



Gender-specific nomogram models to predict the prognosis of male and female lung adenocarcinoma patients: a population-based analysis

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Background: Epidemiological and clinical prognosis differences between male and female lung adenocarcinoma (LUAD) patients have been frequently reported. To improve prognosis determinations, gender-specific nomogram models should be developed and validated to predict the prognosis of patients with LUAD.

Methods: Using the Surveillance, Epidemiology, and End Results (SEER) database, LUAD patients diagnosed between 2010 and 2015 were used as SEER training and internal validation testing sets. Patients in Tianjin Chest Hospital with postoperative pathological diagnosis of LUAD from January 1, 2015 to October 1, 2016 were considered as Chinese external testing sets. Using the Kaplan-Meier method and log-rank tests, we compared all the included male and female LUAD patients' overall survival (OS) and lung cancer-specific survival (LCSS) rates. The female and male patients from SEER database were randomly divided into training and internal validation groups at a 7:3 ratio. Variables ($P < 0.05$) in the multivariable LCSS Cox regression analysis were independent prognostic predictors of the nomogram models. Harrell's concordance index (C-index), calibration curves, decision curve analysis (DCA) curves, receiver operating characteristic (ROC) curves, and the area under the curves (AUCs) were used to test the calibration and accuracy of the gender-specific nomogram models.

Results: A total of 32,654 LUAD patients (17,372 females and 15,282 males) were identified. Ten variables [age, marital status, tumor site, differentiation grade, derived American Joint Committee on Cancer (AJCC) stage, tumor size, historic stage, surgery, derived AJCC N stage and chemotherapy] were statistically significant in the multivariate LCSS Cox regression analysis, and visualized through the nomogram models. The female and male training nomogram C-indexes were 0.827 and 0.811, respectively. The 3- and 5-year AUCs of the LCSS were 0.881 and 0.872 in the female training set, respectively, and 0.879 and 0.881 in the male training set, respectively. The DCA results indicated that these nomogram models were excellent predictors of LUAD prognosis and can be used to supplement the prognostication of tumor, node, and metastasis (TNM) stage.

Conclusions: Given the different incidence and prognosis of LUAD between men and women, we developed gender-specific nomogram models with good discrimination and calibration capacity to predict 3- and 5-year LUAD-specific survival.

Keywords: Nomogram model; prognosis; lung adenocarcinoma (LUAD); gender

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Introduction

Lung cancer is the leading cause of cancer-related death around the world (1,2). In 2020, approximately 1.8 million people died from lung cancer worldwide. It is estimated that there will be 235,760 new lung and bronchus cancer cases in the United States in 2021 (3). To address this major global health problem, etiological treatment and prognosis are essential. In relation to smoking factors, epidemiological studies showed that in America, among patients with lung cancer, 19% were female non-smokers, 9% were male non-smokers (4). In Japan and South Korea, about one-third of non-small lung cancer patients are non-smokers (5,6). In addition to smoking, Jin *et al.* (7-9) believes that hormonal factors may play a role in the occurrence and development of lung cancer, and also in lung adenocarcinoma (LUAD) (10,11). LUAD is one of the most prevalent pathological subtypes of lung cancer, and accounts for more than about one-third of lung cancers (12-14). Among lung cancer non-smokers, the incidence of LUAD is higher in females than males (15-17), and gender is considered as an independent prognostic factor for LUAD (12,18). In a Swedish national cohort study, female LUAD patients generally had a better prognosis in lung cancer-specific survival (LCSS) across tumor, node, and metastasis (TNM) stages (19). Behrens *et al.* pointed women with LUAD have a higher density of tumor-associated immune infiltrating cells in their tumor tissues than male LUAD patients (20). Meanwhile, Woolston *et al.* believe female and male LUAD patients have different KRAS/EGFR mutations patterns, and effects of relevant copy number variation (cnv) may contribute to gender-specific prognosis of LUAD (21). Huang *et al.* (11) believe that estrogen promotes LUAD development through estrogen receptor beta (ER- β) pathway. Chen *et al.* (22) suggest that the ER- β may play a significant role in LUAD progression via the mitogen-activated protein kinase kinase/extracellular signal-regulated kinase signaling pathway; however, ER- β overexpression in males indicates better survival (23). Wheatley-Price *et al.* (24) noted that female LUAD patients receiving platinum-based chemotherapy had more positive prognostic effects than male LUAD patients. Given the different LUAD incidence rates and prognosis between males and females, the prognosis of

LUAD for men and women need to be analyzed separately (18,25). Nomograms, which are graphical models that predict the prognosis of cancer patients, have been shown to improve prognosis determinations and treatment stratifications in patients with thyroid carcinoma (26), uterine cervical carcinoma (27), colon cancer (28), and gastric carcinoma (29). Survival prediction nomogram tools demonstrate excellent predictive power in different cancers and medicine (30). However, to date, no gender-specific nomogram models for predicting the prognosis of male and female LUAD patients appear to have been established. Accordingly, there is a need for separately modeling the gender-specific prognosis of LUAD. For the purpose of achieving accurate individualized treatment, more clinical variables besides age and American Joint Committee on Cancer (AJCC) TNM stage should be incorporated to reach the individualized and efficient prediction. In this analysis, we gathered useful information about LUAD patients from the Surveillance, Epidemiology, and End Results (SEER) database. To supplement internal validation testing sets, pathologically diagnosed LUAD patients after operation in Tianjin Chest Hospital from January 1, 2015 to October 1, 2016 were taken into consideration. We then conducted a Cox regression analysis to identify relevant prognostic-related factors and establish gender-specific nomogram models for male and female LUAD patients. These reliable and practical nomogram prediction models will be useful in providing individual treatment advice and improving clinical decisions.

We present the following article in accordance with the TRIPOD reporting checklist (available at <https://dx.doi.org/10.21037/atm-21-5367>).

