

# Predicting Individual Survival After Curative Esophagectomy for Squamous Cell Carcinoma of Esophageal

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## Research article

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# Abstract

## Background

Esophageal cancer is one of the leading causes of cancer-related death worldwide<sup>1</sup>. Despite significant progress in the overall treatment of esophageal cancer in recent years, the prognosis for patients who require surgery remains poor.

## Methods

The current paper studied the clinicopathological features of 503 patients who underwent radical esophagectomy at the Huashan Hospital of Fudan University between January 2005 and January 2015. Nomograms which predicted esophageal squamous cell carcinoma (ESCC) survival rates were established using the Cox proportional hazards regression model. Discrimination and calibration, calculated after bootstrapping, were used as a measure of accuracy.

## Results

Multivariate analyses were used to select five independent prognostic variables to build the nomogram. These variables were pathological T stage, pathological N factor, rate of positive LNs, history of chronic obstructive pulmonary disease (COPD) and postoperative sepsis. The nomogram was built to predict the rates of overall survival (OS) and disease-free survival (DFS). The concordance indices of the nomogram prediction of OS and DFS were 0.720 and 0.707, respectively. Compared to the conventional TNM staging system, the nomogram has better predictive accuracy for survival (OS 0.720 vs 0.672,  $P < 0.001$ ; DFS 0.707 vs 0.667,  $P < 0.001$ ).

## Conclusions

The aims of this study were to assess comorbidities and postoperative complications in patients with esophageal cancer and to design a nomogram for the prediction of long-term survival in patients with ESCC. To the best of the knowledge of the authors of this study, this is the first attempt to establish an ESCC nomogram based on comorbidities and postoperative complications using a relatively large cohort of patients.

## Background

Esophageal cancer is one of the leading causes of cancer-related death worldwide<sup>1</sup>. Despite significant progress in the overall treatment of esophageal cancer in recent years, the prognosis for patients who require surgery remains poor. The establishment of an accurate cancer staging system is valuable for both the provision of information as well as to guide patient follow-up and subsequent treatment. The most commonly used staging system for ESCC is the tumor node metastasis (TNM) classification system from the seventh edition of the American Joint Committee on Cancer (AJCC). However, studies have demonstrated that other clinicopathological factors, such as lymph node ratio<sup>2-4</sup>, comorbidities<sup>5,6</sup>,

and postoperative complications<sup>2</sup>, are also significant prognostic variables. However, there are no models which concurrently take comorbidities and postoperative complications into account in constructing an accurate predictive model. The aims of this study were to assess comorbidities and postoperative complications in patients with esophageal cancer and to design a nomogram for the prediction of long-term survival in patients with resected ESCC. To the best of the knowledge of the authors of this study, this is the first attempt to establish an ESCC nomogram based on comorbidities and postoperative complications using a relatively large cohort of patients.

## Methods

A total of 503 patients participated in the present study. These were patients who had undergone potential curative esophagectomy for squamous cell carcinoma of the esophagus between January 2005 and January 2015 in Huashan hospital at Fudan University, a tertiary referral center with significant experience in esophageal surgery. The patients in this study (1) underwent a transthoracic esophagectomy with mediastinal and two-field abdominal lymphadenectomy with R0 resection, (2) had no in-hospital mortality, and (3) did not have other malignancy or distant metastasis. The surgical methods used have been previously described<sup>7</sup>.

The patient information collected included demographic information such as age, sex, body mass index (BMI), tobacco use, alcohol use, preoperative albumin, preoperative platelet, preoperative white blood cell (WBC) and preoperative neutrophil to lymphocyte ratio (NLR). Additional variables included comorbidities, clinicopathological features, postoperative complications, and survival.

Comorbidities were identified during preoperative evaluation from physician or other healthcare professional notes and subsequently confirmed via the appropriate medical tests. Comorbidities included history of cardiovascular disease (previous myocardial infarction, heart failure, peripheral arterial disease, or cerebrovascular disease), history of chronic obstructive pulmonary disease (COPD)<sup>6</sup>, history of hepatitis, history of hypertension, and history of diabetes (with or without complications). Renal comorbidities were too rare to include in the statistical analyses.

Clinicopathological factors were evaluated in accordance with the guidelines for clinical and pathological studies on carcinoma of the esophagus. Tumor staging was based on the TNM classification specified by the International Union Against Cancer<sup>8</sup>, and depth of invasion and lymph node metastasis were determined from the pathology of surgically resected specimens. Postoperative pathological T (pT), N (pN), and Stage (pStage) factors were used for all cases. For patients who received preoperative therapy, the depth of invasion was determined not only by the microscopic distribution of viable cancers, but also by scar tissue and the disappearance of normal structures such as the lamina propria and proper muscular layer.

AJCC recommends removing a sufficient number of LNs during the operation as well as the detection of at least 12 nodes. However, in clinical practice, due to various factors such as individual physical

condition, operating conditions, and pathological diagnosis, it is difficult to ensure the removal of a sufficient number of LNs from each patient, and this may result in the stage migration phenomenon. The metastatic lymph node ratio is the ratio of metastatic LNs to the number of total detected LNs, which may be affected by variability in detection. This variable was also included in the present study.

This paper evaluated the postoperative complications that developed within 30 days after esophagectomy that required either medication or surgical intervention. A postoperative pulmonary complication was defined as the presence of one or more of the following postoperative conditions: initial ventilator support for more than 48 hours or reintubation for respiratory failure; the need for tracheostomy; pneumonia; or acute respiratory distress syndrome (ARDS). Postoperative anastomotic leakage was defined in terms of the clinical signs of leaking, such as erythema, skin edema, emission of pus from a surgical wound or cervical drain or a radiographically apparent leak confirmed by performing an esophagography or computed tomography or both. Cardiovascular morbidity was defined as the presence of any cardiac disease or cerebrovascular disease, such as arrhythmia, ischemic heart disease, or pericardial fluid collection requiring pharmacological, electrical, or interventional treatment, or the presence of any thrombosis in line with the common terminology criteria for adverse events (CTCAE) version 4.03<sup>2</sup>. Sepsis was defined as the clinical signs of SIRS along with a culture or visual identified infection.

