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Development and Validation of a Nomogram Prognostic Model for Small-Cell Lung Cancer Patients

Shidan Wang[1], Lin Yang[1,2], Bo Ci[1], Matthew Maclean[1], David E. Gerber[3,4], Guanghua Xiao[1,3,4], Yang Xie[1,3,4]

[1]Quantitative Biomedical Research Center, Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas, Texas, 75390, USA

[2]Department of Pathology, National Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China

[3]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, 75390, USA

[4]Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, Texas, 75390, USA

Correspondence to: Yang Xie, yang.xie@utsouthwestern.edu

RUNNING HEAD: Nomogram for Small-Cell Lung Cancer Patients

Keywords: small-cell lung cancer, nomogram, prognostic model.

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Abstract

Background: Small-cell lung cancer (SCLC) accounts for almost 15% of lung cancer cases in the United States. Nomogram prognostic models could greatly facilitate risk stratification and treatment planning, as well as more refined enrollment criteria for clinical trials. We developed and validated a new nomogram prognostic model for SCLC patients using a large SCLC patient cohort from the National Cancer Database (NCDB).

Methods: Clinical data of 24,680 SCLC patients diagnosed from 2004 to 2011 were used to develop the nomogram prognostic model. The model was then validated using an independent cohort of 9,700 SCLC patients diagnosed from 2012 to 2013. The prognostic performance was evaluated using p value, concordance index and integrated Area Under the (time-dependent Receiver Operating Characteristic) Curve.

Results: The following variables were contained in the final prognostic model: age, gender, race, ethnicity, Charlson/Deyo Score, TNM Stage (assigned according to the AJCC 8th edition), treatment type (combination of surgery, radiation therapy and chemotherapy), and laterality. The model was validated in an independent testing group with a concordance index of 0.722 ± 0.004 and an integrated AUC of 0.79. The nomogram model has a significantly higher prognostic accuracy than previously developed models, including the AJCC 8th edition TNM-staging system. We implemented the proposed nomogram and four previously published nomograms in an online webserver.

Conclusions: We developed a nomogram prognostic model for SCLC patients, and validated the model using an independent patient cohort. The nomogram performs better than earlier models, including models using AJCC staging.

Key Words: Small-cell lung cancer, patient prognosis, nomogram prognostic model

Introduction

Lung cancer is the leading cause of death from cancer in the United States and worldwide. Small-cell lung cancer (SCLC) accounts for 13.6% of all lung cancer cases [1, 2]. Compared to non-small-cell lung cancer (NSCLC), in which the 5-year survival rate is 18.0%, SCLC has only a 6.2% 5-year survival rate, and is characterized by a more rapid tumor growth rate and death from recurrent disease [3, 4]. Over the last several decades, there have been only modest improvements in patient survival [5] and no molecularly targeted therapy has proven beneficial for SCLC patients [6]. Nomogram prognostic models that predict patient outcomes may facilitate better treatment stratification and outcome evaluation, as well as more refined patient enrollment criteria for clinical trials in SCLC. Furthermore, a recent study in breast cancer [7] showed that user-friendly online prognostic tools could greatly enhance patient care. However, currently there are no such online tools available for prognosis of SCLC.

To date there are three studies of nomograms in SCLC, published by Xie et al [4], Pan et al [8], and Xiao et al[9]. The nomograms developed from those studies provide useful tools for clinicians and researchers to stratify the risk of SCLC patients. However, two of the studies simply classified patients as limited or extensive stage without using the more accurate TNM staging proposed by the International Association for the Study of Lung Cancer (IASLC) [10]. Furthermore, there is a lack of independent validation for these models, probably due to the limited sample size (n = 938[4], 275[8], and 647[9] separately). Other non-nomogram prognostic models include the Manchester score and Spain score. However, both of these were developed on small sample sets (n = 407 for Manchester score and n = 341 for Spain score) and divide patients into only three risk groups [11, 12].

The goal of this study was to identify prognostic factors for SCLC patients, and then develop and validate a new nomogram prognostic model in a large SCLC patient cohort. The National Cancer

Database (NCDB) includes over 200,000 patients diagnosed with SCLC from 2004 to 2013 in the United States, of which 34,380 SCLC patients without any missing values were used to develop and validate our nomogram prognostic model. The SCLC cases in the NCDB dataset were separated into a training cohort and a validation cohort based on the year of diagnosis. The model was developed from the training cohort of 24,680 SCLC patients diagnosed from 2004 to 2011, and then validated in the validation cohort of 9,700 SCLC patients diagnosed from 2012 to 2013. The prognostic performance was evaluated using p value, concordance index and integrated Area Under the Curve. In order to facilitate public usage, we implemented our nomogram and the previous ones by Xie et al. in an online webserver. Compared to the previously published models, our model has the following advantages: 1) it was validated in an independent set; 2) it was developed and validated with a much larger sample size; 3) it was developed across multiple facilities and facility types, which greatly diminishes sample selection bias; 4) it utilizes accurate SCLC staging criteria: the AJCC 8th edition TNM staging system proposed by IASLC [13, 14]; and 5) it provides an online webserver so that clinicians can use the nomogram model easily.

Methods

Source of data

202,194 SCLC cases were identified from NCDB and 34,380 of them met our inclusion criterion that they do not contain any missing data for selected variables. The source of missing values is listed in **Supplementary Table 1**. The cases are independent and recorded by annual reports from all the CoC-accredited programs from 2004 to 2013. 24,680 cases that were diagnosed from 2004 to 2011 were assigned to the training group and used to develop the nomogram prognostic model. The 9,700 cases diagnosed from 2012 to 2013 were assigned to the testing group and used to validate the model.

Nomogram development

The nomogram was developed using the training cohort of 24,680 patients diagnosed from 2004 to 2011. Overall survival was defined as the length of time from diagnosis to death or last contact, and used as the primary outcome. Two extra variables were first constructed based on NCDB variables: treatment was defined as the stratification result of surgery, chemotherapy and radiation therapy; and TNM stage was defined according to the coding guidelines of the Collaborative Staging Manual and Coding Instructions for the new 8th edition lung cancer staging system defined by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) [15-18], and followed Yang et al's method [19]. Stages IA1, IA2, and IA3 were combined together in our study as stage IA, since no significant prognostic differences were detected among the three sub-stages [14]. The assumptions were made here that the timing and sequence of the treatments were interchangeable, and none of these are salvage treatment due to recurrence/progression. The input variables were age, gender, race, Hispanic origin, Charlson/Deyo Score, sequence number, primary site, laterality, grade (tumor's resemblance to normal tissue), 8th edition TNM stage and treatment type.

Univariate Cox regression and Wald test were then used to screen for variables that were significantly correlated with overall survival in the training group. Predictors with a p-value less than 0.05 were fed to a multivariate Cox regression model. Backward stepwise selection based on Bayesian Information Criterion (BIC) was used to further eliminate redundant variables. The resulting multivariate Cox regression model was used to calculate risk score and build the final nomogram prognostic model.