Methods

Ethical review

This retrospective cohort study used data from the previously collected identifiable SEER database (the SEER-program, <https://seer.cancer.gov>) and Tianjin Chest hospital. All of the procedures performed in this study were conducted in accordance with the Declaration of Helsinki (as revised in 2013), and written informed consents have

been provided by all included patients from Tianjin Chest Hospital. The study was approved by institutional ethics board of Tianjin Chest Hospital (ethical approval number: 2021LW-016).

Study population

In this retrospective study, data from SEER database were obtained using SEER*STAT 8.3.9 software according to the site code classifications (C34.0–34.9) and International Classification of Diseases for Oncology terrain code “8140/3: Adenocarcinoma NOS”. Patients diagnosed with LUAD in SEER database from 2010–2015 were identified. Postoperative patients who were pathologically diagnosed with LUAD from January 1, 2015 to October 1, 2016 in Tianjin Chest Hospital were collected. To be eligible for inclusion in this study, participants had to meet the following criteria: (I) have complete medical information, including information about age, surgery methods, derived AJCC stage, derived AJCC N stage, tumor site, laterality, tumor historic stage, tumor size, and tumor differentiated grade; (II) have a pathologically confirmed diagnosis of LUAD; (III) have been diagnosed with primary malignant tumor (LUAD); and (IV) have accurate follow-up data. Patients were excluded from the study if information about their sex, age, laterality, tumor site, tumor differentiation grade, derived AJCC stage, derived AJCC N stage, tumor size, historic stage, and surgery was uncertain. A total of 32,654 patients (17,372 female LUAD patients and 15,282 male LUAD patients) met the inclusion criteria and were incorporated into this study. According to a 7:3 ratio, male and female patients in SEER database were randomly divided into the following groups: (I) a male training data set of 10,649 patients; (II) a female training set of 12,101 patients; (III) a male internal testing data set of 4,564 patients; and (IV) a female internal testing data set of 5,187 patients. The included LUAD patients from our hospital were deemed as Chinese external validation cohorts. The gender-specific nomogram models were developed separately based on the male and female LUAD training cohorts, and were verified separately by the male and female LUAD internal and external testing cohorts.

Collection variables

Information was collected about the following variables for the analysis: overall survival (OS), LCSS, age, gender, tumor site, laterality, tumor differentiation grade, derived AJCC

stage, tumor size, historical stage, derived AJCC N stage, surgery information, chemotherapy, and marital status. LCSS was defined as the date of diagnosis to the date of cancer-specific death; deaths by other causes were regarded as the results of other observations. OS was defined as the time from the date of lung cancer diagnosis to death by any cause. The operation information was divided into no surgery, lobectomy (including lobectomy, pneumonectomy, and bronchial sleeve resection), segmentectomy, and wedge resection.

Statistical methods

Using the Kaplan-Meier method and log-rank tests, we compared all included male and female cancer patients' OS and LCSS rates (see *Figure 1*). Univariate and multivariate Cox regression models were used to analyze the effects of prognostic factors through R packages “survival”, “plyr” (results of univariate cox analyses are provided in *Tables S1,S2*). The variables ($P < 0.05$) in the multivariable Cox regression analysis among the male and female training cohorts were considered independent prognostic predictors for the establishment of the nomograms. We also calculated the hazard ratios and 95% confidence intervals using Cox multivariable regression. All the reported P values were bilateral. R version 4.0.3 (R) was used to establish and verify the gender-specific nomogram models. Internal verification was evaluated using bootstrap verification. A total of 1,000 re-samplings were performed. The testing cohort was used to check the accuracy of the nomogram models. The calibration curves, concordance index (C-index), decision curve analysis (DCA) curves, receiver operating characteristic (ROC) curves, and area under the curves (AUCs) were used to evaluate the validity of the nomogram models.

The “survival”, “forestmodel”, “rms”, “ggplot2”, “cmprsk”, and “survivalROC” R packages were used to establish and verify our gender-specific nomogram models.

Results

Patient characteristics

This study reviewed 32,654 primary LUAD patients (15,282 males and 17,372 females). Among them, 153 patients in our hospital with postoperative pathological returns of LUAD from January 1, 2015 to October 1, 2016 were enrolled as Chinese validation cohorts. Patients' information is displayed in *Table 1*. There were no significant differences

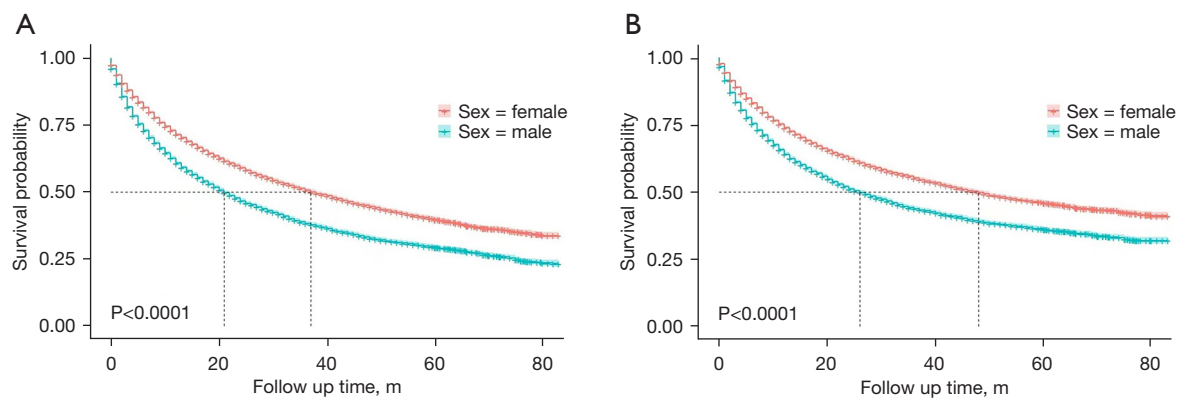


Figure 1 Kaplan-Meier curves for patients with LUAD. (A) OS for male and female LUAD. (B) LCSS for male and female LUAD. LUAD, lung adenocarcinoma; OS, overall survival; LCSS, lung cancer-specific survival.

between the training and validation cohorts.

