The Prognostic Value of TNI (Tumor-Nutrition-Inflammation Index) in Patients with Advanced Lung Cancer

Huan Wang
the Fourth Affiliated Hospital Zhejiang University School of Medicine
Yuting Shi
the Fourth Affiliated Hospital Zhejiang University School of Medicine
Yueli Shi
the Fourth Affiliated Hospital Zhejiang University School of Medicine
Mengqing Cao
the Fourth Affiliated Hospital Zhejiang University School of Medicine
Long Zhang
the Fourth Affiliated Hospital Zhejiang University School of Medicine
Yuan Wu
the Fourth Affiliated Hospital Zhejiang University School of Medicine
Yun Xu
the Fourth Affiliated Hospital Zhejiang University School of Medicine
Kai Wang
the Fourth Affiliated Hospital Zhejiang University School of Medicine
Xianwu Weng (8020187@zju.edu.cn)
the Fourth Affiliated Hospital Zhejiang University School of Medicine

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Abstract

Purpose: As the third most common cancer type behind breast cancer and prostate cancer, lung cancer has the highest mortality rate all over the world. Identification of easily accessible and inexpensive potential biomarkers for advanced lung cancer is necessary.

Patients and Methods: A total of 195 patients with advanced lung cancer including non-small lung cancer and small cell lung cancer, who received first-line chemotherapy, were included in this study. Then they were randomized as training set and validation set, and the total population were classified as testing set. The optimized cut-off values of AGR and SIRI (AGR=albumin/globulin; SIRI=neutrophil*monocyte/lymphocyte) were determined by survival function analysis based on R software. COX regression analysis was performed to acquire the independent factors for establishing the nomogram model. The predictive accuracy was verified through ROC curve and calibration curves after index concordance.

Results: The optimized cut-off values of AGR and SIRI (AGR=albumin/globulin; SIRI=neutrophil*monocyte/lymphocyte) were 1.22 and 1.60, respectively. Cox analysis revealed that liver metastasis, SCC (squamous cell carcinoma antigen), AGR, and SIRI were independent prognostic factors for advanced lung cancer. A nomogram model comprising these independent prognostic parameters was built for the TNI (tumor-nutrition-inflammation index) score calculation. Patients were divided into four groups based on TNI quartile values. Kaplan-Meier analysis and log-rank test indicated that a higher TNI had a worse OS ($P<0.05$). The C-index and 1-year AUC areas were 0.756 (0.723-0.788) and 75.62, respectively. High consistency between the predicted and actual survival proportions in the TNI model is shown in the calibration curves. A nomogram prognostic model for predicting survival time rates based on TNI in the total population was established to directly observe the survival rate of patients with advanced lung cancer.

Conclusion: TNI may be used as a practical and precise analytical tool for survival prediction in patients with advanced lung cancer.

1. Introduction

Lung cancer is the third most common cancer type next to breast and prostate cancers. It also has the highest mortality rate worldwide[1, 2]. Most lung cancer patients are diagnosed at an advanced stage with a poor prognosis and short survival time. Therefore, it is vital to explore potential biomarkers that may predict survival time and identify patients who may benefit from early treatment. The widely accepted biomarkers in immunotherapy are immune checkpoints, such as programmed cell death protein 1/Programmed cell death 1-ligand 1 and cytotoxic T-lymphocyte-associated protein 4. EGFR, RAS, and TP53 are biomarkers that are commonly used in target therapy for lung cancer. However, the detection of these biomarkers requires invasive procedures to obtain pathological tissue, which is costly. Therefore, it is optimal to identify potential biomarkers that are easily accessible and inexpensive.

Laboratory blood tests, including various indicators such as absolute white cell counts, albumin, globulin, neutrophils, monocytes, and lymphocytes, are widely used in clinical practice. Previous studies suggest that these blood indicators can be used as predictive and prognostic biomarkers for various tumors, including

lung cancer[3–5]. Albumin and globulin are the most common clinical nutritional indicators. Inflammatory indicators, including neutrophils, monocytes, and lymphocytes, usually reflect the inflammatory state. It has also been reported that low AGR or high SIRI is associated with poorer survival outcomes[6–8]. Nutritional and inflammatory indicators are related to the prognosis of patients with cancer[2, 9, 10]. Nevertheless, these studies focused on a single marker, patients at a certain stage, or a particular cytological classification. Few studies have explored the association between combined factors and the prognosis of advanced lung cancer. This study aimed to explore the prognostic significance of integrated nutritional and inflammatory values in patients with advanced lung cancer.