## **Statistical**

Statistical analyses were performed using the statistical package R for Windows (version 3.4.2, <http://www.r-project.org/>). For the purpose of developing the nomograms, the outcome predictor was developed with the clinical experience of the authors as well as through a search of the prior literature. Quantitative data were expressed as medians and as an interquartile range (IQR), and categorical data were expressed numerically and as a percentage. The Kaplan-Meier method was used for estimating OS and DFS. The Cox regression analysis was used for univariate and multivariate analyses. Variables with a p value of 0.05 or less in the univariate analyses were subjected to a multivariable Cox regression analysis. A final model selection was performed using a backward stepwise regression with Akaike's Information Criterion (AIC)<sup>9</sup>. There was a graphical assessment of proportional hazards assumptions as well as a test of non-linear terms for significance using analysis of variance (ANOVA). A nomogram was formulated based on the results of the multivariate analysis using the rms statistical package<sup>10</sup>.

Discrimination and calibration were used to test the accuracy of the nomograms. The discrimination of the nomogram was measured using a concordance index (C-index) and bootstrap bias-corrected estimates of C-index. Calibration curves, which measure the relationship between the outcomes predicted by the models and the observed outcomes in the patients, were used to assess calibration accuracy in predicting the probability of overall survival probability and progression-free survival probability for 1 year, 3 years and 5 years. The analyses were performed using a bootstrapping strategy with 200 replications. The nomogram and the pathological staging systems were compared using the rcorr.cens package.

The total points for each patient were calculated according to the established nomogram. 3 groups of patients with high, moderate and low risk of survival were delineated using maximally selected rank statistics as implemented in the Maxstat package<sup>11</sup>. Survival curves were created with the Kaplan-Meier method, and finally, using risk group as a factor, compared using the log-rank test.

All statistical tests were two-sided, and *p* values of less than 0.05 were considered to be statistically significant.

## Results

### Clinicopathologic Characteristics of Patients

A total of 503 patients were enrolled in this study, and patient characteristics are displayed in table 1. The median age of diagnosis was 62 years. The median number of resected LNs was 13 (range from 8-19). The majority of patients were male (81.7%). The most common comorbidity was a history of hypertension (34.4%), and a total of 148 (29.4%) patients suffered from postoperative pulmonary complications.

### OS and DFS of patients

The median OS was 4 years (95%CI, 3.50 to 4.83 years), and the 1-, 3-, and 5-year OS rates were 82.5%, 57.5%, and 42.3%, respectively. The median DFS was 3.33 years (95%CI, 2.92 to 4.00 years), and the 1-, 3-, and 5-year disease free rates were 77.6%, 52.1%, and 40.9%, respectively. The median follow-up time was 4.62 years (range, 1.21 to 17.08 years).

### Independent Prognostic Factors

To determine the factors which were independently prognostic of patient survival, OS and DFS were analyzed using the Cox proportional hazards model. Table 2 and table 3 highlight all parameters found to be of potential significance in the univariate analysis and included in the multivariate analysis. The multivariate analyses indicated that history of COPD, pathological T stage, pathological N factor, rate of positive LNs, and postoperative sepsis were independent risk factors for OS and DFS.

### Prognostic Nomogram for OS and DFS

The prognostic nomograms that integrated all independent factors for OS and DFS in the primary cohort are shown in Figure 1A and Figure 1B, respectively. The calibration plot for the probability of survival at 1/3/5 year(s) after surgery demonstrates an optimal concordance between the nomogram prediction and the actual observation (Figure 2).

### Validation of Predictive Accuracy of the Nomogram for OS and DFS

The C-index of the nomogram for OS was 0.720 (95% CI, 0.682 to 0.758), and the bias-corrected C-index was 0.712. The C-index and bias-corrected C-index of the nomogram for DFS were 0.707 (95% CI, 0.670 to 0.744) and 0.700, respectively. With regards to the pathological stage, the C-index and bias-corrected C-index for OS (0.672 and 0.669) and DFS (0.669 and 0.666) were significantly lower than the C-index of the nomogram ( $P < 0.001$ ,  $P < 0.001$ ).

Risk stratification based on the score from the nomogram supported the predictive efficacy in the long-term survival of the established model (Figure 3 and Figure 4). The patients were divided into three risk groups according to their total score for OS (low risk group:  $>22$  and  $\leq 74$ , moderate risk group:  $>74$  and  $\leq 155$ , high risk group:  $>155$  and  $\leq 271$ ) and DFS (low risk group:  $>22$  and  $\leq 83$ , moderate risk group:  $>83$  and  $\leq 161$ , high risk group:  $>161$  and  $\leq 274$ ), respectively.

## Discussion

This study examined the predictive factors of long-term survival in 503 patients who had undergone resection of ESCC. Cancer characteristics are closely related with the long-term survival of ESCC patients. However, a large number of studies have illustrated that many other clinicopathological factors are also associated with prognosis. The present study found that a history of COPD and postoperative sepsis were significantly related to OS and DFS in patients with ESCC. A clinical nomogram was developed which included pathological T stage, pathological N factor, rate of positive LNs, history of COPD and postoperative sepsis. Subsequently, a risk stratification system was constructed based on the nomogram score. The developed nomograms are more accurate than the conventional staging system for predicting prognosis in ESCC patients, and calibration plots indicated concordance between prediction and actual observation. The C-index values for OS and DFS were 0.720 and 0.707, respectively.

Many prior studies have demonstrated that comorbidities have an impact on the prognosis of ESCC patients<sup>5,6,12,13</sup>. History of COPD is one of the most common conditions, accounting for 11.5% of newly diagnosed ESCC cancer patients. Furthermore, there is an association with a significantly worse prognosis<sup>14,15</sup>. COPD is a disease which is characterized by completely irreversible and usually progressive obstruction of the airways, which are associated with inflammation<sup>16</sup>. Furthermore, in patients with ESCC, following esophageal carcinoma resection and intrathoracic gastroesophagostomy, part of the thoracic cavity is occupied by the stomach that has been pulled up. This leads to further impairment of respiratory motion as well as poorer pulmonary function. Secondly, immune dysfunction plays an important role in the occurrence of COPD<sup>16</sup>, which may facilitate the rapid development of microscopic residual disease into clinically manifested recurrence. Thirdly, COPD was found to be a risk factor for pulmonary complications following surgery<sup>17</sup>. Postoperative pulmonary complications may be correlated with a worse prognosis<sup>2</sup>, although this was not found in the present study. Altogether, COPD may play an important role in predicting long-term survival, and the current study found it to be an independent predictor of death among patients with ESCC. However, further mechanistic study is necessary.