Nomogram establishment

LUAD patients from training cohorts (10,649 male and 12,101 female LUAD patients) were reckoned to develop the gender-specific nomogram models. The construction of the model is composed of 10 relevant clinical variables which provide personalized prognostic factors for the LCSS of male and female LUAD patients. As *Figure 2* shows, 10 variables (age, marital status, tumor site, tumor differentiation grade, derived AJCC stage, tumor size, historic stage, surgery, derived AJCC N stage and chemical treatment) were analyzed as independent factors for LUAD patients. Based on the independent prognostic factors of male and female LUAD, we constructed gender-specific nomogram models for 3- and 5-year LUAD patients' LCSS (see *Figure 2A-2D*). Results of univariate cox analyses have been provided in [Tables S1,S2](#).

Nomogram validation

The gender-specific nomogram models have an excellent performance among LUAD patients, the C-indexes for the female and male LUAD training nomogram models were 0.827 and 0.811, respectively. Again, C-indexes for the female and male LUAD internal validation models were 0.823 and 0.811, for external Chinese female and male validation models were 0.89 and 0.831, respectively. The calibration curves (see *Figure 3*) showed consistency between predicted and actual patient survival. The ROC curves and AUC values (see *Figure 4*) were used to evaluate

the accuracy of the nomogram models (all AUC values >0.8). The DCA curves (see *Figure 5*) were used to compare our nomogram models with other models. The results showed that our gender-specific models are excellent predictors of LUAD prognosis and can be used to supplement prognostication of TNM stage.

Clinical use

For example, consider a 60-year-old married female patient with a regional 3-cm poorly differentiated and AJCC TNM stage II LUAD tumor in the lower lobe, who underwent lobectomy treatment without chemotherapy. The 3- and 5-year LCSS probabilities were about 64% and 50%, respectively, and we highly recommended that the patient undergo chemotherapy to increase her LCSS probability. Lobectomy is still considered as the best surgery method for this patient.

Discussion

Lung cancer is one of the most common cancers and the leading cause of cancer-related death worldwide (1-3). LUAD is the most prevalent subtype of non-small lung cancer (31), and is more common in females than in males (32). In prognosis, the survival rates of male and female LUAD patients differ; in a national cohort study of 23,465 LUAD participants, the prognosis of female LUAD patients in LCSS among TNM stages was kind of higher than that of male patients (19). Meanwhile, female LUAD patients may receive more benefits from using platinum-based chemical drugs (24). Townsend *et al.* (33) proposed

Table 1 Characteristics of patients with LUAD

Characteristics	Female patients with LUAD, n (%)				Male patients with LUAD, n (%)			
	SEER training cohort (n=12,101)	SEER testing cohort (n=5,187)	SEER overall (n=17,288)	Chinese validation cohort (n=84)	SEER training cohort (n=10,649)	SEER testing cohort (n=4,564)	SEER overall (n=15,213)	Chinese validation cohort (n=69)
Age (years)								
≤60	3,287 (27.2)	1,373 (26.5)	4,660 (27.0)	42 (50.0)	2,884 (27.1)	1,247 (27.3)	4,131 (27.2)	29 (42.0)
60 < age ≤70	3,917 (32.4)	1,623 (31.3)	5,540 (32.0)	35 (41.7)	3,710 (34.8)	1,615 (35.4)	5,325 (35.0)	33 (47.8)
>70	4,897 (40.5)	2,191 (42.2)	7,088 (41.0)	7 (8.3)	4,055 (38.1)	1,702 (37.3)	5,757 (37.8)	7 (10.1)
Site								
Upper lobe	7,435 (61.4)	3,178 (61.3)	10,613 (61.4)	38 (45.2)	6,985 (65.6)	2,982 (65.3)	9,967 (65.5)	32 (46.4)
Middle lobe	625 (5.2)	282 (5.4)	907 (5.2)	9 (10.7)	492 (4.6)	232 (5.1)	724 (4.8)	8 (11.6)
Lower lobe	3,729 (30.8)	1,580 (30.5)	5,309 (30.7)	35 (41.7)	2,883 (27.1)	1,242 (27.2)	4,125 (27.1)	24 (34.8)
Overlapping lesion of lung	112 (0.9)	60 (1.2)	172 (1.0)	2 (2.4)	118 (1.1)	33 (0.7)	151 (1.0)	5 (7.2)
Main bronchus	200 (1.7)	87 (1.7)	287 (1.7)	–	171 (1.6)	75 (1.6)	246 (1.6)	–
Grade								
Well differentiated	1,905 (15.7)	824 (15.9)	2,729 (15.8)	33 (39.3)	1,179 (11.1)	485 (10.6)	1,664 (10.9)	28 (40.6)
Moderately differentiated	4,985 (41.2)	2,170 (41.8)	7,155 (41.4)	6 (7.1)	3,941 (37.0)	1,677 (36.7)	5,618 (36.9)	5 (7.2)
Poorly differentiated	5,113 (42.3)	2,150 (41.4)	7,263 (42.0)	45 (53.6)	5,424 (50.9)	2,352 (51.5)	7,776 (51.1)	36 (52.2)
Undifferentiated	98 (0.8)	43 (0.8)	141 (0.8)	–	105 (1.0)	50 (1.1)	155 (1.0)	–
Laterality								
Right	7,240 (59.8)	3,101 (59.8)	10,341 (59.8)	57 (67.9)	6,437 (60.4)	2,710 (59.4)	9,147 (60.1)	45 (65.2)
Left	4,842 (40.0)	2,083 (40.2)	6,925 (40.1)	27 (32.1)	4,204 (39.5)	1,850 (40.5)	6,054 (39.8)	24 (34.8)
Bilateral	19 (0.2)	3 (0.1)	22 (0.1)	–	8 (0.1)	4 (0.1)	12 (0.1)	–
Derived AJCC stage								
I	4,689 (38.7)	2,051 (39.5)	6,740 (39.0)	51 (60.7)	3,346 (31.4)	1,447 (31.7)	4,793 (31.5)	44 (63.8)
II	1,347 (11.1)	563 (10.9)	1,910 (11.0)	12 (14.3)	1,218 (11.4)	526 (11.5)	1,744 (11.5)	7 (10.1)
III	2,157 (17.8)	934 (18.0)	3,091 (17.9)	19 (22.6)	2,021 (19.0)	860 (18.8)	2,881 (18.9)	17 (24.6)
IV	3,908 (32.3)	1,639 (31.6)	5,547 (32.1)	2 (2.4)	4,064 (38.2)	1,731 (37.9)	5,795 (38.1)	1 (1.4)
Historic stage								
Regional	3,704 (30.6)	1,621 (31.3)	5,325 (30.8)	53 (63.1)	3,243 (30.5)	1,379 (30.2)	4,622 (30.4)	38 (55.1)
Localized	4,151 (34.3)	1,803 (34.8)	5,954 (34.4)	25 (29.8)	2,967 (27.9)	1,294 (28.4)	4,261 (28.0)	28 (40.6)
Distant	4,246 (35.1)	1,763 (34.0)	6,009 (34.8)	6 (7.1)	4,439 (41.7)	1,891 (41.4)	6,330 (41.6)	3 (4.3)