2. Patients And Methods

2.1 *Patients*

A retrospective analysis was conducted those enrolled patients with a definite diagnosis of stage IV lung cancer treated in the respiratory medicine department of the Fourth Affiliated Hospital of Zhejiang University School of Medicine in the past 5 years from February 2015 to December 2019. The inclusion and exclusion criteria were as follows:

Inclusion criteria: at least 18 years of age with a definite diagnosis of stage IV lung cancer by CT or MRI imaging examination and pathological examination; initial first-line chemotherapy was treated in the Fourth Affiliated Hospital; all patients were ECOG PS 0–1; complete clinical and follow-up information; and sufficient pre-treatment routine blood laboratory test data.

Exclusion criteria: patients without a diagnosis of lung cancer; patients with repeat names and hospital admission number; without complete clinical information; without sufficient follow-up information; no available routine blood laboratory data; and no history of acute infection.

The study was approved by the Research Ethics Committee of the Fourth Affiliated Hospital of Zhejiang University School of Medicine (reference number: K2021063).

2.2 *Data collection*

Clinical information was collected from the electronic medical record system. CT or MRI imaging and pathology examinations were performed by at least two professional physicians. Laboratory test data were selected within two weeks prior to the first-line chemotherapy by detecting the patient's peripheral blood.

2.3 *Follow-up*

All patients were followed up every three months. The estimated endpoints were the overall survival (OS). OS was defined as the interval from the start of first-line chemotherapy up to the time of the patient's last follow-up or the time of death. All patients were followed up to January, 2021.

2.4 *The evaluation of AGR and SIRI*

The albumin, globulin, neutrophil, monocyte, and lymphocyte values were collected to calculate the AGR and SIRI (AGR = albumin/globulin; SIRI = neutrophil*monocyte/lymphocyte). The optimized cut-off values were dichotomized through survival function using R software 3.6.2. According to the optimized cut-off value, all included patients were classified into elevate and low groups. The cut-off values were 1.22, and 1.60, respectively.

2.5 *Statistical analysis*

All statistical analyses were performed using R software (R 3.6.2 version), SPSS software (IBM SPSS statistical 20.0 version), and GraphPad software (GraphPad Prism 6 version). All count data were extracted as continuous variable values or percentage values. Chi-square or Fisher's exact tests were used to compare categorical variables. Kaplan-Meier (KM) survival curves and log-rank tests were used to explore the distribution of the OS of categorical variables. Univariate and multivariate Cox regression analyses were performed to analyze the significant independent prognostic factors. The statistical significance threshold was set to P value of less than 0.05.

3. Results

3.1 *Patients selection*

This retrospective analysis study included 945 patients with lung cancer initially, who were hospitalized in the respiratory medicine department of the Fourth Affiliated Hospital of Zhejiang University School of medicine in the past 5 years from February 2015 to December 2019. Based on the inclusion and exclusion criteria, 395 patients without complete information, 20 patients without first-line chemotherapy, 277 patients without follow-up information, and 108 patients without sufficient laboratory test data. Finally, 195 patients were included in this retrospective study. In addition, R software was used to randomly group the patients to a 7:3 ratio. A total of 136 patients were assigned to the training group to establish the nomogram prediction model and 59 patients were assigned to the validation cohort. The total patients were assigned to the testing cohort to assess the model (Fig. 1).

3.2 *Association between AGR, SIRI and the OS*

The characteristic variables of the training cohort are summarized in Table 1. The median value of age was regarded as the cut-off value. The cutoff values of CRP, CEA, and CA19-9, are defined by the maximum of the normal range setting by the Fourth Affiliated Hospital of Zhejiang University School of Medicine. The training cohort consisted of 96 (70.6%) men and 40 (29.4%) women. In addition, Table 1 shows that low AGR is significantly associated with other prognostic outcomes, including no history of lung cancer operation ($P = 0.005$), body mass index (BMI) of ≥ 18.5 ($P = 0.008$), carcinoembryonic antigen (CEA) of ≥ 5 ($P = 0.018$), and an increased C-reactive protein (CRP) level ($P < 0.001$). It was significantly different when comparing high SIRI with sex ($P = 0.002$), pathology ($P = 0.008$), and CRP ($P < 0.001$).