N staging is essentially based on the number of metastatic LNs, but the main source of error in the number of metastatic LNs lies in the variation in the total number of examined LNs. In this study, the median number of examined LNs was 13 (range of 8-19), which can easily result in the stage migration phenomenon in these patients. The present study indicated that current AJCC staging is unable to satisfactorily distinguish between the prognosis for stage III and stage IV groups, and these results are demonstrated in *Figure 3B* and *Figure 4B*. The ratio of metastatic lymph nodes is affected by the number of examined LNs. Additionally, this study found that the lymph node ratio is an independent predictor of survival in patients undergoing esophagectomy for ESCC, which was consistent with the prior literature<sup>3, 4, 18</sup>. Lymph node ratio may compensate for deficiencies in the AJCC nodal categories, and combining the lymph node ratio and AJCC nodal categories may more accurately predict survival than the current staging system<sup>19</sup>.

Sepsis was the only postoperative variable associated with long-term mortality, a finding consistent with the previous literature<sup>20</sup>. In cancer patients, the occurrence of postoperative sepsis is associated with aggressive immunosuppression<sup>21</sup>, which is potentially associated with cancer recurrence and mortality<sup>19, 20</sup>.

The present study has some limitations. Firstly, it was a retrospective design and a single-center study. Nonetheless, the study utilized a database of more than 500 cases from a single institution that used relatively standardized surgical techniques and postoperative management, thus avoiding some of the limitations of multicenter, population-based, or nationwide studies. Secondly, this study did not include external validation. Although 200 bootstrap resamples were carried out for internal validation, there still exists a risk of bias. Thirdly, patients had median number of only 13 examined LNs. Thus, this data may not be suitable for patients with more extensive lymphadenectomy. However, previous studies have suggested that extensive lymphadenectomy did not provide any survival benefit. Moreover, extensive lymphadenectomy introduces additional risks for complications and may delay postoperative recovery time and reduce quality of life.

## Conclusions

In conclusion, this is the first study to concurrently determine the value of including comorbidities and complications in predicting prognosis for patients with resected ESCC. This study has incorporated pathological T stage, pathological N factor, rate of positive LNs, history of COPD and postoperative sepsis into a nomogram to predict OS and DFS for ESCC patients. This practical system may help clinicians in both decision making and clinical study design. Further studies may help to extend the validation of the method and improve the model through parameter optimization.

## Abbreviations

esophageal squamous cell carcinoma (ESCC), chronic obstructive pulmonary disease (COPD), overall survival (OS), disease-free survival (DFS), tumor node metastasis (TNM), American Joint Committee on

Cancer (AJCC), body mass index (BMI), white blood cell (WBC), neutrophil to lymphocyte ratio (NLR), acute respiratory distress syndrome (ARDS), common terminology criteria for adverse events (CTCAE), interquartile range (IQR), Akaike's Information Criterion (AIC), analysis of variance (ANOVA)

## Declarations

**Ethics approval and consent to participate** This study was approved by the ethics committees of Huashan hospital, Fudan University, China, which waived the requirement for informed consent due to the use of anonymized retrospective data that were routinely collected during the health-screening process.

**Consent for publication:** Not applicable

**Availability of data and materials:** The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests:** The authors declare that they have no competing interests

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**Authors' contributions:** XH analyzed and interpreted the patient data regarding the hematological disease and the transplant. ZC and LG collected the data, and ZZ was a major contributor in writing the manuscript. BZ and NW designed the thoughts and methods of this research. All authors read and approved the final manuscript

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## Tables

**Table1: Clinical, Epidemiological, or Pathological Feature**

|                                   | Median/N | IQR/Percentage |
|-----------------------------------|----------|----------------|
| Age, year                         | 62       | 56-67          |
| Sex                               |          |                |
| Male                              | 411      | 81.7%          |
| Female                            | 92       | 18.3%          |
| BMI, kg/m <sup>2</sup>            | 22.23    | 20.07-24.19    |
| Tobacco use                       |          |                |
| No                                | 338      | 67.2%          |
| Yes                               | 165      | 32.8%          |
| Alcohol use                       |          |                |
| No                                | 381      | 75.7%          |
| Yes                               | 122      | 24.3%          |
| Comorbidities                     |          |                |
| History of hypertension           |          |                |
| No                                | 330      | 65.6%          |
| Yes                               | 173      | 34.4%          |
| History of diabetes               |          |                |
| No                                | 381      | 75.7%          |
| Yes                               | 122      | 24.3%          |
| History of COPD                   |          |                |
| No                                | 445      | 88.5%          |
| Yes                               | 58       | 11.5%          |
| History of hepatitis              |          |                |
| No                                | 428      | 85.1%          |
| Yes                               | 75       | 14.9%          |
| History of cardiovascular disease |          |                |
| No                                | 422      | 83.9%          |
| Yes                               | 81       | 16.1%          |
| Preoperative albumin, g/L         | 41.00    | 39.00-43.00    |