Table 1 (continued)

Table 1 (continued)

Characteristics	Female patients with LUAD, n (%)				Male patients with LUAD, n (%)			
	SEER training cohort (n=12,101)	SEER testing cohort (n=5,187)	SEER overall (n=17,288)	Chinese validation cohort (n=84)	SEER training cohort (n=10,649)	SEER testing cohort (n=4,564)	SEER overall (n=15,213)	Chinese validation cohort (n=69)
Surgery								
No surgery	5,984 (49.5)	2,462 (47.5)	8,446 (48.9)	–	5,867 (55.1)	2,566 (56.2)	8,433 (55.4)	–
Wedge resection	829 (6.9)	394 (7.6)	1,223 (7.1)	1 (1.2)	653 (6.1)	286 (6.3)	939 (6.2)	–
Segmental resection	219 (1.8)	98 (1.9)	317 (1.8)	3 (3.6)	151 (1.4)	57 (1.2)	208 (1.4)	3 (4.3)
Lobectomy	5,069 (41.9)	2,233 (43.1)	7,302 (42.2)	80 (95.2)	3,978 (37.4)	1,655 (36.3)	5,633 (37.0)	66 (95.7)
Derived AJCC N stage								
N0	6,616 (54.7)	2,891 (55.7)	9,507 (55.0)	66 (78.6)	5,242 (49.2)	2,234 (48.9)	7,476 (49.1)	58 (84.1)
N1	1,180 (9.8)	476 (9.2)	1,656 (9.6)	10 (11.9)	1,084 (10.2)	484 (10.6)	1,568 (10.3)	5 (7.2)
N2	3,329 (27.5)	1,409 (27.2)	4,738 (27.4)	8 (9.5)	3,182 (29.9)	1,367 (30.0)	4,549 (29.9)	6 (8.7)
N3	976 (8.1)	411 (7.9)	1,387 (8.0)	–	1,141 (10.7)	479 (10.5)	1,620 (10.6)	–
Chemotherapy								
No/unknown	7,117 (58.8)	3,049 (58.8)	10,166 (58.8)	24 (28.6)	5,889 (55.3)	2,549 (55.9)	8,438 (55.5)	25 (36.2)
Yes	4,984 (41.2)	2,138 (41.2)	7,122 (41.2)	60 (71.4)	4,760 (44.7)	2,015 (44.1)	6,775 (44.5)	44 (63.8)
Size (cm)								
Size ≤3	6,355 (52.5)	2,686 (51.8)	9,041 (52.3)	64 (76.2)	4,666 (43.8)	1,984 (43.5)	6,650 (43.7)	55 (79.7)
Size >3	5,746 (47.5)	2,501 (48.2)	8,247 (47.7)	20 (23.8)	5,983 (56.2)	2,580 (56.5)	8,563 (56.3)	14 (20.3)
Married								
No/unknown	6,703 (55.4)	2,824 (54.4)	9,527 (55.1)	48 (57.1)	4,074 (38.3)	1,737 (38.1)	5,811 (38.2)	33 (47.8)
Yes	5,398 (44.6)	2,363 (45.6)	7,761 (44.9)	36 (42.9)	6,575 (61.7)	2,827 (61.9)	9,402 (61.8)	36 (52.2)

LUAD, lung adenocarcinoma; SEER, Surveillance, Epidemiology, and End Results; AJCC, American Joint Committee on Cancer.

that based on gender molecular differences, sex differences and sex steroids may affect the incidence and outcomes of lung cancer. It should be noted that Behrens *et al.* consider a higher density of tumor-associated immune infiltrating cells can be found in female LUAD patients' tumor tissue (20). Gender has been considered as an independent prognostic factor for LUAD (18). Sex-related molecular differences can influence the outcome of LUAD (25). Thus, for personalized medicine paradigm, it is reasonable for us to separate LUAD patients by gender to analyze prognosis. Accordingly, excluding gender factors, patients' basic clinical information, AJCC stage, and treatment information are worth considering independent predictors of the possibility of long-term survival and can be used in the establishment

of new tools. So the aim of this article is to separately predict the long-term prognosis of LUAD for men and women. For the purpose of achieving accurate individualized treatment, we can incorporate more clinical variables besides age and AJCC TNM stage to make the individualized and more accurate prediction. As previous studies have shown, the support of partners can positively affect patients' expectations and promote their active treatment (34), married LUAD patients have more advantages than unmarried LUAD patients in terms LCSS. Additionally, consistent with the AJCC's TNM system and previous studies (35,36), stage I LUAD patients had a significantly better LCSS rate than stage II/III/IV patients. This study had several limitations. First, it was a retrospective study; thus, selection bias could