Subsequently, Cox univariate and multivariate regression analyses included variables that were significant in Table 1 or meaningful related clinical work. Univariate Cox analysis indicated that a history of lung cancer operation, liver metastasis, history of smoking, BMI, CA19-9, squamous cell carcinoma antigen (SCC), CRP,

AGR, and SIRI were significantly associated with OS (P < 0.05; Fig. 2). Multivariate Cox proportional hazard analysis revealed that liver metastasis, SCC, AGR, and SIRI were independent prognostic factors in advanced lung cancer (P < 0.05; Fig. 3).

To explore the prognostic value of AGR and SIRI in patients with advanced lung cancer. KM analysis and log-rank test demonstrated that the relationship between low AGR or high SIRI and poorer OS was statistically significant in the training set (hazard ratio [HR] = 2.435 [1.55–4.88], P = 0.007; Figure. 4A). The lower AGR group had shorter 5-year OS rate (0% vs 42.3%) and median OS time (15.0 months vs 30.3 months) in comparison with the elevated AGR level group. When patients with advanced lung cancer were in hyperinflammatory states, it revealed that high SIRI level had significant 5-year OS rate (0% vs 54.9%) and median OS time (16.7 months vs NA; HR = 3.135(1.77–5.24); P < 0.001; Figure. 4D). Similar results were confirmed in the validation and testing sets (P < 0.05; Fig. 4B-C and E-F).

3.3 *The analysis of the prognostic value of TNI*

The potential value of the clinical factors in the training set were further explored. As known, SCC and liver metastasis are important biomarkers for lung cancer screening[11, 12]. However, not all patients with high SCC or liver metastasis have a poor survival time. SCC or liver metastasis alone are insufficient as a prognostic biomarker for patients with advanced lung cancer. Therefore, more prognostic biomarkers for lung cancer need to be explored. To predict survival precisely and quantitatively, a nomogram model based on relevant parameters was established. The total points were calculated by determining the score of the parameters by establishing the nomogram shown in Fig. 5A. Liver metastasis had the largest interval while the SCC risk score indicated the minimum range in this model. The total point was defined as the TNI, which was calculated for each patient based on the model. We could get a formula: TNI = 10*liver metastasis^{yes} + 5.37* SSC^{high} + 5.69*AGR^{low} + 5.55*SIRI^{high}. TNI scores were calculated using the R software for each patient with advanced lung cancer. Then, patients were divided into four groups based on their TNI quartile values. KM analysis and log-rank test indicated that the high-risk TNI group significantly predicted poorer OS compared to the other groups, as shown in Fig. 5B (P < 0.05).

To verify whether the nomogram model is applicable to both the validation and test sets. The TNI score for each patient was disposed in the same manner as the training set. The survival curves were still statistically significant, as plotted in Supplementary Fig. 1A-B (P < 0.05). In order to further validate the diagnostic ability of the nomogram model, the concordance index (C-index) and time-dependent receiver characteristic operator (ROC) curves were drafted by R studio according to the SCC combined liver metastasis model, AGR combined SRI model, and TNI model, respectively. The results showed that the C-index was 0.658(0.621–0.694), 0.703(0.666–0.739), and 0.756(0.723–0.788), respectively. The 1-year AUC areas were 68.93, 67.34, and 75.62, respectively (Supplementary Fig. 1C; Supplementary Table 1). This demonstrated that TNI had a higher diagnostic ability than the other two models. It showed elevated consistency for comparing predicted and actual survival proportions for the TNI model in the training, validation, and testing sets, which were revealed by calibration curves at 1 year, 2 years, and 3 years (Supplementary Fig. 2A-I).