Model validation

To validate our model, four criteria were used to evaluate prediction performance in the testing set. First, the cases were grouped according to their predicted risk score, and Kaplan-Meier survival curves and

Wald test were used to compare survival differences among the groups. Second, a concordance index (c-index) was calculated to estimate the similarity between the ranking of true survival time and of predicted risk score. The theoretical value of the c-index is between 0 and 1; a c-index larger than 0.5 indicates prediction performance better than random guessing. When evaluating the performances of different models, c-indexes from different models were compared using z-test. Third, the area under the curve (AUC) of time-dependent receiver operating characteristics (ROC) [20, 21] was calculated at each month from the 1st to the 30th month. Integrated AUC was calculated by averaging the 30 AUC values. Fourth, calibration curves were plotted to evaluate the consistency between predicted survival probability and actual survival proportion at 1 and 2 years, separately[22]. A perfect prediction would result in a 45-degree calibration curve (i.e. the identity line).

The other two models, the AJCC 8th edition TNM staging system and the traditional limited/extensive staging system, were also tested for prognostic performance in the testing group. C-index and integrated AUC were used to compare this nomogram with the two staging systems. Here, extensive stage was defined based on the presence of distant metastases (M1 stage) [23, 24]. All other cases (M0 stage) were grouped as limited stage. To compare performance of the proposed nomogram with TNM staging system and limited/extensive staging system, a nonparametric approach proposed by Kang et al was used to compare the correlated C-indexes with right-censored survival outcome[25].

All computations were conducted in the R environment, version 3.3.2 [26]. R packages “survival” (version 2.40-1), “timeROC” (version 0.3), “rms” (version 5.1-2), and “compare” (version 1.3.1) were used. Results with p-value ≤ 0.05 were considered statistically significant.

Implementation of this and previously published models

To facilitate researchers' and clinicians' usage of our model, we created a user-friendly webserver for our nomogram and the models from Pan et al[8], Xiao et al[9], and the two models from Xie et al[4]. The nomogram from this study calculates the risk score, plots the survival curve and provides survival probabilities for 120 months at 6-month increments. The Pan et al model provides 1-year and 2-year survival probabilities. The Xiao et al model provides 3-year and 5-year survival probabilities. The Xie et al models for both extensive and limited stage cases provide 6-month and 12-month survival probabilities and predicted median survival time. Data points were read from Figure 1 of the Pan et al publication[8], Figure 1B of the Xiao et al publication[9], and Figures 1 and 2 of the Xie et al publication [4], and the corresponding survival probability for a given score was calculated by linear interpolation.

Results

Characteristics of the training and validation cohorts

In total, 202,194 SCLC cases were identified in NCDB, among which, 34,380 cases that did not contain any missing variables were included in this study. Based on year of diagnosis, included cases were divided into two distinct groups: cases that were diagnosed from 2004 to 2011 (n = 24,680) were used as the training cohort, while cases that were diagnosed from 2012 to 2013 (n = 9,700) were used as the validation cohort. The follow-up time ranged from 0 to 10.76 years (median 0.64 year) for the training cohort, and from 0 to 2.92 years (median 0.53 year) for the testing cohort. Characteristics of the two sets are shown in **Table 1**. In comparing the training and testing sets, the demographic variables were similar, while the clinical variables, including Charlson/Deyo score, 8th AJCC stage, and laterality, were significantly different.

Building nomogram prognostic model in training cohort

In univariate analysis, age, gender, race, Hispanic origin, Charlson/Deyo score, TNM stage by AJCC 8th edition, treatment type, primary site, laterality, and grade were significantly associated with overall survival in the training group **(Table 2)**. After stepwise selection to further remove potential redundancy, age, sex, race, ethnicity, Charlson/Deyo score, TNM stage by AJCC 8th edition, treatment type, and laterality were used in the final nomogram model (coefficients summarized in **Table 3**). The final risk score was calculated by adding up the score of each item using the nomogram depicted in **Figure 1a**. The TNM stage defined by the AJCC 8th edition showed the largest range of risk scores, followed by the treatment type and age. The predicted survival probability using the Cox regression model of risk scores was plotted in **Figure 1b**.

Validation in testing cohort and sensitivity analysis in regards to missing data

The proposed nomogram was validated in the independent testing set (n=9,700). The survival difference between any two adjacent groups, which were grouped by predicted risk score, was significant (p-value < 0.05, **Figure 2a & 2b**). The median survival times of score groups ranged from 0.7 months (when risk score > 18) to 30.9 months (when risk score < 6). The c-index was 0.722 ± 0.004 and the integrated AUC was 0.79 from the 1st month to the 30th month (**Figure 2c, Supplementary Table 2**). A calibration curve at 1 year (**Figure 2d**) or 2 years (**Figure 2e**) also showed high consistency between predicted survival probability and actual survival proportion.

With regard to prognostic ability, the proposed nomogram performed better than the two commonly used SCLC staging systems, the AJCC TNM system and limited/extensive staging system (**Figure 2c, Supplementary Table 2, Supplementary Figure 1 a&b**). The AUC of the nomogram was the highest throughout the 1st to the 30th month, followed by the 8th edition TNM staging system. The integrated AUC of the proposed nomogram was 0.789, while those of the 8th edition TNM staging system and the limited/extensive staging system were 0.634 and 0.598, respectively. The c-index of this nomogram

(0.722 ± 0.004) was also significantly higher than the c-indexes of the 8th edition TNM staging system (0.550 ± 0.003, p-value < 0.001) and the limited/extensive staging system (0.539 ± 0.002, p-value < 0.001), confirming the strong prognostic power of this proposed nomogram.

To evaluate the robustness of our model to missing data, a sensitivity analysis was performed on the excluded cases diagnosed from the year 2012 to 2013 (n = 11,020). The missed variables were imputed using corresponding modes in the training cohort (**Table 1**): missed stages (n = 10,416) were imputed as "stage IVA"; missed treatment types (n = 508) were imputed as "No Surgery, Chemo Done, Radiation Done"; missed Hispanic origins (n = 819) were imputed as "False". Under the circumstance of having at least one variable imputed, the survival difference between any two adjacent predicted risk groups was still significant (**Supplementary Figure 2 a&b**). The c-index was 0.691 ± 0.004, and the integrated AUC was 0.734 (**Supplementary Figure 2c**). A calibration curve at 1 year (**Supplementary Figure 2d**) or 2 years (**Supplementary Figure 2e**) still showed high consistency between predicted survival probability and actual survival proportion, proving the robustness of this nomogram to missing data.

Development of webserver for easy access of our own and previously published models

An online version of our nomogram (**Figure 3a**) can be accessed at http://lce.biohpc.swmed.edu/lungcancer/sclc_nomogram, to assist researchers and clinicians. Online implementation of the other nomograms from Pan et al[8], Xiao et al[9], and Xie et al[4] are also available (**Figure 3b-d**). Predicted survival probability across time can be easily determined by inputting clinical features and reading output figures and tables generated by the webserver.

Discussion

In this study, a nomogram prognostic model was developed and validated using a large cohort of SCLC cases across the United States. This nomogram, based on routinely available demographic, staging and

treatment information, predicts the survival probability for individual SCLC patients. The publicly accessible online implementation will assist clinicians in making treatment decisions.