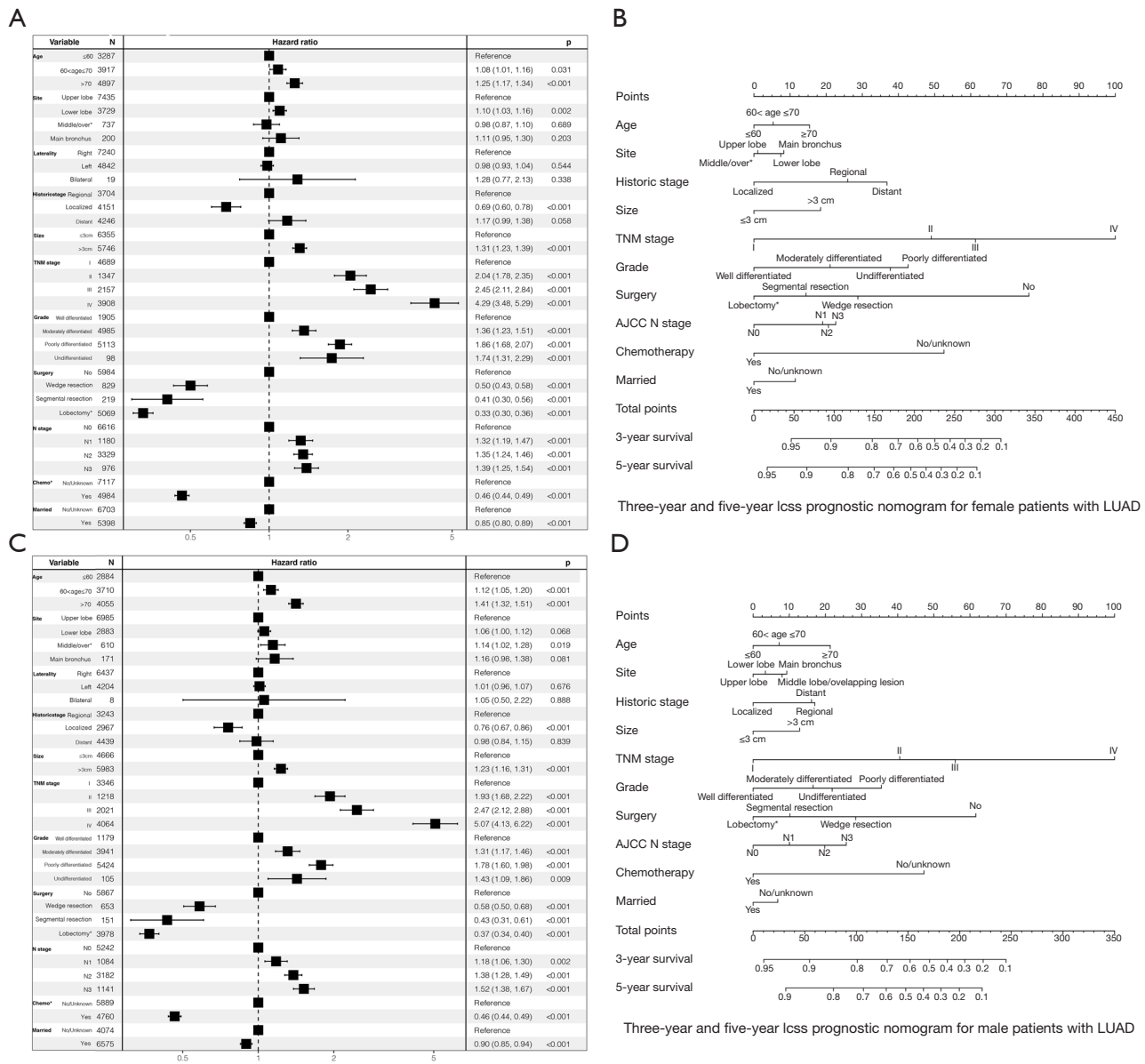


Figure 2 Multivariable LCSS Cox regression analysis and nomogram models for female and male LUAD patients. (A,B) Nomogram for female 3- and 5-year LCSS. (C,D) Nomogram for male 3- and 5-year LCSS. Middle/over*, overlapping lesion of lung; lobectomy*, lobectomy + pneumonectomy + bronchial sleeve resection; chemo*, chemotherapy. LCSS, lung cancer-specific survival; LUAD, lung adenocarcinoma; TNM, tumor, node, and metastasis; AJCC, American Joint Committee on Cancer.

not be avoided. Second, many variables affect the prognosis of male and female LUAD patients, including smoking and sex hormone levels, but the SEER database did not provide information on all these variables. Notably, our study also had many advantages. First, this appears to be the first research to separate the prognostic factors of LUAD by gender, and then successfully construct and verify gender-

specific nomogram models. Second, this study used large-scale cohorts to validate the nomograms. The gender-specific nomogram models provide personalized factors for the prognosis of male and female LUAD patients. The C-indexes of our nomogram models were very high (all >8), similarly the AUC values of our research were also perfect (all >8). Thus, our nomogram models are highly reliable.