|   |        |               |
|---|--------|---------------|
| Preoperative platelet, *10 <sup>9</sup> | 194.00 | 157.00-239.00 |
| Preoperative WBC, *10 <sup>9</sup>      | 5.88   | 4.89-7.23     |
| Preoperative NLR                        | 2.25   | 1.67-3.17     |
| Length of tumor, cm                     | 3.00   | 2.00-4.50     |
| Location of tumor                       |        |               |
| Upper                                   | 82     | 16.3%         |
| Middle                                  | 302    | 60.0%         |
| Lower                                   | 119    | 23.7%         |
| Differentiation of tumor                |        |               |
| Well                                    | 65     | 12.9%         |
| Moderate                                | 299    | 59.4%         |
| Poor                                    | 139    | 27.6%         |
| Pathological T stage                    |        |               |
| T1                                      | 73     | 14.5%         |
| T2                                      | 146    | 29.0%         |
| T3                                      | 242    | 48.1%         |
| T4                                      | 42     | 8.3%          |
| Pathological N factor                   |        |               |
| N0                                      | 263    | 52.3%         |
| N1                                      | 140    | 27.8%         |
| N2                                      | 70     | 13.9%         |
| N3                                      | 30     | 6.0%          |
| Pathological stage                      |        |               |
| I                                       | 72     | 14.3%         |
| II                                      | 227    | 45.1%         |
| III                                     | 135    | 26.8%         |
| IV                                      | 69     | 13.7%         |
| Number of dissected LNs                 | 13     | 8-19          |
| Number of positive LNs                  | 0      | 0-2           |

|                                       |     |        |
|---------------------------------------|-----|--------|
| Rate of positive LNs                  | 0   | 0-0.17 |
| Postoperative complications           |     |        |
| Postoperative pulmonary complications | 148 | 29.4%  |
| Postoperative anastomotic leakage     | 29  | 5.8%   |
| Postoperative cardiovascular disease  | 107 | 21.3%  |
| Sepsis                                | 34  | 6.8%   |

Data are expressed as median (Interquartile range, IQR), N (percentage, %). BMI: body mass index; COPD: chronic obstructive pulmonary disease; NLR: neutrophil to lymphocyte ratio.

Table 2: Univariable and multivariable Cox analysis of prognostic factors for overall survival in 503 patients with esophageal squamous cell carcinoma

|                                   | Univariable analysis |         | Multivariable analysis |         |
|-----------------------------------|----------------------|---------|------------------------|---------|
|                                   | HR (95% CI)          | P-value | HR (95% CI)            | P-value |
| Age, year                         | 1.01 (0.99-1.03)     | 0.11    |                        |         |
| Sex                               |                      |         |                        |         |
| Male                              | Ref                  |         |                        |         |
| Female                            | 0.74 (0.54-1.02)     | 0.07    |                        |         |
| BMI, kg/m <sup>2</sup>            | 0.97 (0.93-1.01)     | 0.12    |                        |         |
| Tobacco use                       |                      |         |                        |         |
| No                                | Ref                  |         |                        |         |
| Yes                               | 1.11 (0.86-1.42)     | 0.42    |                        |         |
| Alcohol use                       |                      |         |                        |         |
| No                                | Ref                  |         |                        |         |
| Yes                               | 1.14 (0.87-1.49)     | 0.35    |                        |         |
| Comorbidities                     |                      |         |                        |         |
| History of hypertension           |                      |         |                        |         |
| No                                | Ref                  |         |                        |         |
| Yes                               | 1.10 (0.85-1.41)     | 0.48    |                        |         |
| History of diabetes               |                      |         |                        |         |
| No                                | Ref                  |         |                        |         |
| Yes                               | 1.18 (0.90-1.56)     | 0.23    |                        |         |
| History of COPD                   |                      |         |                        |         |
| No                                | Ref                  |         | Ref                    |         |
| Yes                               | 1.50 (1.08-2.10)     | 0.02    | 1.79 (1.27-2.53)       | <0.001  |
| History of hepatitis              |                      |         |                        |         |
| No                                | Ref                  |         |                        |         |
| Yes                               | 1.03 (0.74-1.44)     | 0.84    |                        |         |
| History of cardiovascular disease |                      |         |                        |         |

|   |                    |        |                  |        |
|---|--------------------|--------|------------------|--------|
| No                                      | Ref                |        |                  |        |
| Yes                                     | 0.92 (0.66-1.29)   | 0.62   |                  |        |
| Preoperative albumin, g/L               | 0.96 (0.93-0.99)   | 0.03   |                  |        |
| Preoperative platelet, *10 <sup>9</sup> | 1 (0.998-1.002)    | 0.63   |                  |        |
| Preoperative WBC, *10 <sup>9</sup>      | 1.06 (1.004-1.129) | 0.04   |                  |        |
| Preoperative NLR                        | 1.06 (1.006-1.117) | 0.03   |                  |        |
| Length of tumor, cm                     | 1.18 (1.11-1.25)   | <0.001 |                  |        |
| Location of tumor                       |                    |        |                  |        |
| Upper                                   | Ref                |        |                  |        |
| Middle                                  | 0.86 (0.62-1.19)   | 0.35   |                  |        |
| Lower                                   | 0.91 (0.62-1.33)   | 0.62   |                  |        |
| Differentiation of tumor                |                    |        |                  |        |
| Well                                    | Ref                |        |                  |        |
| Moderate                                | 1.69 (1.09-2.62)   | 0.02   |                  |        |
| Poor                                    | 2.19 (1.37-3.49)   | <0.001 |                  |        |
| Pathological T stage                    |                    |        |                  |        |
| T1                                      | Ref                |        | Ref              |        |
| T2                                      | 2.51 (1.43-4.41)   | 0.001  | 1.82 (1.02-3.22) | 0.004  |
| T3                                      | 4.76 (2.80-8.10)   | <0.001 | 3.01 (1.74-5.20) | <0.001 |
| T4                                      | 6.33 (3.44-11.67)  | <0.001 | 3.17 (1.66-6.07) | <0.001 |
| Pathological N factor                   |                    |        |                  |        |
| N0                                      | Ref                |        | Ref              |        |
| N1                                      | 2.24 (1.67-3.00)   | <0.001 | 1.80 (1.30-2.49) | <0.001 |
| N2                                      | 3.78 (2.34-6.10)   | <0.001 | 2.26 (1.27-4.00) | 0.005  |
| N3                                      | 5.73 (4.10-8.01)   | <0.001 | 3.63 (2.32-      | <0.001 |