Compared with other prognostic indexes, such as the Manchester Score [11] and the Spain prognostic index [12], our model calculates individualized survival probability rather than assigning cases into a few risk groups, thus better capturing heterogeneity across patients. Compared with the previously published nomogram by Xie et al., this model used a much larger training dataset and involved multiple treatment facilities, which allowed for smaller sampling bias. The internal c-index of this model was 0.744 ± 0.002, higher than in previously published models (0.73 for both nomograms in [4]). Independent validation of our model showed significantly different outcomes among different score groups (**Figure 2a&b**). A high concordance index (0.722 ± 0.004) and integrated AUC score (0.789, **Figure 2c, Supplementary Table 2**) in the testing set also indicated the strong predictive ability of our nomogram model. In addition, combining demographic, clinical and treatment information together produced a nomogram with better performance than using staging information alone (**Figure 2b, Supplementary Table 2**). Thus, this comprehensive and individualized risk score calculation method could be used as stratification criteria in randomized studies and clinical trials.

In this nomogram, age, gender, race, ethnicity, Charlson/Deyo score, AJCC 8th edition stage, treatment type and laterality were kept after univariate Cox regression screening and backward stepwise selection. Age, gender, and Charlson/Deyo score have previously been shown significantly relevant to survival of SCLC patients [4, 27]. Noticeably, AJCC 8th edition stage contributed the most to the final risk score (**Figure 1a**), with clear distinctions between each two adjacent TNM stages (**Table 3**), and showed better prognostic performance than the limited/extensive staging system with higher c-index and AUC (**Figure 2b, Supplementary Table 2**). The significant contribution of TNM stage to this nomogram externally validates the performance of the 8th edition TNM lung cancer classification system, and

highlights the importance of applying this more accurate staging system to SCLC rather than using the traditional limited/extended staging [10, 13, 28].

This proposed nomogram also illustrates the prognostic implications of using different treatment methods (**Figure 1a, Table 3**). As expected, cases treated with both surgery and chemo-radiation therapy have the lowest risk score and cases not treated with any method have the highest risk score. Furthermore, the nomogram **(Figure 1b)** is consistent with current research in that it predicts better survival for surgery with chemo-radiation (treatment type 7 and 8) than for surgery with chemotherapy alone (type 3 and 4) [21]. However, the risk scores of different treatment methods are not recommended for direct use as a guideline for treatment selection, since clinical treatment decisions should be made based on multiple factors such as TNM stage and patient comorbidities (**Supplementary Table 3**)[3].

There were several limitations in the development of this nomogram. The first limitation was a lack of some routinely available clinical data, such as the neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR). The absence of this information prevented direct comparison of performance between our model and another published nomogram [4]. Constructing a prognostic model using both the factors identified in our model and other lab tests such as NLR would thus be beneficial in creating an even more accurate prognostic prediction. The second limitation was the inability to capture interaction terms among the predictors. For example, patients with early stage disease (stage I & II) were more likely to receive surgery than patients with late stage disease (stage III and IV). The interactions between stage and treatment strategies are worth further investigation. To satisfy the requirement for convenience and interpretability of the nomogram, interaction terms were not considered in this model. However, a more complex model considering all potential interaction terms would be expected to have better prognostic performance. The third limitation was that the sequence of treatment was not considered. Since neither recurrence nor progression is recorded in the dataset, we have to consider the treatment as

baseline variables instead of time-varying covariates. By including the treatment as baseline covariates, we assume that the exact treatment combination was decided and given at the time of diagnosis. This assumption is necessary in order to incorporate the treatment information into the model, when the exact time of the treatment is missing. Finally, out of 200,000 SCLC patients from the NCDB, there are only 34,380 patients without missing values. This large percent of missing data might introduce some selection bias.

Conclusion

We developed a nomogram prognostic model for SCLC patients, and validated the model using an independent patient cohort. The proposed nomogram shows better prognostic performance than other existing models. This nomogram and previously published prognostic models were implemented on an online webserver. Researchers, clinicians and patients can easily predict the survival probability for each individual patient using this webserver.

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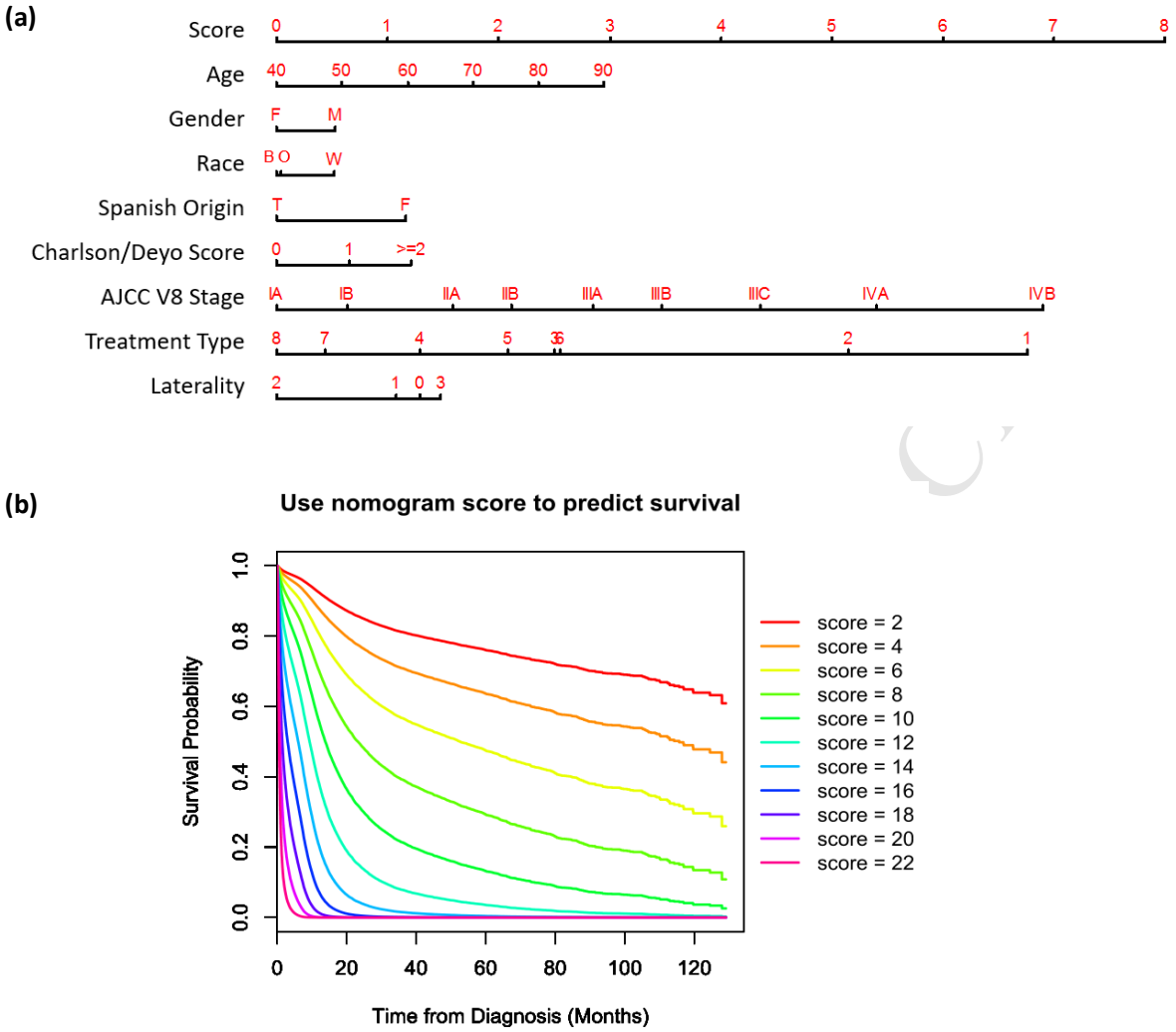
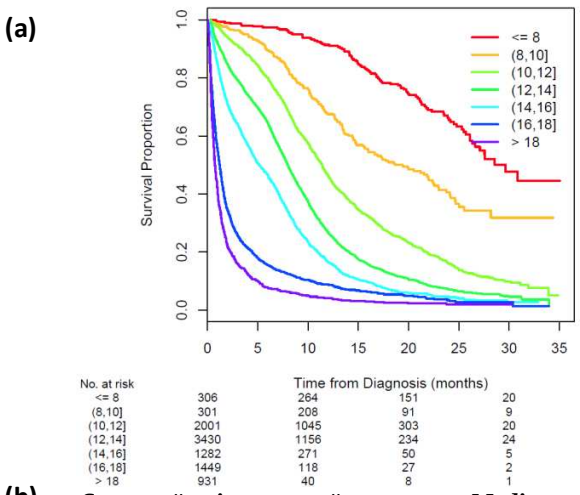
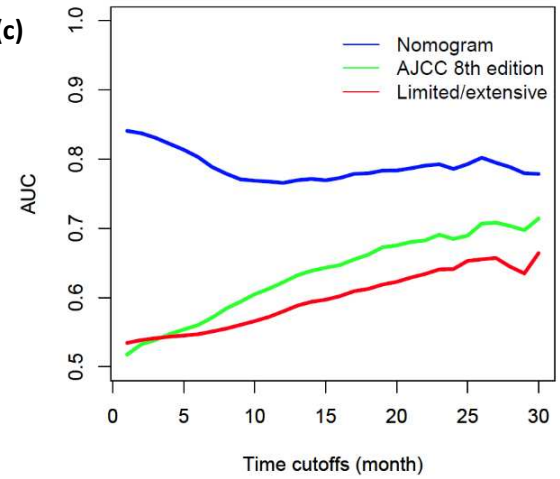