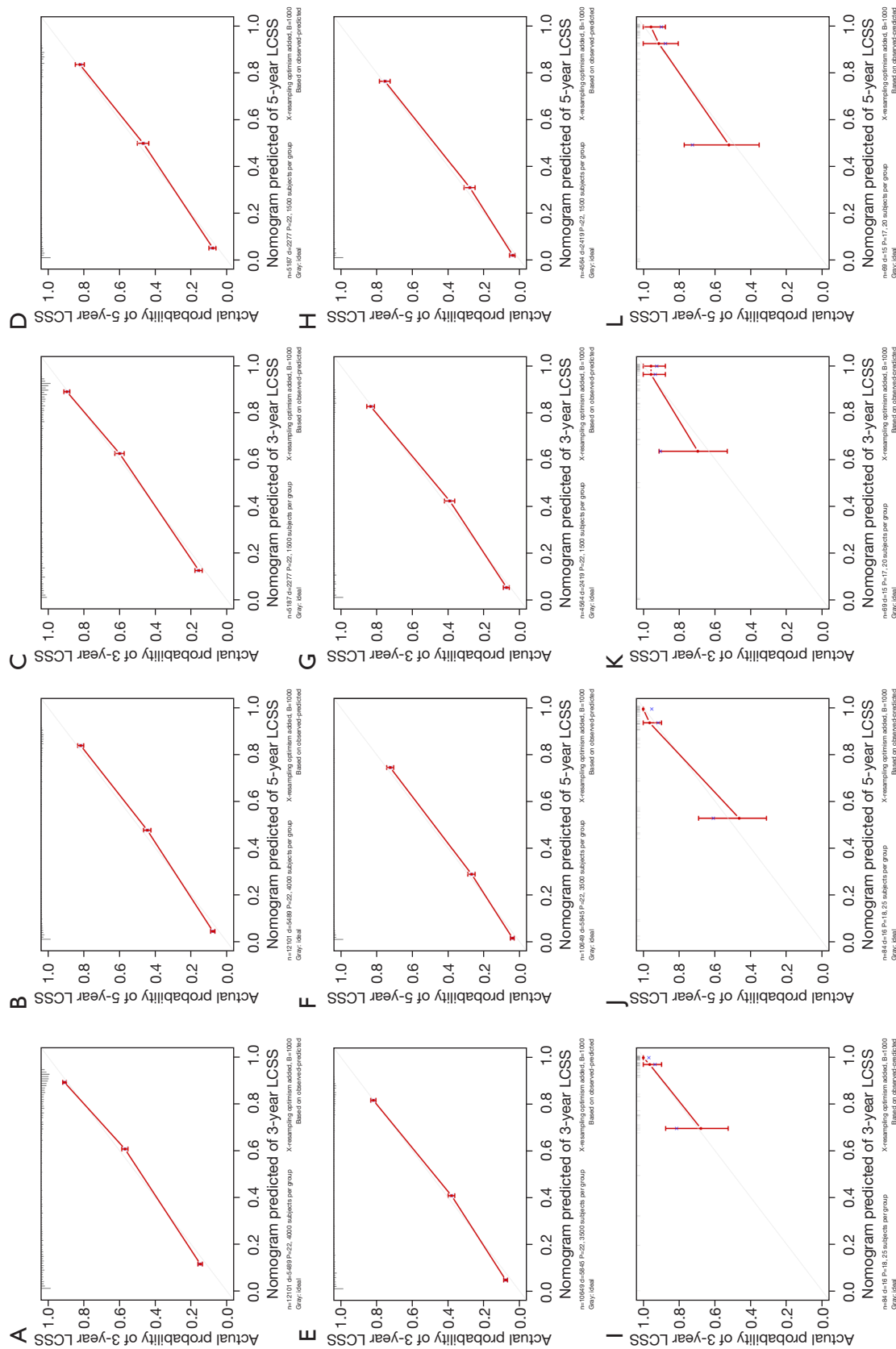


Figure 3 Calibration curves for 3- and 5-year LCSS. (A) Calibration curves for 3-year LCSS in female training cohort. (B) Calibration curves for 5-year LCSS in female SEER testing cohort. (C) Calibration curves for 3-year LCSS in female SEER testing cohort. (D) Calibration curves for 5-year LCSS in female SEER testing cohort. (E) Calibration curves for 3-year LCSS in male training cohort. (F) Calibration curves for 5-year LCSS in male training cohort. (G) Calibration curves for 3-year LCSS in Chinese female validation cohort. (H) Calibration curves for 5-year LCSS in Chinese female validation cohort. (I) Calibration curves for 3-year LCSS in Chinese male validation cohort. (J) Calibration curves for 5-year LCSS in Chinese male validation cohort. (K) Calibration curves for 3-year LCSS in Chinese male validation cohort. (L) Calibration curves for 5-year LCSS in Chinese male validation cohort. LCSS, lung cancer-specific survival; SEER, Surveillance, Epidemiology, and End Results.