Based on the TNI scores, the patients' clinical characteristics in the total population are shown in Supplementary Table 2. We then performed Cox univariate and multivariate regression analyses, as shown in

Supplementary Table 3. BMI, CRP, and TNI were independent prognostic factors in patients with advanced lung cancer ($P < 0.05$). A nomogram prognostic model was established to predict survival time rates according to these three independent risk factors in the total population (Fig. 6). Using the prognostic model, we can intuitively observe the survival rate of patients with advanced lung cancer.

The regimen of lung cancer has entered an era of precision treatment, so subgroup analysis was conducted in the lung cancer subtypes, patients were divided into EGFR-mutation and non-EGFR-mutation groups for exploring the potential significance of TNI. The optime cut-off was obtained using the R package. As shown in Supplementary Fig. 3A-3B. Both subgroups showed longer survival time in patients with low TNI. Additionally, when patients were separated into chemotherapy and targeted and immunotherapy groups according to the First-line chemotherapy regimen, the results demonstrated that patients with high TNI had worse OS (Supplementary Fig. 3C-3D). So, we could conclude that TNI may be a potential biomarker for patients screening and treatment regimens options influencing.

4. Discussion

In this study, we found that liver metastasis, SCC, AGR, and SIRI were independent significant prognostic factors in patients with advanced lung cancer, which is consistent with previous studies[8, 13]. Liver metastasis and SCC are widely accepted biomarkers in clinical studies. AGR has been reported to be related to long-term survival in various tumors, and it has been suggested that AGR is an independent prognostic factor[7, 14]. A meta-analysis of 12 studies on AGR and gastric cancer outcomes found that a higher AGR was associated with longer survival time[15]. SIRI has also been demonstrated as an effective prognostic biomarker for solid tumors, including stage III non-small cell lung cancer[8, 16–19]. However, the use of these indicators as independent prognostic biomarkers remains controversial. Therefore, a TNI index, a novel scoring tool that is calculated by risk scores based on these four indicators was established. It has been suggested that the TNI index is effective in differentiating nutritional and inflammatory risks in patients with advanced lung cancer. Therefore, TNI may be a potential biomarker for effectively and precisely predicting the survival rate of patients with advanced lung cancer. Herein, a nomogram prognostic model based on the TNI was also built, which helped to intuitively observe the survival rate of patients with advanced lung cancer.

Albumin, synthesized in the liver, is considered the most essential protein in human plasma. It maintains several bodily activities, including nutrition and osmotic pressure, transporting and binding hormones, pharmaceuticals, fatty acids, and cations[13]. There is a close relationship between serum albumin level and nutritional status. Previous studies have revealed that albumin participates in the inflammatory response process[20, 21]. Upregulation of albumin through the activation of tumor necrosis factor-α, interleukin-1, and interleukin-6 promotes tumor proliferation and metastasis[22]. Moreover, albumin nano vectors play a crucial role in increasing the availability of drugs and drug delivery, such as albumin paclitaxel[23]. Low albumin levels are associated with poor liver function, and patients with advanced cancer were reported to display a high incidence of malnutrition due to cancer cachexia and cancer-associated bleeding[24]. Globulin, also called immunoglobulin, contains a large number of immune-related products that can trigger antigen binding and recognition, complement activation, and Fc receptor binding by stimulating the lymphatic system[25]. It has been confirmed that globulin plays an important role in the immune microenvironment[26, 27], but

whether it could affect tumor immunotherapy remains to be unexplored. Studies have shown that neutrophils can promote tumor metastasis through arachidonate 5-lipoxygenase-dependent leukotriene synthesis[28]. In addition, it can inhibit the activation of CD + T cells and increase the secretion of cathepsin G, neutrophil elastase, and other factors that promote tumor metastasis[29, 30]. Monocytes can differentiate into macrophages or dendritic cells, which are involved in the immune response. Studies have confirmed that the CCL2-CC chemokine receptor 2 signaling pathway can be blocked by reducing the activation and proliferation of monocytes to promote tumor cell metastasis inhibition[31]. Lymphocytes are a type of cell line with immune recognition function. It can be divided into T lymphocytes, B lymphocytes, and natural killer (NK) cells. T lymphocytes, such as CD4 + cells, which play a crucial role in the tumor immune response, release immunoregulatory factors and inhibit tumor growth, metastasis, and other processes[32]. B lymphocytes and NK cells play a crucial role in tumor immune response and inhibition of tumor proliferation and metastasis through the secretion of tumor-specific antibodies[33, 34]. When the above indicators are combined, whether they will comprehensively affect anti-tumor efficacy? This mechanism needs to be further explored.