Figure 1 Nomogram to calculate risk score and predict survival probability. **(a)** Race includes black (B), white (W) and other (O). Treatment types include: no surgery, no chemo, no radiation (1); no surgery, no chemo, radiation done (2); no surgery, chemo done, no radiation (3); no surgery, chemo done, radiation done (4); surgery done, no chemo, no radiation (5); surgery done, no chemo, radiation done (6); surgery done, chemo done, no radiation (7); and surgery done, chemo done, radiation done (8). Laterality of tumor origin includes: not a paired site (0), only one side (either left or right) is involved (1), bilateral involvement (2), paired site with unknown origin side or midline tumor (3). **(b)** Predicted patient survival probability curve corresponding to risk scores ranging from 2 to 22.





(b)

Score	*#patients*	*#events*	*Median survival (mos)*	*HR*	*p-value*
≤ 8	306	98	29.63 (26.64-NA)	-	-
(8,10]	301	156	19.42 (15.67-22.54)	(8,10] vs ≤ 8: 2.3 (1.78-2.96)	< 0.001
(10,12]	2001	1512	11.4 (10.94-11.73)	(10,12] vs (8,10]: 2 (1.7-2.36)	< 0.001
(12,14]	3430	2929	7.98 (7.75-8.21)	(12,14] vs (10,12]: 1.63 (1.53-1.74)	< 0.001
(14,16]	1282	1144	5.16 (4.67-5.85)	(14,16] vs (12,14]: 1.44 (1.35-1.55)	< 0.001
(16,18]	1449	1273	1.22 (1.12-1.31)	(16,18] vs (14,16]: 1.93 (1.78-2.1)	< 0.001
> 18	931	867	0.72 (0.66-0.82)	> 18 vs (16,18]: 1.37 (1.25-1.49)	< 0.001

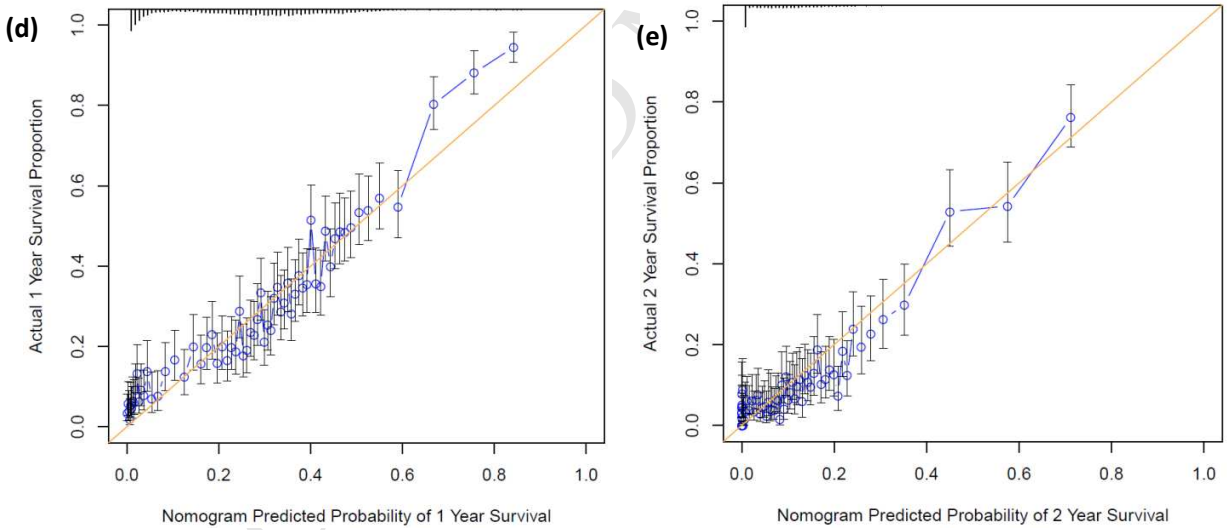


Figure 2 Validation of proposed nomogram prognostic model in the testing set. **(a)** Risk scores of testing set cases were calculated according to the model in Figure 1 and grouped into 8 subgroups. K-M plot was depicted for each group. **(b)** Summary of groups in (a). Hazard Ratio (HR) was calculated using Coxph regression model between each two adjacent lines. P-value was calculated using Wald test. **(c)** Area under the curve (AUC) was calculated for three prognostic models for every month from the 1st to the 30th month. Blue: nomogram developed in this study; green: AJCC 8th TNM staging system; red: limited/extensive staging system. **(d, e)** Calibration curves compare predicted and actual survival proportions at 1 year (d) and 2 years (e), separately. Each point in the plot refers to a group of patients, with the nomogram predicted probability of survival shown on x-axis and actual survival proportion shown on y-axis. Distributions of predicted survival probabilities are plotted at the top. Error bars represent 95% confidence intervals.