|                                       |                    |        |                  |       |
|---------------------------------------|--------------------|--------|------------------|-------|
|                                       |                    |        | 5.68)            |       |
| Pathological stage                    |                    |        |                  |       |
| I                                     | Ref                |        |                  |       |
| II                                    | 2.43 (1.41-4.18)   | 0.001  |                  |       |
| III                                   | 6.82 (3.95-11.77)  | <0.001 |                  |       |
| IV                                    | 6.61 (3.71-11.76)  | <0.001 |                  |       |
| Number of dissected LNs               | 1.01 (0.99-1.02)   | 0.37   |                  |       |
| Number of positive LNs                | 1.13 (1.10-1.17)   | <0.001 |                  |       |
| Rate of positive LNs                  | 10.06 (6.34-15.97) | <0.001 | 2.01 (0.91-4.43) | 0.008 |
| Postoperative complications           |                    |        |                  |       |
| Postoperative pulmonary complications | 1.20 (0.92-1.55)   | 0.18   |                  |       |
| Postoperative anastomotic leakage     | 1.59 (0.97-2.60)   | 0.07   |                  |       |
| Postoperative cardiovascular disease  | 1.10 (0.82-1.46)   | 0.54   |                  |       |
| Sepsis                                | 1.82 (1.18-2.82)   | 0.007  | 2.04 (1.31-3.18) | 0.002 |

BMI: body mass index; COPD: chronic obstructive pulmonary disease; NLR: neutrophil to lymphocyte ratio;

Table 3: Univariable and multivariable Cox analysis of prognostic factors for disease free survival in 503 patients with esophageal squamous cell carcinoma

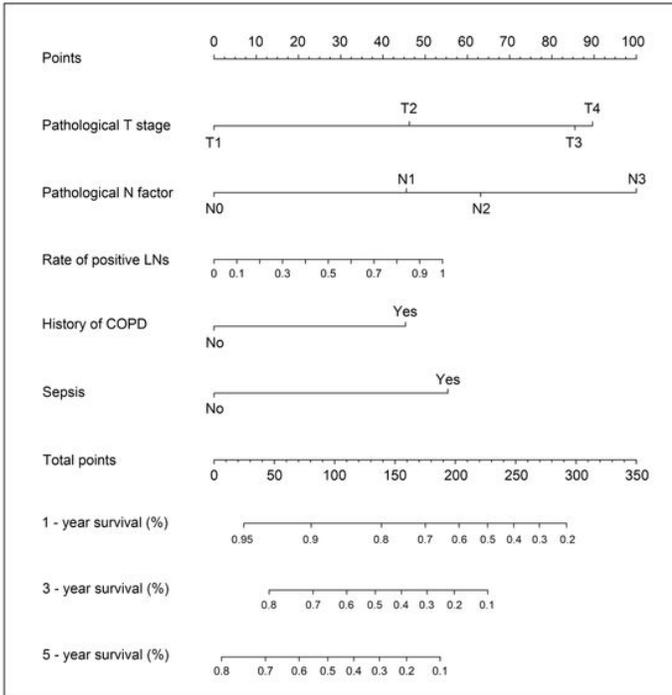
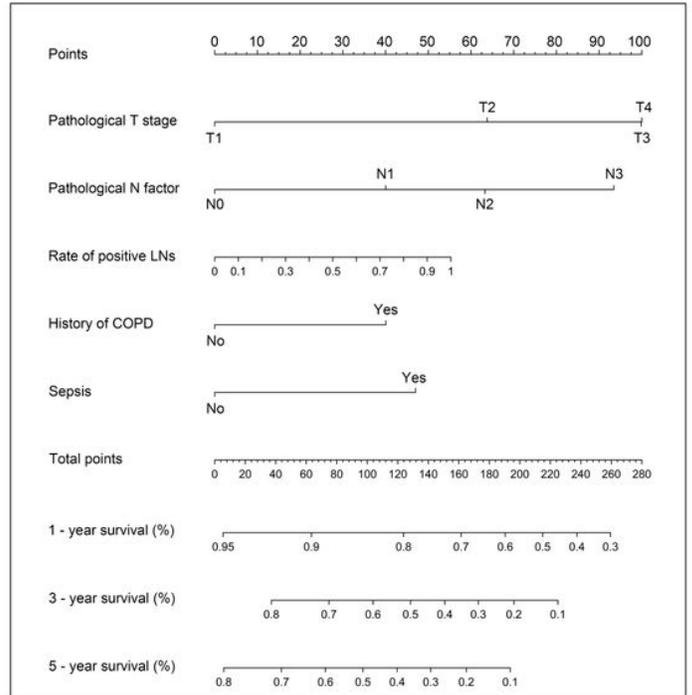
|                         | Univariable analysis |         | Multivariable analysis |         |
|-------------------------|----------------------|---------|------------------------|---------|
|                         | HR (95% CI)          | P-value | HR (95% CI)            | P-value |
| Age, year               | 1.01 (0.99-1.02)     | 0.17    |                        |         |
| Sex                     |                      |         |                        |         |
| Male                    | Ref                  |         |                        |         |
| Female                  | 0.75 (0.54-1.02)     | 0.07    |                        |         |
| BMI, kg/m <sup>2</sup>  | 0.97 (0.94-1.01)     | 0.20    |                        |         |
| Tobacco use             |                      |         |                        |         |
| No                      | Ref                  |         |                        |         |
| Yes                     | 1.07 (0.84-1.36)     | 0.60    |                        |         |
| Alcohol use             |                      |         |                        |         |
| No                      | Ref                  |         |                        |         |
| Yes                     | 1.12 (0.86-1.45)     | 0.42    |                        |         |
| Comorbidities           |                      |         |                        |         |
| History of hypertension |                      |         |                        |         |
| No                      |                      |         |                        |         |
| Yes                     | 1.11 (0.87-1.41)     | 0.42    |                        |         |
| History of diabetes     |                      |         |                        |         |
| No                      | Ref                  |         |                        |         |
| Yes                     | 1.26 (0.96-1.64)     | 0.09    |                        |         |
| History of COPD         |                      |         |                        |         |
| No                      | Ref                  |         | Ref                    |         |
| Yes                     | 1.42 (1.02-1.97)     | 0.04    | 1.65 (1.17-2.31)       | 0.004   |
| History of hepatitis    |                      |         |                        |         |