This study has several limitations. First, as mentioned, although this study had an external verification of the validation cohort and the testing cohort based on the results of the training set, it is still a single-center retrospective study, and a more multicenter retrospective studies with more patients and high-quality prospective studies are needed in the future. Second, this study only included patients with advanced lung cancer, without patients who underwent surgery or had sufficient concurrent infection. Third, this study focused on the evaluation of the nutritional and inflammatory status of patients with advanced lung cancer before first-line chemotherapy. Since the influence of subsequent chemotherapy or radiotherapy and other anti-tumor therapies on the overall nutritional inflammation level of patients has not been thoroughly explored, it is unknown whether the TNI index can be used as an indicator for the dynamic monitoring indicator in the treatment stage. Fourth, the patients included in this study started in February 2015, hence a short follow-up time. The follow-up time should be extended in future studies to make the results more reliable. Finally, the cut-off value adopted in this study was optimized by calculation using R software. Whether this value can better classify patients, or whether it can be applied in a larger population for business reasons, still needs further exploration.

5. Conclusions

In conclusion, to our knowledge, this study is the first to combine nutritional, inflammatory, and clinical indicators to establish an integrated biomarker and nomogram model for predicting survival outcomes. This provides a practical analytical tool for more accurate prediction of survival outcomes in patients with advanced lung cancer. This analysis may provide a strong support for the selection of clinical treatment strategies.

Abbreviations

AGR albumin/globulin; SIRI neutrophils*monocytes/lymphocytes; OS Overall Survival; KM Kaplan-Meier; CEA Carcinoembryonic Antigen; CA199 Carbohydrate Antigen 199; BMI Body Mass Index; CRP c-creative protein;

SCC squamous cell carcinoma antigen; HR hazard ratio; TNI tumor-nutrition-inflammation index; C-index concordance index; ROC Receiver Characteristic Operator; NK natural killer.

Declarations

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

ETHICS STATEMENT

The collection and analysis of all samples in this study were approved by the Ethics Committee of the Fourth Affiliated Hospital Zhejiang University School of Medicine (reference number: K2021063). 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.

DATA AVAILABILITY STATEMENT

All data in our study are available from the corresponding authors upon reasonable request.

AUTHOR CONTRIBUTIONS

All authors contributed to data analysis, drafting or revising of the article, approved the final version to be published; and agreed to be accountable for all aspects of the work. All authors have read and approved the final manuscript.

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Tables

Table 1 Clinical characteristics of the patients with different AGR and SIRI according the optimize cut-off in training dataset.

	No. of patients (N=136)	AGR<1.22 (N=64)	AGR≥1.22 (N=72)	P-value	SIRI<1.60 (N=61)	SIRI≥1.60 (N=75)	P-value
Gender				0.492			0.002
female	40(29.4%)	17(26.6%)	23(31.9%)		26(42.6%)	14(18.7%)	
male	96(70.6%)	47(73.4%)	49(68.1%)		35(57.4%)	61(81.3%)	
Age				0.089			0.875
≤60	37(27.2%)	13(20.3%)	24(33.3%)		17(27.9%)	20(26.7%)	
>60	99(72.8%)	51(79.7%)	48(66.7%)		44(72.1%)	55(73.3%)	
History of LC operation				0.005			0.135
no	102(75.0%)	55(85.9%)	47(65.3%)		42(68.9%)	60(80.0%)	
yes	34(25.0%)	9(14.1%)	25(34.7%)		19(31.1%)	15(20.0%)	
Differentiation				0.172			0.078
poor	36(26.5%)	19(29.7%)	17(23.6%)		12(19.7%)	24(32.0%)	
moderate-well	13(9.6%)	3(4.7%)	10(13.9%)		9(14.8%)	4(5.3%)	
unknown	87(64.0%)	42(65.6%)	45(62.5%)		40(65.6%)	47(62.7%)	
Pathology				0.700			0.008
adenocarcinoma	72(52.9%)	35(54.7%)	37(51.4%)		40(65.6%)	32(42.7%)	
non-adenocarcinoma	64(47.1%)	29(45.3%)	35(48.6%)		21(34.4%)	43(57.3%)	
Mutation				0.822			0.204
positive	56(41.2%)	28(43.8%)	28(38.9%)		30(49.2%)	26(34.7%)	
negative	41(30.1%)	19(29.7%)	22(30.6%)		17(27.9%)	24(32.0%)	
unknown	39(28.7%)	17(26.6%)	22(30.6%)		14(23.0%)	25(33.3%)	
Bone metastasis				0.763			0.179
no	114(83.8%)	53(82.8%)	61(84.7%)		54(88.5%)	60(80.0%)	
yes	22(16.2%)	11(17.2%)	11(15.3%)		7(11.5%)	15(20.0%)	
Brain metastasis				0.869			0.596
no	114(83.8%)	54(84.4%)	60(83.3%)		50(82.0%)	64(85.3%)	
yes	22(16.2%)	10(15.6%)	12(16.7%)		11(18.0%)	11(14.7%)	

