyata H, Ozawa S, et al. Comparison of short-term outcomes between open and minimally invasive esophagectomy for esophageal cancer using a nationwide database in Japan. Ann Surg Oncol 2017;24:1821–7.
- [7] Takeuchi H, Miyata H, Gotoh M, et al. A risk model for esophagectomy using data of 5354 patients included in a Japanese nationwide web-based database. Ann Surg 2014;260:259–66.
- [8] Ryan CE, Paniccia A, Meguid RA, McCarter MD. Transthoracic anastomotic leak after esophagectomy: current trends. Ann Surg Oncol 2017;24:281–90.
- [9] Kamarajah SK, Lin A, Tharmaraja T, et al. Risk factors and outcomes associated with anastomotic leaks following esophagectomy: a systematic review and meta-analysis. Dis Esophagus 2020;33:doz089.
- [10] Papenfuss WA, Kukar M, Oxenberg J, et al. Morbidity and mortality associated with gastrectomy for gastric cancer. Ann Surg Oncol 2014;21:3008–14.
- [11] Aahlin EK, Olsen F, Uleberg B, et al. Major postoperative complications are associated with impaired long-term survival after gastro-esophageal and pancreatic cancer surgery: a complete national cohort study. BMC Surg 2016;16:32.
- [12] Mariette C, De Botton ML, Piessen G. Surgery in esophageal and gastric cancer patients: what is the role for nutrition support in your daily practice? Ann Surg Oncol 2012;19:2128–34.
- [13] Gawande AA, Kwaan MR, Regenbogen SE, et al. An Apgar score for surgery. J Am Coll Surg 2007;204:201–8.
- [14] Sanders J, Keogh BE, Van der Meulen J, et al. The development of a postoperative morbidity score to assess total morbidity burden after cardiac surgery. J Clin Epidemiol 2012;65:423–33.
- [15] Ueno M, Uchiyama K, Ozawa S, et al. A new prediction model of postoperative complications after major hepatectomy for hepatocellular carcinoma. Dig Surg 2009;26:392–9.
- [16] Ra J, Paulson EC, Kucharczuk J, et al. Postoperative mortality after esophagectomy for cancer: development of a preoperative risk prediction model. Ann Surg Oncol 2008;15:1577–84.
- [17] Law S, Wong KH, Kwok KF, et al. Predictive factors for postoperative pulmonary complications and mortality after esophagectomy for cancer. Ann Surg 2004;240:791–800.
- [18] Sauvanet A, Mariette C, Thomas P, et al. Mortality and morbidity after resection for adenocarcinoma of the gastroesophageal junction: predictive factors. J Am Coll Surg 2005;201:253–62.
- [19] Ferguson MK, Durkin AE. Preoperative prediction of the risk of pulmonary complications after esophagectomy for cancer. J Thorac Cardiovasc Surg 2002;123:661–9.
- [20] Zingg U, Langton C, Addison B, et al. Risk prediction scores for postoperative mortality after esophagectomy: validation of different models. J Gastrointest Surg 2009;13:611–8.
- [21] Doyle DJ, Garmon EH. American Society of Anesthesiologists Classification (ASA Class). Treasure Island: StatPearls; 2020.
- [22] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–13.
- [23] Zafirellis KD, Fountoulakis A, Dolan K, et al. Evaluation of POSSUM in patients with oesophageal cancer undergoing resection. Br J Surg 2002;89:1150–5.
- [24] Abunasra H, Lewis S, Beggs L, et al. Predictors of operative death after oesophagectomy for carcinoma. Br J Surg 2005;92:1029–33.

- [25] Lagarde SM, Reitsma JB, Maris AK, et al. Preoperative prediction of the occurrence and severity of complications after esophagectomy for cancer with use of a nomogram. Ann Thorac Surg 2008;85:1938–45.
- [26] Nozoe T, Kimura Y, Ishida M, et al. Correlation of pre-operative nutritional condition with post-operative complications in surgical treatment for oesophageal carcinoma. Eur J Surg Oncol 2002;28: 396–400.
- [27] Grotenhuis BA, Wijnhoven BP, Grune F, et al. Preoperative risk assessment and prevention of complications in patients with esophageal cancer. J Surg Oncol 2010;101:270–8.
- [28] Ida S, Watanabe M, Yoshida N, et al. Sarcopenia is a predictor of postoperative respiratory complications in patients with esophageal cancer. Ann Surg Oncol 2015;22:4432–7.
- [29] Woodruff PG, Barr RG, Bleecker E, et al. Clinical significance of symptoms in smokers with preserved pulmonary function. N Engl J Med 2016;374:1811–21.

- [30] Vestbo J, Hurd SS, Agusti AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2013;187:347–65.
- [31] Yoshida N, Baba Y, Hiyoshi Y, et al. Duration of smoking cessation and postoperative morbidity after esophagectomy for esophageal cancer: how long should patients stop smoking before surgery? World J Surg 2016;40:142–7.
- [32] Sihag S, Kosinski AS, Gaissert HA, et al. Minimally invasive versus open esophagectomy for esophageal cancer: a comparison of early surgical outcomes from The Society of Thoracic Surgeons National Database. Ann Thorac Surg 2016;101:1281–8. discussion 8-9.
- [33] Valsangkar N, Salfity HVN, Timsina L, et al. Operative time in esophagectomy: does it affect outcomes? Surgery 2018;164:866-71.
- [34] Jung MR, Park YK, Seon JW, et al. Definition and classification of complications of gastrectomy for gastric cancer based on the accordion severity grading system. World J Surg 2012;36:2400–11.