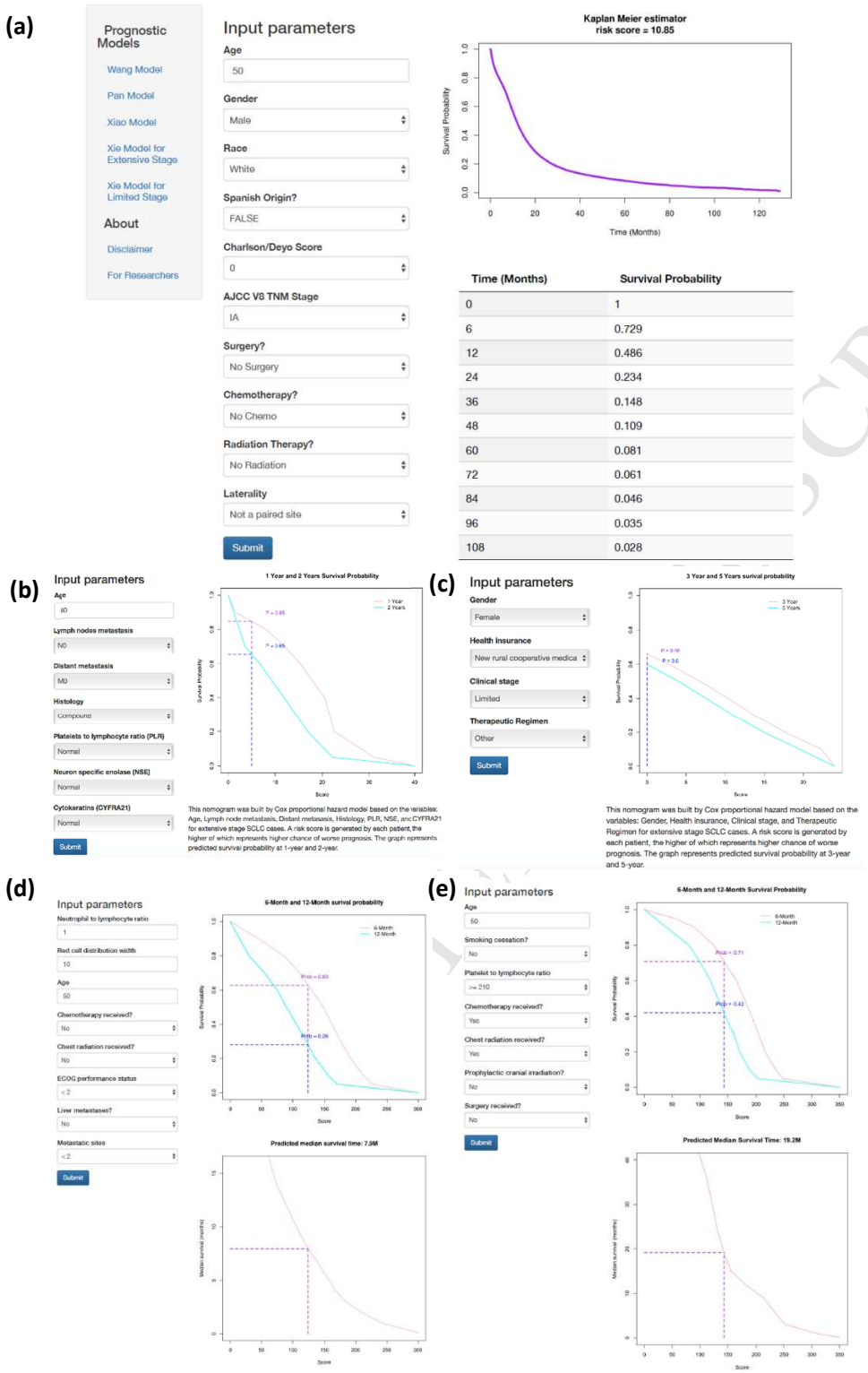


Figure 3 Online webserver interface for our nomogram as well as previous prognostic models. **(a)** The newly developed nomogram in this study (Wang model). **(b-e)** Published nomograms by Pan et al (b), Xiao et al (c), and Xie et al (d: Extensive Stage; e: Limited Stage).

Table 1 Characteristics of training set and testing set. P-values were calculated by Chi-square test.

	Training set (%)	*Testing set (%)*	*p-value*
No. of cases	24,680	9,700	
Year of diagnosis	2004-2011	2012-2013	
Age			0.09
< 65y	9,559 (38.7)	3,855 (39.7)	
≥ 65y	15,121 (61.3)	5,845 (60.3)	
Gender			0.9
Male	12,240 (49.6)	4,803 (49.5)	
Female	12,440 (50.4)	4,897 (50.5)	
Race			0.73
White	22,276 (90.3)	8,779 (90.5)	
Black	1,912 (7.7)	727 (7.5)	
Other	492 (2)	194 (2)	
Hispanic origin			0.91
Non-Hispanic	24,084 (97.6)	9,463 (97.6)	
Hispanic	596 (2.4)	237 (2.4)	
Charlson/Deyo score			<0.001
0	13,288 (53.8)	5,031 (51.9)	
1	7,629 (30.9)	3,061 (31.6)	
≥ 2	3,763 (15.2)	1,608 (16.6)	
Sequence number			0.82
0	24,084 (97.6)	9,463 (97.6)	
1	527 (2.1)	213 (2.2)	
≥ 2	69 (0.3)	24 (0.2)	
AJCC V8 TNM stage			<0.001
IA	1,207 (4.9)	160 (1.6)	
IB	463 (1.9)	74 (0.8)	
IIA	140 (0.6)	18 (0.2)	
IIB	853 (3.5)	97 (1)	
IIIA	1,548 (6.3)	156 (1.6)	
IIIB	902 (3.7)	89 (0.9)	
IIIC	208 (0.8)	27 (0.3)	
IVA	14,699 (59.6)	6,655 (68.6)	
IVB	4,660 (18.9)	2,424 (25)	
Treatment			<0.001
No surgery, no chemo, no radiation	5,025 (20.4)	2,213 (22.8)	
No surgery, no chemo, radiation done	1,230 (5)	520 (5.4)	
No surgery, chemo done, no radiation	7,668 (31.1)	3,473 (35.8)	
No surgery, chemo done, radiation done	7,901 (32)	3,050 (31.4)	
Surgery done, no chemo, no radiation	856 (3.5)	116 (1.2)	
Surgery done, no chemo, radiation done	64 (0.3)	8 (0.1)	
Surgery done, chemo done, no radiation	1,000 (4.1)	165 (1.7)	
Surgery done, chemo done, radiation done	936 (3.8)	155 (1.6)	
Primary site			<0.001
C340	2,298 (9.3)	911 (9.4)	
C341	11,019 (44.6)	4,152 (42.8)	
C342	968 (3.9)	368 (3.8)	
C343	4,959 (20.1)	1,923 (19.8)	
C348	485 (2)	200 (2.1)	
C349	4,951 (20.1)	2,146 (22.1)	
Laterality			<0.001

Not a paired site	2,298 (9.3)	911 (9.4)	
Only one side involved	20,447 (82.8)	8,016 (82.6)	
Bilateral involvement	624 (2.5)	154 (1.6)	
Paired site but lateral origin unknown; midline tumor	1,311 (5.3)	619 (6.4)	
Grade			<0.001
Well differentiated	88 (0.4)	8 (0.1)	
Moderately differentiated	179 (0.7)	39 (0.4)	
Poorly differentiated	2,795 (11.3)	899 (9.3)	
Undifferentiated	5,037 (20.4)	1,457 (15)	
Cell type not determined, not stated or not applicable	16,581 (67.2)	7,297 (75.2)	

Table 2 Univariate analysis results summary. HR: Hazard Ratio, CI: Confidence Interval.