Adrenal metastasis				0.413			0.707
no	124(91.2%)	57(89.1%)	67(93.1%)		55(90.2%)	69(92.0%)	
yes	12(8.8%)	7(10.9%)	5(6.9%)		6(19.8%)	6(8.0%)	
Liver metastasis				0.514			0.097
no	123(90.4%)	59(92.2%)	64(88.9%)		58(95.1%)	65(86.7%)	
yes	13(9.6%)	5(7.8%)	8(11.1%)		3(4.9%)	10(13.3%)	
History of smoke				0.479			0.112
no	70(51.5%)	35(54.7%)	35(48.6%)		36(59.0%)	34(45.3%)	
yes	66(48.5%)	29(45.3%)	37(51.4%)		25(41.0%)	41(54.7%)	
History of alcohol				0.427			0.619
no	102(75.0%)	50(78.1%)	52(72.2%)		47(77.0%)	55(73.3%)	
yes	34(25.0%)	14(21.9%)	20(27.8%)		14(23.0%)	20(26.7%)	
Hypertension				0.444			0.264
no	89(65.4%)	44(68.8%)	45(62.5%)		43(70.5%)	46(61.3%)	
yes	47(34.6%)	20(31.2%)	27(37.5%)		18(29.5%)	29(38.7%)	
Diabetes				0.606			0.881
no	121(89.0%)	56(87.5%)	65(90.3%)		54(88.5%)	67(89.3%)	
yes	15(11.0%)	8(12.5%)	7(9.7%)		7(11.5%)	8(10.7%)	
BMI				0.008			0.407
18.5	12(8.8%)	10(15.6%)	2(2.8%)		4(6.6%)	8(10.7%)	
≥18.5	124(91.2%)	54(84.4%)	70(97.2%)		57(93.4%)	67(89.3%)	
CEA				0.018			0.88
≤5	57(41.9%)	20(31.2%)	37(51.4%)		26(42.6%)	31(41.3%)	
5	79(58.1%)	44(68.8%)	35(48.6%)		35(57.4%)	44(58.7%)	
CA199				0.078			0.602
≤43	95(69.9%)	40(62.5%)	55(76.4%)		44(72.1%)	51(68.0%)	
43	41(30.1%)	24(37.5%)	17(23.6%)		17(27.9%)	24(32.0%)	
SCC				0.113			0.361
≤1.5	88(64.7%)	37(57.8%)	51(70.8%)		42(68.9%)	46(61.3%)	
1.5	48(35.3%)	27(42.2%)	21(29.2%)		19(31.0%)	29(38.7%)	

AFP				0.734		0.589
≤7	111(81.6%)	53(82.8%)	58(80.6%)		51(83.6%)	60(80.0%)	
7	25(18.4%)	11(17.2%)	14(19.4%)		10(16.4%)	15(20.0%)	
CRP				0.001			0.001
≤5.5	63(46.3%)	14(21.9%)	49(68.1%)		40(65.6%)	23(30.7%)	
5.5	73(53.7%)	50(78.1%)	23(31.9%)		21(34.4%)	52(69.3%)	