|   |                     |        |                  |        |
|---|---------------------|--------|------------------|--------|
| No                                      | Ref                 |        |                  |        |
| Yes                                     | 0.96 (0.69- 1.33)   |        |                  |        |
| History of cardiovascular disease       |                     |        |                  |        |
| No                                      | Ref                 |        |                  |        |
| Yes                                     | 0.91 (0.66-1.26)    |        |                  |        |
| Preoperative albumin                    | 0.96 (0.93-0.99)    | 0.04   |                  |        |
| Preoperative platelet, *10 <sup>9</sup> | 1.001 (0.999-1.003) | 0.436  |                  |        |
| Preoperative WBC, *10 <sup>9</sup>      | 1.05 (0.99-1.12)    | 0.08   |                  |        |
| Preoperative NLR                        | 1.05 (0.99-1.11)    | 0.05   |                  |        |
| Length of tumor, cm                     | 1.17 (1.11-1.25)    | <0.001 |                  |        |
| Location of tumor                       |                     |        |                  |        |
| Upper                                   | Ref                 |        |                  |        |
| Middle                                  | 0.85 (0.62-1.17)    | 0.33   |                  |        |
| Lower                                   | 0.93 (0.65-1.35)    | 0.71   |                  |        |
| Differentiation of tumor                |                     |        |                  |        |
| Well                                    | Ref                 |        |                  |        |
| Moderate                                | 1.62 (1.07-2.46)    | 0.02   |                  |        |
| Poor                                    | 2.04 (1.31-3.18)    | 0.002  |                  |        |
| Pathological T stage                    |                     |        |                  |        |
| T1                                      | Ref                 |        | Ref              |        |
| T2                                      | 2.92 (1.67-5.09)    | <0.001 | 2.21 (1.25-3.89) | 0.006  |
| T3                                      | 5.23 (3.08-8.89)    | <0.001 | 3.46 (2.00-5.97) | <0.001 |
| T4                                      | 6.42 (3.48-11.82)   | <0.001 | 3.47 (1.82-6.60) | <0.001 |
| Pathological N factor                   |                     |        |                  |        |
| N0                                      | Ref                 |        | Ref              |        |
| N1                                      | 2.09 (1.58-2.78)    | <0.001 | 1.65 (1.30-2.49) | 0.002  |

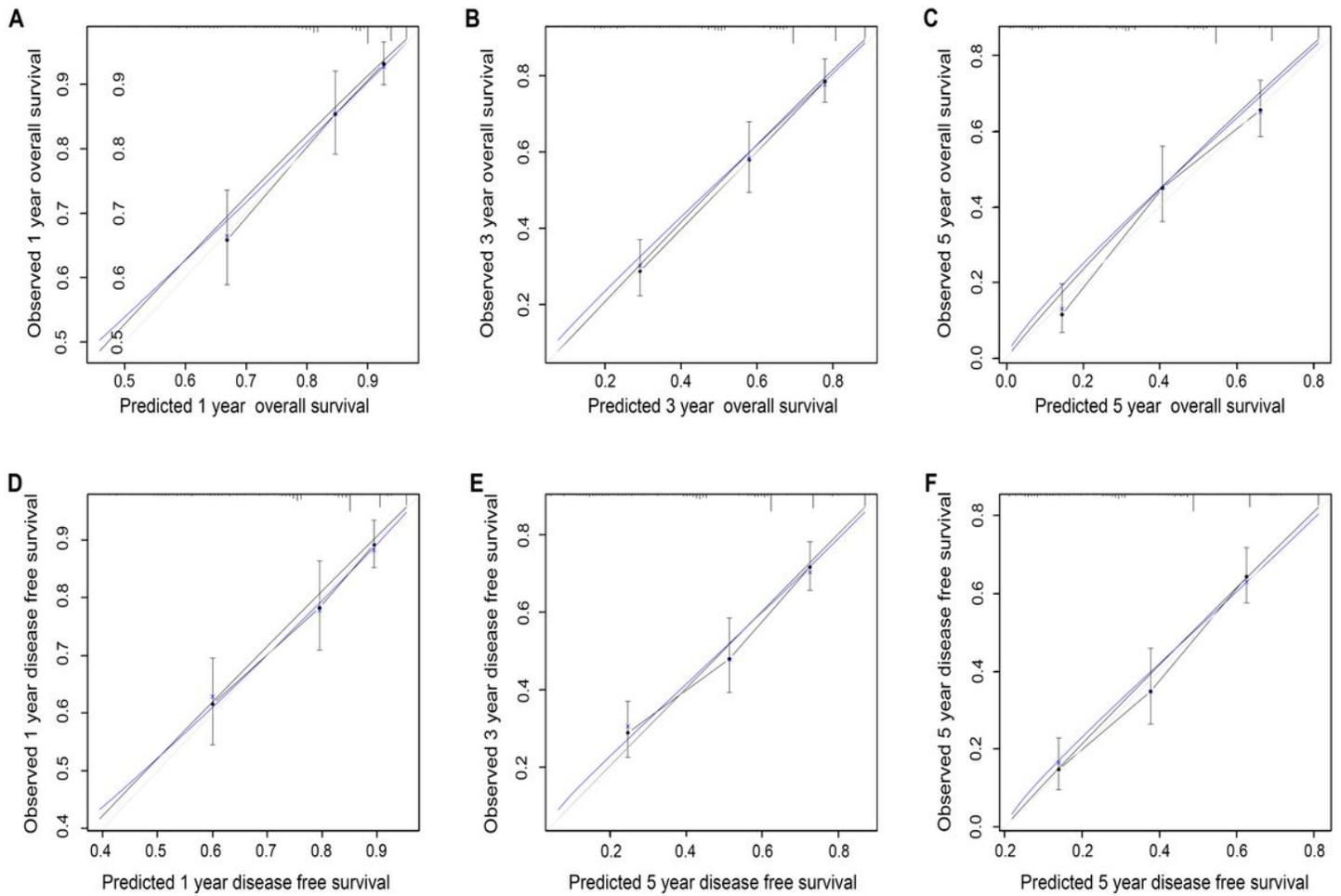
|                                       |                   |        |                  |        |
|---------------------------------------|-------------------|--------|------------------|--------|
| N2                                    | 3.72 (2.37-5.84)  | <0.001 | 2.20 (1.27-3.79) | 0.005  |
| N3                                    | 5.11 (3.68-7.09)  | <0.001 | 3.20 (2.07-4.93) | <0.001 |
| Pathological stage                    |                   |        |                  |        |
| I                                     | Ref               |        |                  |        |
| II                                    | 2.80 (1.63-4.81)  | <0.001 |                  |        |
| III                                   | 7.23 (4.19-12.46) | <0.001 |                  |        |
| IV                                    | 7.02 (3.96-12.45) | <0.001 |                  |        |
| Number of dissected LNs               | 1.01 (0.99-1.02)  | 0.28   |                  |        |
| Number of positive LNs                | 1.13 (1.10-1.17)  | <0.001 |                  |        |
| Rate of positive LNs                  | 9.19 (5.8-14.58)  | <0.001 | 1.99 (0.90-4.36) | 0.009  |
| Postoperative complications           |                   |        |                  |        |
| Postoperative pulmonary complications | 1.21 (0.94-1.56)  | 0.14   |                  |        |
| Postoperative anastomotic leakage     | 1.44 (0.88-2.35)  | 0.15   |                  |        |
| Postoperative cardiovascular disease  | 1.11 (0.84-1.47)  | 0.46   |                  |        |
| Sepsis                                | 1.66 (1.07-2.57)  | 0.02   | 1.79 (1.16-2.79) | 0.009  |