Variable	*HR (95% CI)*	*p-value*
Age	1.023 (1.023-1.024)	< 0.001
Sex (Female vs. Male)	0.84 (0.83-0.85)	< 0.001
Race		
White	1 (reference)	-
Black	0.97 (0.95-0.99)	0.006
Other	0.94 (0.90-0.97)	0.001
Hispanic origin (Yes vs. No)	0.95 (0.92-0.99)	0.028
Charlson/Deyo score		
0	1 (reference)	-
1	1.22 (1.20-1.24)	< 0.001
≥ 2	1.59 (1.56-0.61)	< 0.001
Sequence number		
0	1 (reference)	-
1	1 (0.98-1.01)	0.82
≥ 2	1.01 (0.92-1.11)	0.83
AJCC V8 TNM stage		
IA	1 (reference)	-
IB	1.22 (1.07-1.39)	< 0.001
IIA	1.63 (1.34-1.98)	< 0.001
IIB	1.6 (1.45-1.78)	< 0.001
IIIA	2.12 (1.94-2.31)	< 0.001
IIIB	2.55 (2.32-2.81)	< 0.001
IIIC	3.26 (2.81-3.78)	< 0.001
IVA	5.25 (4.88-5.65)	< 0.001
IVB	7.04 (6.51-7.61)	< 0.001
Treatment		
No surgery, no chemo, no radiation	1 (reference)	-
No surgery, no chemo, radiation done	0.72 (0.7-0.74)	< 0.001
No surgery, chemo done, no radiation	0.46 (0.45-0.47)	< 0.001
No surgery, chemo done, radiation done	0.26 (0.25-0.26)	< 0.001
Surgery done, no chemo, no radiation	0.19 (0.18-0.2)	< 0.001
Surgery done, no chemo, radiation done	0.28 (0.24-0.33)	< 0.001
Surgery done, chemo done, no radiation	0.13 (0.13-0.14)	< 0.001
Surgery done, chemo done, radiation done	0.13 (0.12-0.14)	< 0.001
Primary site		
C340	1 (reference)	-
C341	0.89 (0.88-0.91)	< 0.001
C342	0.9 (0.87-0.92)	< 0.001
C343	0.96 (0.94-0.98)	< 0.001
C348	1.07 (1.03-1.11)	< 0.001
C349	1.13 (1.11-1.16)	< 0.001
Laterality		
Not a paired site	1 (reference)	-
Only one side involved	0.94 (0.93-0.96)	< 0.001
Bilateral involvement	1.47 (1.4-1.54)	< 0.001
Paired site but lateral origin unknown; midline tumor	1.18 (1.15-1.21)	< 0.001
Grade		
Well differentiated	1 (reference)	-
Moderately differentiated	0.99 (0.86-1.14)	0.86

Poorly differentiated	1.29 (1.15-1.46)	< 0.001
Undifferentiated	1.39 (1.23-1.56)	< 0.001
Cell type not determined, not stated or not applicable	1.44 (1.28-1.62)	< 0.001

Table 3 Hazard Ratio (HR) and 95% confidence interval of nomogram parameters.

	HR (95% CI)	*p-value*
Age	1.01 (1.01-1.02)	< 0.001
Sex (Female vs. Male)	0.88 (0.85-0.9)	< 0.001
Race		
White	1 (reference)	-
Black	0.88 (0.84-0.92)	< 0.001
Other	0.89 (0.8-0.98)	0.02
Hispanic origin (Yes vs. No)	0.75 (0.68-0.82)	< 0.001
Charlson/Deyo score		
0	1 (reference)	-
1	1.18 (1.14-1.21)	< 0.001
>= 2	1.36 (1.31-1.41)	< 0.001
AJCC V8 TNM stage		
IA	1 (reference)	-
IB	1.17 (1.02-1.35)	0.02
IIA	1.49 (1.2-1.84)	< 0.001
IIB	1.7 (1.52-1.9)	< 0.001
IIIA	2.04 (1.83-2.26)	< 0.001
IIIB	2.38 (2.11-2.68)	< 0.001
IIIC	2.97 (2.5-3.54)	< 0.001
IVA	3.86 (3.48-4.27)	< 0.001
IVB	5.62 (5.06-6.24)	< 0.001
Treatment		
No surgery, no chemo, no radiation	1 (reference)	-
No surgery, no chemo, radiation done	0.67 (0.63-0.71)	< 0.001
No surgery, chemo done, no radiation	0.35 (0.33-0.36)	< 0.001
No surgery, chemo done, radiation done	0.25 (0.24-0.26)	< 0.001
Surgery done, no chemo, no radiation	0.31 (0.28-0.35)	< 0.001
Surgery done, no chemo, radiation done	0.35 (0.27-0.46)	< 0.001
Surgery done, chemo done, no radiation	0.21 (0.19-0.23)	< 0.001
Surgery done, chemo done, radiation done	0.18 (0.17-0.2)	< 0.001
Laterality		
Not a paired site	1 (reference)	-
Only one side involved	0.95 (0.91-0.99)	0.02
Bilateral involvement	0.72 (0.66-0.79)	< 0.001
Paired site but lateral origin unknown; midline tumor	1.05 (0.98-1.13)	0.19

Supplementary Material

Supplementary Table 1 Comparison of characteristics between included and excluded cases with source of missing data shown in bold.