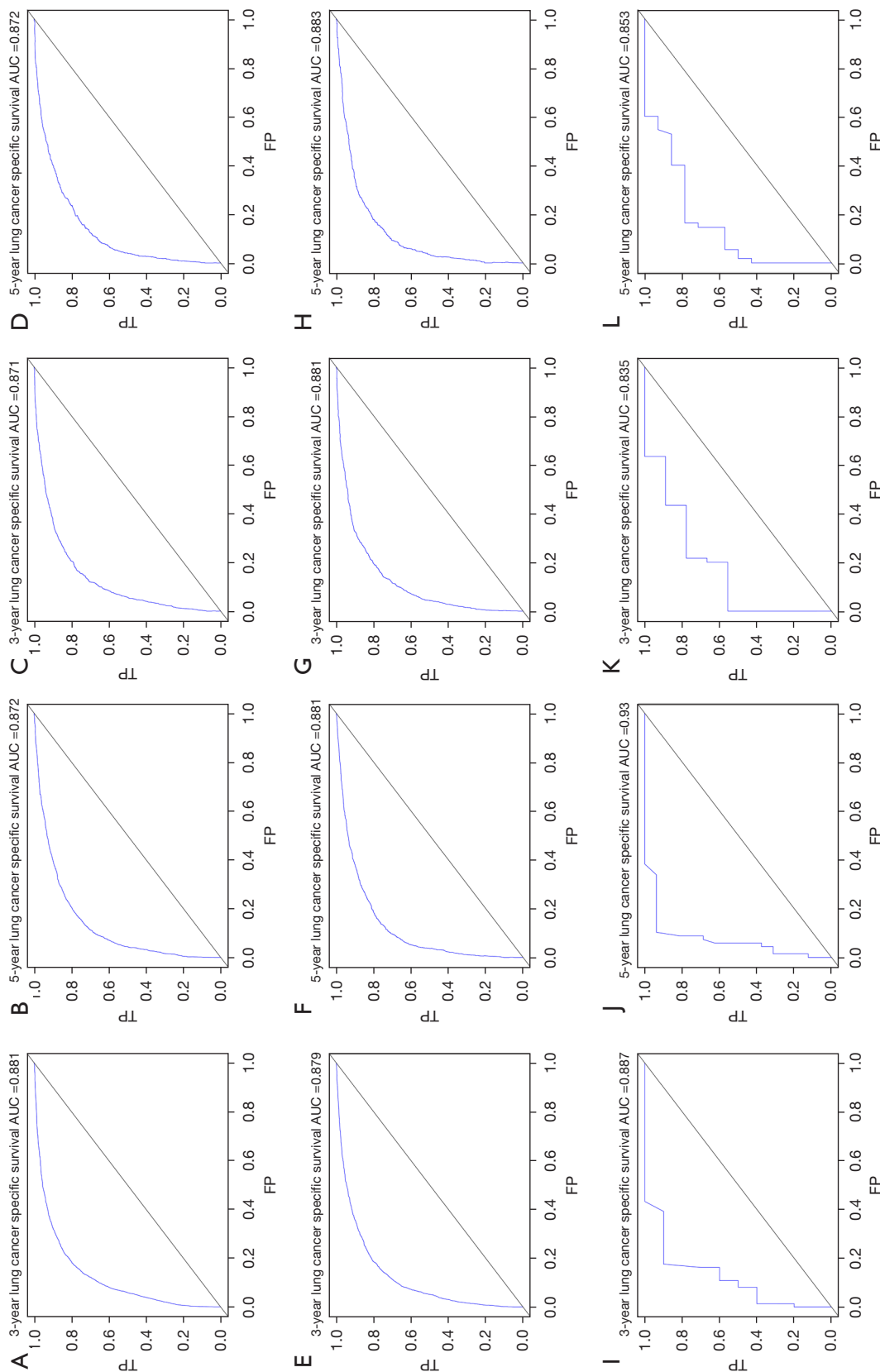


Figure 4 ROC curves and AUC values for nomogram models. (A) ROC curves and AUC values for 3-year LCSS in female training cohort. (B) ROC curves and AUC values for 5-year LCSS in female training cohort. (C) ROC curves and AUC values for 3-year LCSS in female SEER testing cohort. (D) ROC curves and AUC values for 5-year LCSS in female SEER testing cohort. (E) ROC curves and AUC values for 3-year LCSS in male training cohort. (F) ROC curves and AUC values for 5-year LCSS in male SEER testing cohort. (G) ROC curves and AUC values for 3-year LCSS in male SEER testing cohort. (H) ROC curves and AUC values for 5-year LCSS in male SEER testing cohort. (I) ROC curves and AUC values for 3-year LCSS in Chinese female validation cohort. (J) ROC curves and AUC values for 5-year LCSS in Chinese female validation cohort. (K) ROC curves and AUC values for 3-year LCSS in Chinese male validation cohort. (L) ROC curves and AUC values for 5-year LCSS in Chinese male validation cohort. ROC, receiver operating characteristic; AUC, area under the curve; LCSS, lung cancer-specific survival; SEER, Surveillance, Epidemiology, and End Results; TP, true positive; FP, false positive.