BMI: body mass index; COPD: chronic obstructive pulmonary disease; NLR: neutrophil to lymphocyte ratio;

## Figures

**A****B****Figure 1**

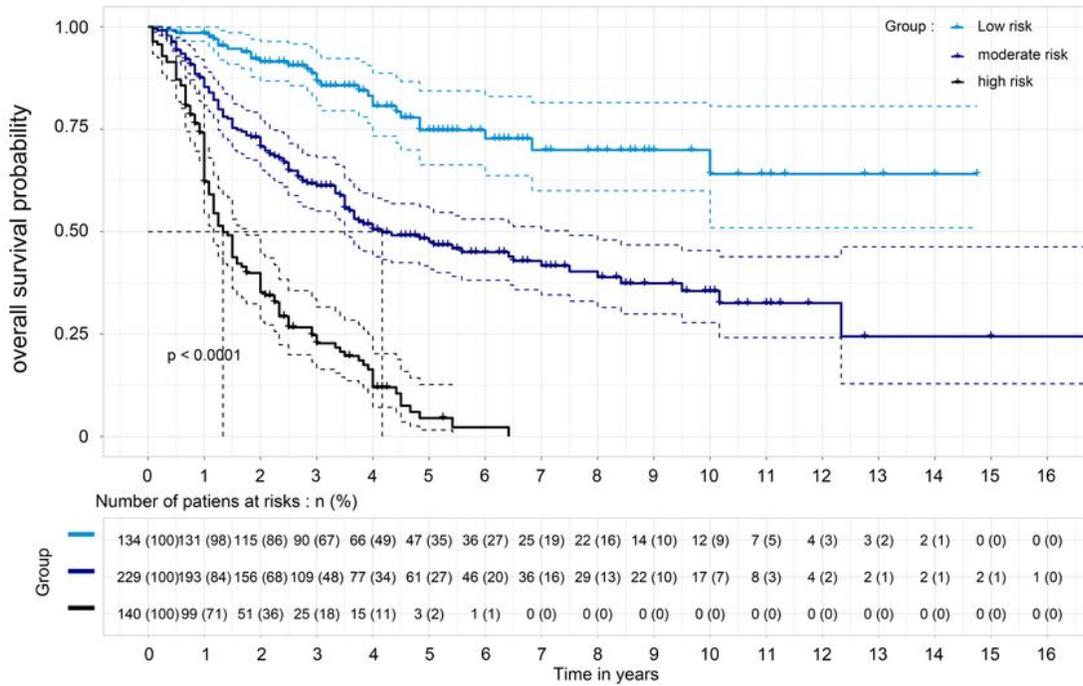
Survival nomogram for patients with resected esophageal squamous cell carcinoma (To use the nomogram, an individual patient's value is located on each variable axis, and a line is drawn upward to determine the number of points received for each variable value. The sum of these number is located on Total Point axis, and a line is drawn downward to the survival axes to determine the likelihood of 1-, 3- or 5-year survival. A is for overall survival, B is for disease free survival).



**Figure 2**

Calibration curve for predicting patient survival at (A)/(D) 1 year, (B)/(E) 3 years and (C)/(F) 5 years in the validation cohort. Nomogram-predicted overall survival/disease free survival (DFS) is plotted on the x-axis; observed overall survival/disease free survival is plotted on the y-axis.