	Excluded (%)	*Included (%)*	*p-value*
No. of cases	167,814	34,380	
Missing survival data	20,569	-	
Year of diagnosis			<0.001
2004-2011	136,346 (81.2)	24,680 (71.8)	
2012-2013	31,468 (18.8)	9,700 (28.2)	
Age			0.002
< 65y	67,012 (39.9)	13,414 (39)	
≥ 65y	100,802 (60.1)	20,966 (61)	
Gender			<0.001
Male	81,426 (48.5)	17,043 (49.6)	
Female	86,388 (51.5)	17,337 (50.4)	
Race			<0.001
White	150,967 (90)	31,055 (90.3)	
Black	12,700 (7.6)	2,639 (7.7)	
Other	4,147 (2.5)	686 (2)	
Hispanic origin			0.90
Non-Hispanic	148,339 (97.6)	33,547 (97.6)	
Hispanic	3,662 (2.4)	833 (2.4)	
Missing	15,813	-	
Charlson/Deyo score			<0.001
0	96,024 (57.2)	18,319 (53.3)	
1	48,774 (29.1)	10,690 (31.1)	
≥ 2	23,016 (13.7)	5,371 (15.6)	
Sequence number			<0.001
0	148,339 (88.4)	33,547 (97.6)	
1	18,972 (11.3)	740 (2.2)	
≥ 2	503 (0.3)	93 (0.3)	
AJCC V8 TNM stage			<0.001
IA	380 (2.8)	1,367 (4)	
IB	119 (0.9)	537 (1.6)	
IIA	48 (0.4)	158 (0.5)	
IIB	257 (1.9)	950 (2.8)	
IIIA	445 (3.3)	1,704 (5)	
IIIB	212 (1.6)	991 (2.9)	
IIIC	60 (0.4)	235 (0.7)	
IVA	8,656 (64.8)	21,354 (62.1)	
IVB	3,172 (23.8)	7,084 (20.6)	
Missing	154,465	-	
Treatment			<0.001
No surgery, no chemo, no radiation	33,639 (20.6)	7,238 (21.1)	
No surgery, no chemo, radiation done	8,573 (5.2)	1,750 (5.1)	
No surgery, chemo done, no radiation	49,145 (30)	11,141 (32.4)	
No surgery, chemo done, radiation done	69,508 (42.5)	10,951 (31.9)	
Surgery done, no chemo, no radiation	698 (0.4)	972 (2.8)	

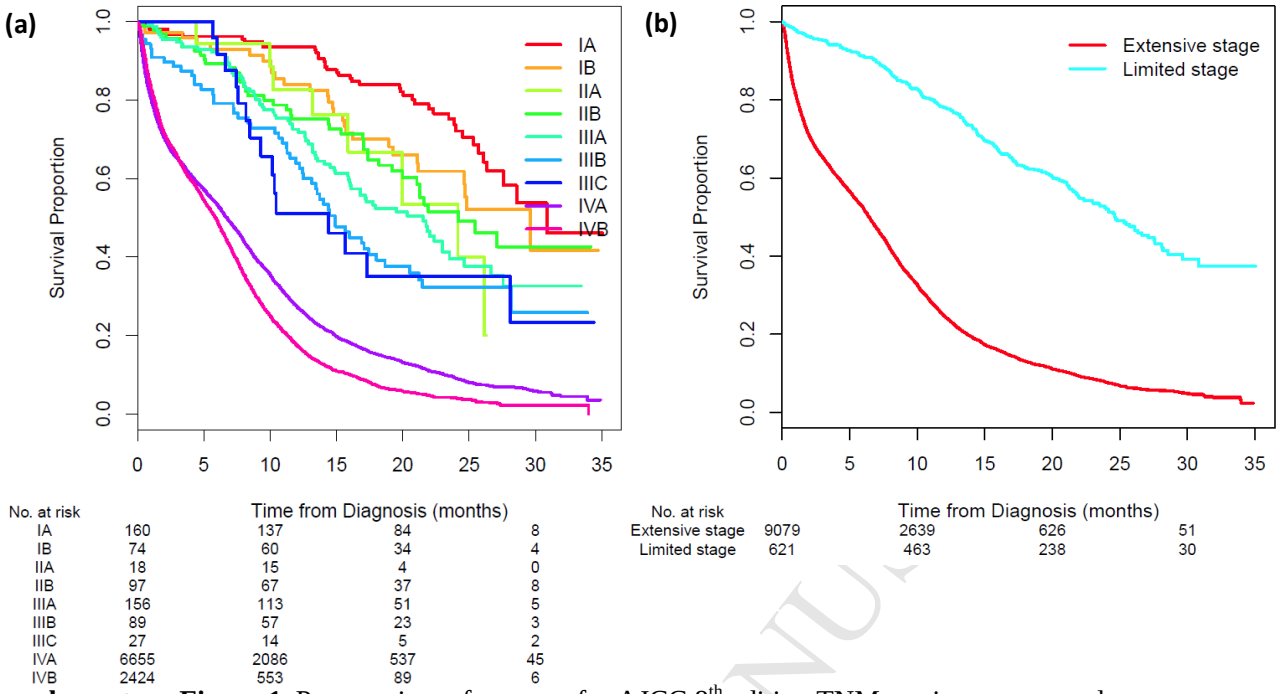
Surgery done, no chemo, radiation done	126 (0.1)	72 (0.2)	
Surgery done, chemo done, no radiation	863 (0.5)	1,165 (3.4)	
Surgery done, chemo done, radiation done	1,096 (0.7)	1,091 (3.2)	
Missing	4,166	-	
Primary site			<0.001
C340	16,995 (10.1)	3,209 (9.3)	
C341	73,408 (43.7)	15,171 (44.1)	
C342	6,566 (3.9)	1,336 (3.9)	
C343	32,198 (19.2)	6,882 (20)	
C348	3,485 (2.1)	685 (2)	
C349	35,162 (21)	7,097 (20.6)	
Laterality			<0.001
Not a paired site	16,995 (10.1)	3,209 (9.3)	
Only one side involved	138,880 (82.8)	28,463 (82.8)	
Bilateral involvement	1,987 (1.2)	778 (2.3)	
Paired site but lateral origin unknown; midline tumor	9,952 (5.9)	1,930 (5.6)	
Grade			<0.001
Well differentiated	286 (0.2)	96 (0.3)	
Moderately differentiated	715 (0.4)	218 (0.6)	
Poorly differentiated	15,310 (9.1)	3,694 (10.7)	
Undifferentiated	39,530 (23.6)	6,494 (18.9)	
Cell type not determined, not stated or not applicable	111,973 (66.7)	23,878 (69.5)	

Supplementary Table 2 Comparison of prognostic performance of three models in testing dataset.

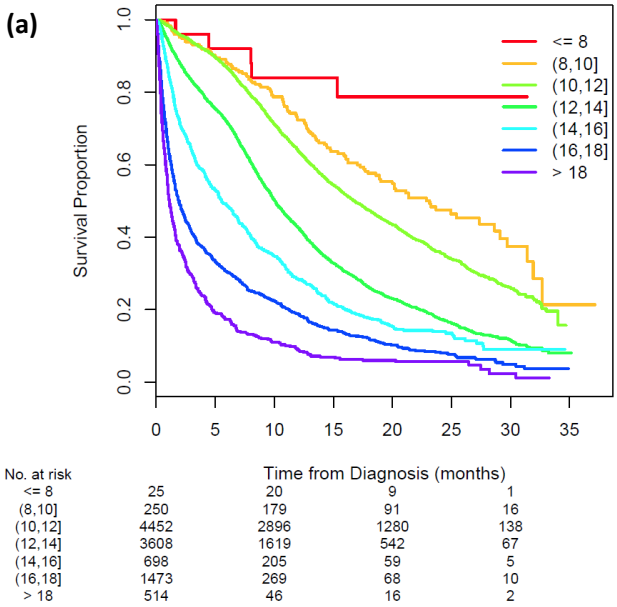
Model	*C-index*	*Average AUC*
Nomogram	0.722 ± 0.004	0.789
8th AJCC TNM stage	0.550 ± 0.003	0.634
Limited/extensive staging	0.539 ± 0.002	0.598