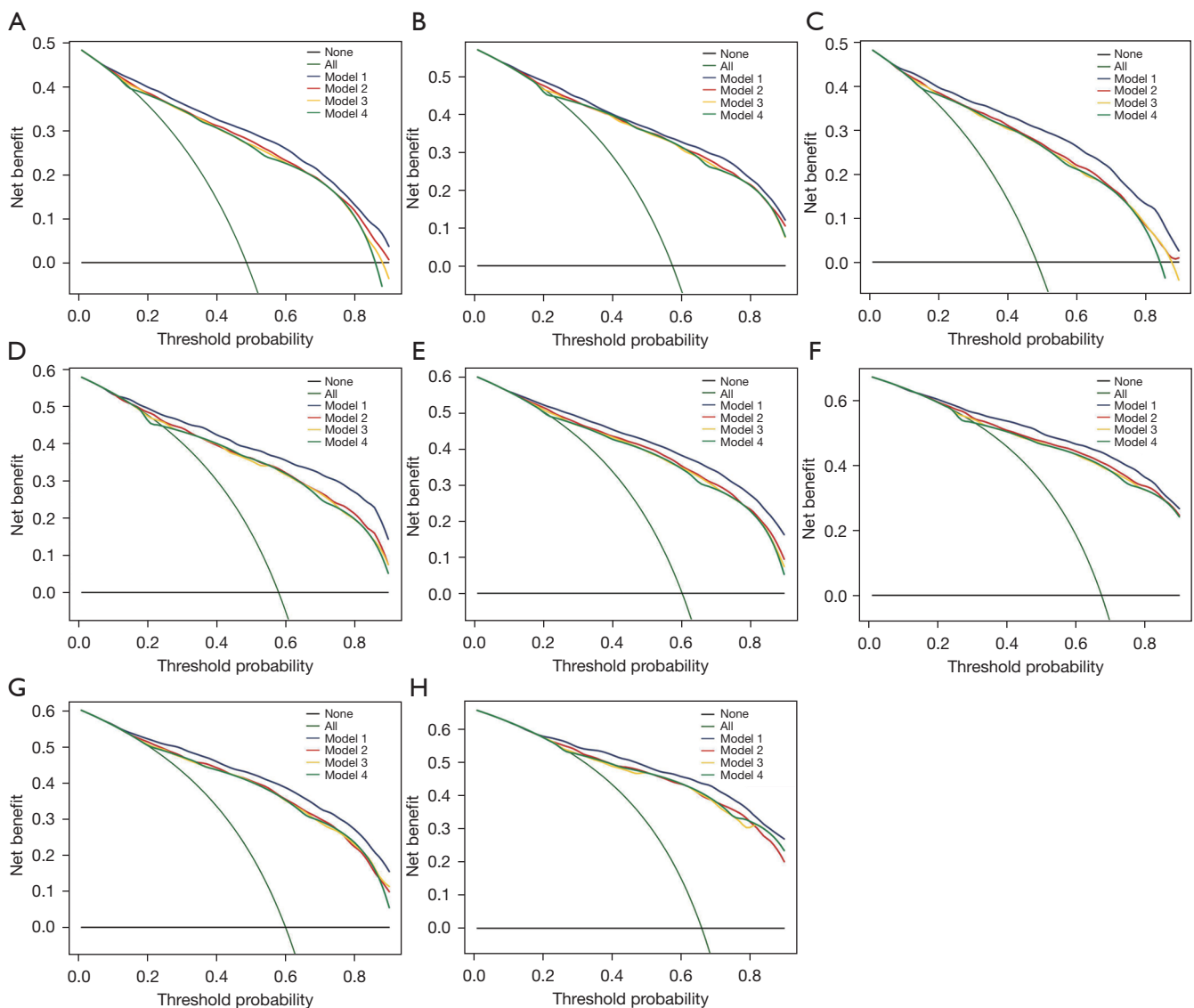


Figure 5 DCA curves for nomogram models and the other three models. (A) DCA curves for 3-year LCSS in female training cohort. (B) DCA curves for 5-year LCSS in female training cohort. (C) DCA curves for 3-year LCSS in female SEER testing cohort. (D) DCA curves for 5-year LCSS in female SEER testing cohort. (E) DCA curves for 3-year LCSS in male training cohort. (F) DCA curves for 5-year LCSS in male training cohort. (G) DCA curves for 3-year LCSS in male SEER testing cohort. (H) DCA curves for 5-year LCSS in male SEER testing cohort. Mode 1: gender-specific nomogram model; model 2: AJCC TNM stage + historic stage + tumor differentiation grade + age + tumor size; model 3: tumor differentiation grade + AJCC TNM stage; model 4: AJCC TNM stage. DCA, decision curve analysis; LCSS, lung cancer-specific survival; SEER, Surveillance, Epidemiology, and End Results; AJCC, American Joint Committee on Cancer; TNM, tumor, node, and metastasis.

Conclusions

We developed gender-specific nomogram models that can be used as a supplement to the AJCC TNM stages to accurately predict the prognosis of male and female LUAD

patients. Excluding gender factors, these nomogram models may help clinicians to accurately predict the prognosis of LUAD patients and make appropriate decisions about treatment strategies.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All of the procedures performed in this study were conducted in accordance with the Declaration of Helsinki (as revised in 2013), and written informed consents have been provided by all included patients from Tianjin Chest Hospital. The study was approved by institutional ethics board of Tianjin chest Hospital (ethical approval number: 2021LW-016).

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Table S1 Univariate cox analyses for male LUAD patients

Characteristics	HR	P	CI
Site			
Upper lobe			
Lower lobe	1.07	0.019	1.01–1.14
Middle lobe/overlapping	1.09	0.124	0.98–1.22
Main bronchus	2.38	0	2.01–2.82
Grade			
Well grade			
Moderate grade	1.58	0	1.42–1.77
Poor grade	2.99	0	2.69–3.32
Undifferentiated grade	2.65	0	2.04–3.45
Laterality			
Right			
Left	1.03	0.351	0.97–1.08
Derived AJCC stage			
I			
II	2.01	0	1.79–2.26
III	4.24	0	3.86–4.65
IV	10.67	0	9.83–11.6
Derived AJCC N stage			
N0			
N1	1.83	0	1.67–2
N2	3.65	0	3.44–3.88
N3	4.82	0	4.46–5.22
Surgery method			
No surgery			
Wedge resection	0.23	0	0.2–0.26
Segmental resection	0.15	0	0.11–0.21
Lobectomy	0.15	0	0.14–0.17
Chemotherapy			
No/unknown			
Yes	1.51	0	1.43–1.59
Tumor size			
≤3 cm			
>3 cm	2.54	0	2.4–2.69
Age			
≤60			
60< age ≤70	0.91	0.006	0.85–0.97
>70	1.17	0	1.1–1.25
Marital			
No married/unknown			
Married	0.83	0	0.79–0.88
Historic stage			
Regional			
Local	0.42	0	0.38–0.46
Distant	3.77	0	3.54–4.01

LUAD, lung adenocarcinoma; AJCC, American Joint Committee on Cancer.

Table S2 Univariate cox analyses for female LUAD patients

Characteristics	HR	P	CI
Site			
Upper lobe			
Lower lobe	1.04	0.238	0.98–1.1
Middle lobe/overlapping	1.02	0.78	0.91–1.14
Main bronchus	2.79	0	2.38–3.27
Grade			
Well grade			
Moderate grade	1.73	0	1.56–1.91
Poor grade	3.52	0	3.19–3.89
Undifferentiated grade	3.22	0	2.44–4.24
Laterality			
Right			
Left	1.02	0.499	0.97–1.07
Derived AJCC stage			
I			
II	2.6	0	2.32–2.92
III	4.86	0	4.43–5.34
IV	12.5	0	11.51–13.58
Derived AJCC N stage			
N0			
N1	2.33	0	2.13–2.56
N2	4.17	0	3.92–4.44
N3	5.72	0	5.26–6.23
Surgery method			
No surgery			
Wedge resection	0.19	0	0.17–0.22
Segmental resection	0.14	0	0.11–0.19
Lobectomy	0.14	0	0.13–0.15
Chemotherapy			
No/unknown			
Yes	1.86	0	1.76–1.96
Tumor size			
≤3 cm			
>3 cm	2.9	0	2.74–3.07
Age			
≤60			
60< age ≤70	0.95	0.194	0.89–1.02
>70	1.19	0	1.12–1.27
Marital			
No married/unknown			
Married	0.84	0	0.8–0.89
Historic stage			
Regional			
Local	0.35	0	0.32–0.39
Distant	3.91	0	3.68–4.17

LUAD, lung adenocarcinoma; AJCC, American Joint Committee on Cancer.