A



B

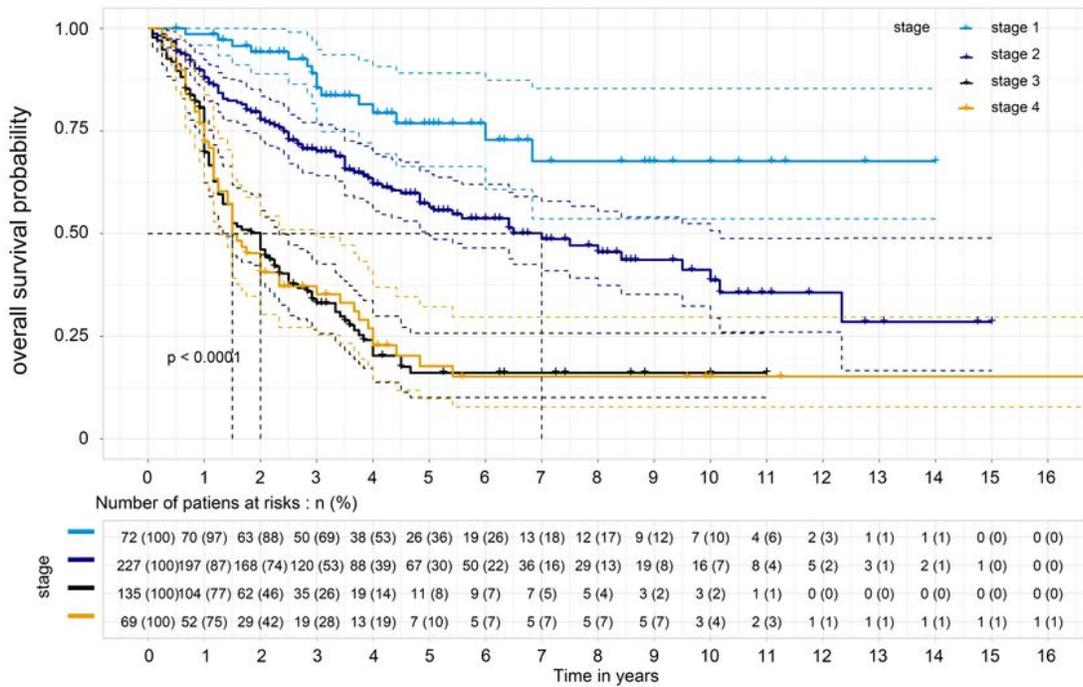
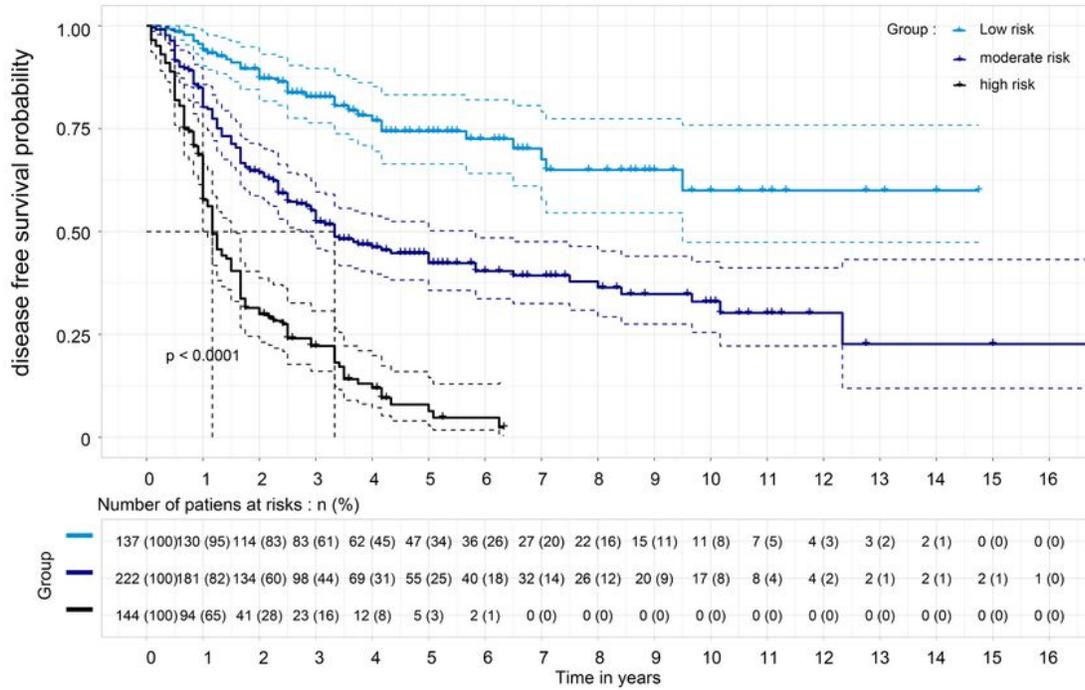


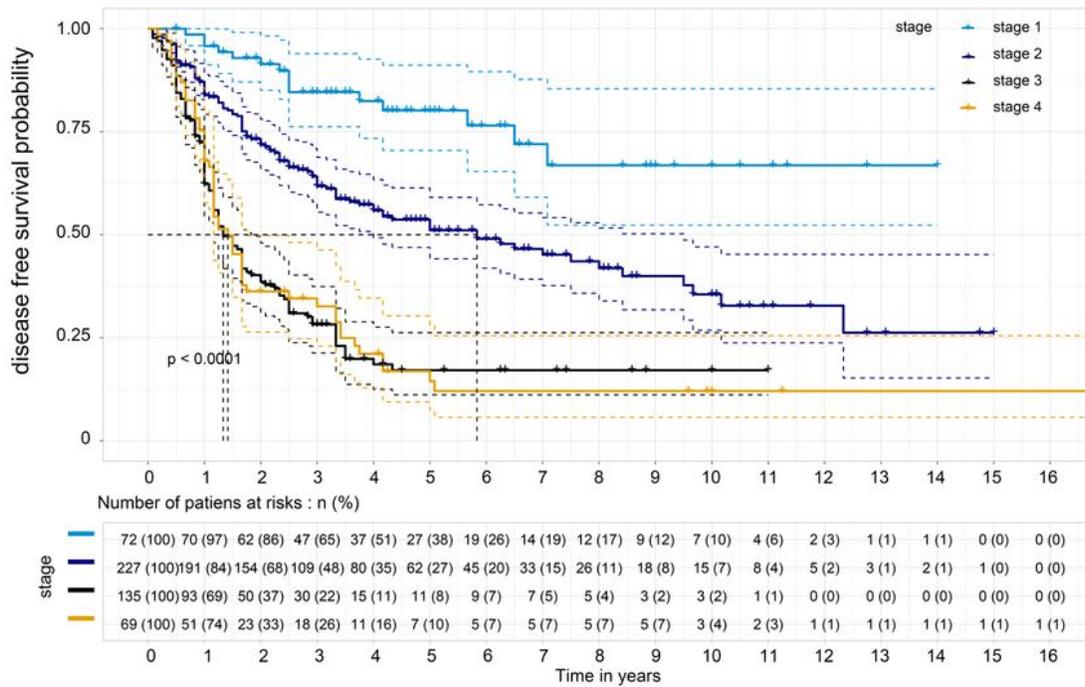
Figure 3

Kaplan-Meier Survival curves of the primary cohort categorized by different staging systems for overall survival. ([A] established model; [B] American Joint Committee on cancer [AJCC] seventh edition)

**A**



**B**



**Figure 4**

Kaplan-Meier Survival curves of the primary cohort categorized by different staging systems for disease free survival. ([A] established model; [B] American Joint Committee on cancer [AJCC] seventh edition)