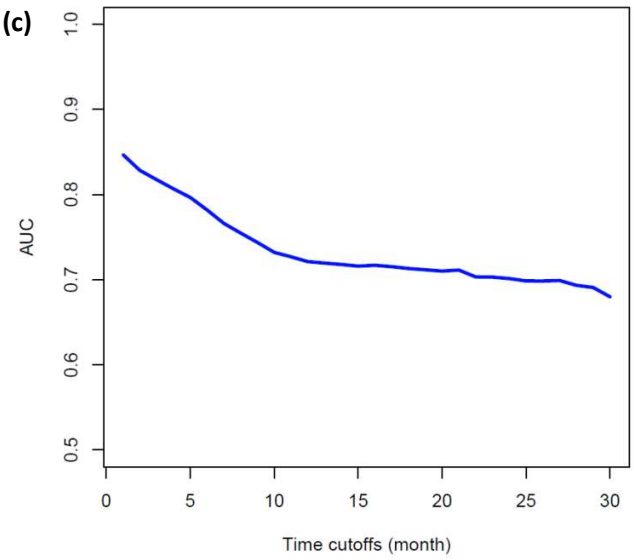
Supplementary Table 3 Comparison of treatment selection among 8th AJCC TNM stages in training set.

Treatment	*Stage I*	*Stage II*	*Stage III*	*Stage IV*
No surgery, no chemo, no radiation	54 (3.2)	38 (3.8)	264 (9.9)	4,669 (24.1)
No surgery, no chemo, radiation done	23 (1.4)	11 (1.1)	45 (1.7)	1,151 (5.9)
No surgery, chemo done, no radiation	50 (3)	68 (6.8)	402 (15.1)	7,148 (36.9)
No surgery, chemo done, radiation done	128 (7.7)	194 (19.5)	1,341 (50.5)	6,238 (32.2)
Surgery done, no chemo, no radiation	526 (31.5)	169 (17)	126 (4.7)	35 (0.2)
Surgery done, no chemo, radiation done	20 (1.2)	15 (1.5)	17 (0.6)	12 (0.1)
Surgery done, chemo done, no radiation	561 (33.6)	236 (23.8)	152 (5.7)	51 (0.3)
Surgery done, chemo done, radiation done	308 (18.4)	262 (26.4)	311 (11.7)	55 (0.3)



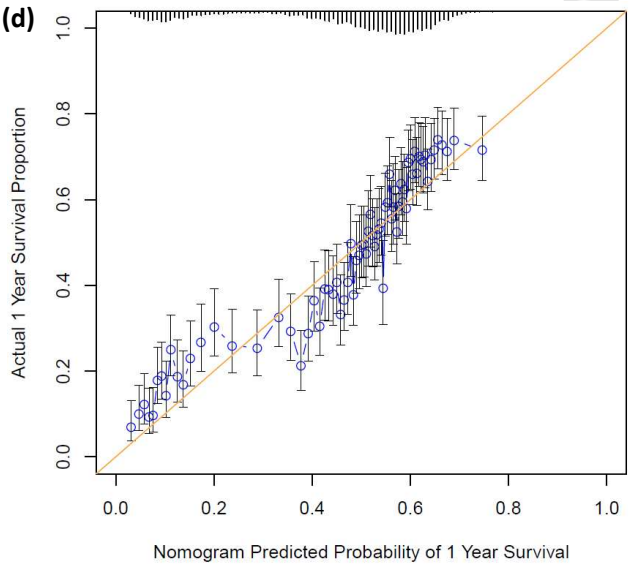
Supplementary Figure 1. Prognostic performance for AJCC 8th edition TNM staging system and limited/extensive staging system. (a) K-M plot grouped by AJCC 8th edition TNM stages. (b) K-M plot grouped by limited/extensive stages.

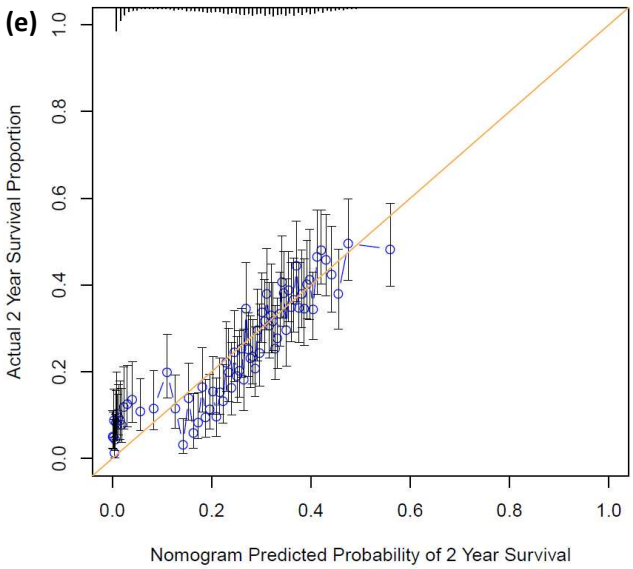




(b)

Score	*#patients*	*#events*	*Median survival (mos)*	*HR*	*p-value*
≤8	25	5	NA (NA-NA)	-	-
(8,10]	250	118	23.16 (18.92-29.11)	≤ 8 vs (2,8]: 2.53 (1.03-6.2)	0.04
(10,12]	4452	2577	16.79 (16.13-17.54)	(10,12] vs (8,10]: 1.37 (1.14-1.64)	< 0.001
(12,14]	3608	2694	10.05 (9.72-10.41)	(12,14] vs (10,12]: 1.82 (1.72-1.92)	< 0.001
(14,16]	698	544	5.55 (4.76-6.70)	(14,16] vs (12,14]: 1.5 (1.37-1.64)	< 0.001
(16,18]	1473	1192	1.94 (1.71-2.20)	(16,18] vs (14,16]: 1.52 (1.37-1.68)	< 0.001
> 18	514	457	1.12 (0.99-1.35)	> 18 vs (16,18]: 1.41 (1.26-1.57)	< 0.001





Supplementary Figure 2 Sensitivity analysis of bias introduced by missing data. Excluded data with diagnostic time ranging from year 2012 to 2013 were used. Missed variables were imputed using mode in the training cohort. **(a)** Risk scores of testing set cases were calculated according to the model in Figure 1 and grouped into 8 subgroups. K-M plot was depicted for each group. **(b)** Summary of groups in (a). Hazard Ratio (HR) was calculated using Coxph regression model between each two adjacent lines. P-value was calculated using Wald test. **(c)** Area under the curve (AUC) was calculated for the proposed nomogram for every month from the 1st to the

30th month. **(d, e)** Calibration curves compare predicted and actual survival proportions at 1 year (d) and 2 years (e), separately. Distributions of predicted survival probabilities are plotted at the top. Error bars represent 95% confidence intervals.