*LC=lung cancer

Figures

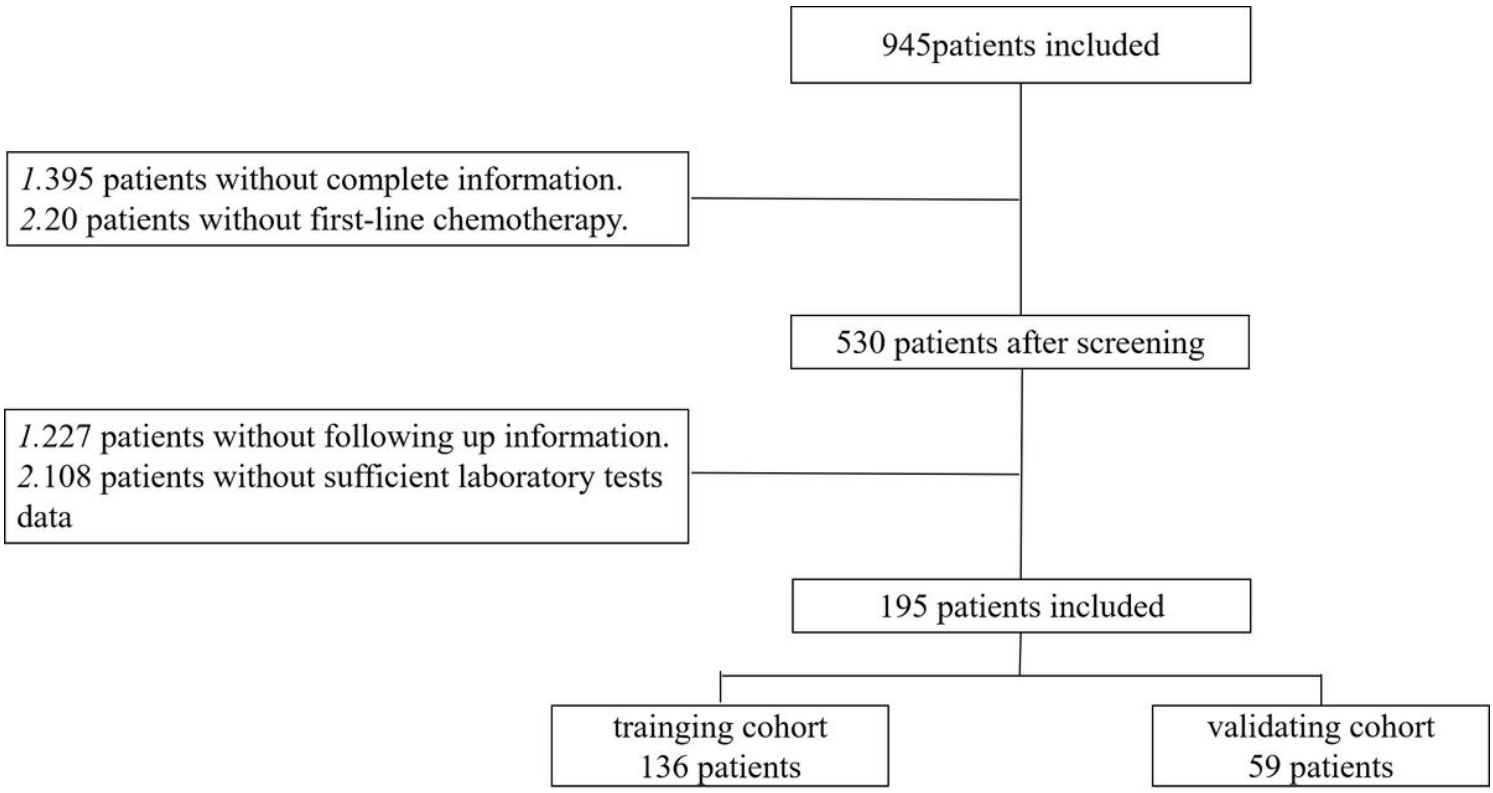


Figure 1

Flowchart of study selection process

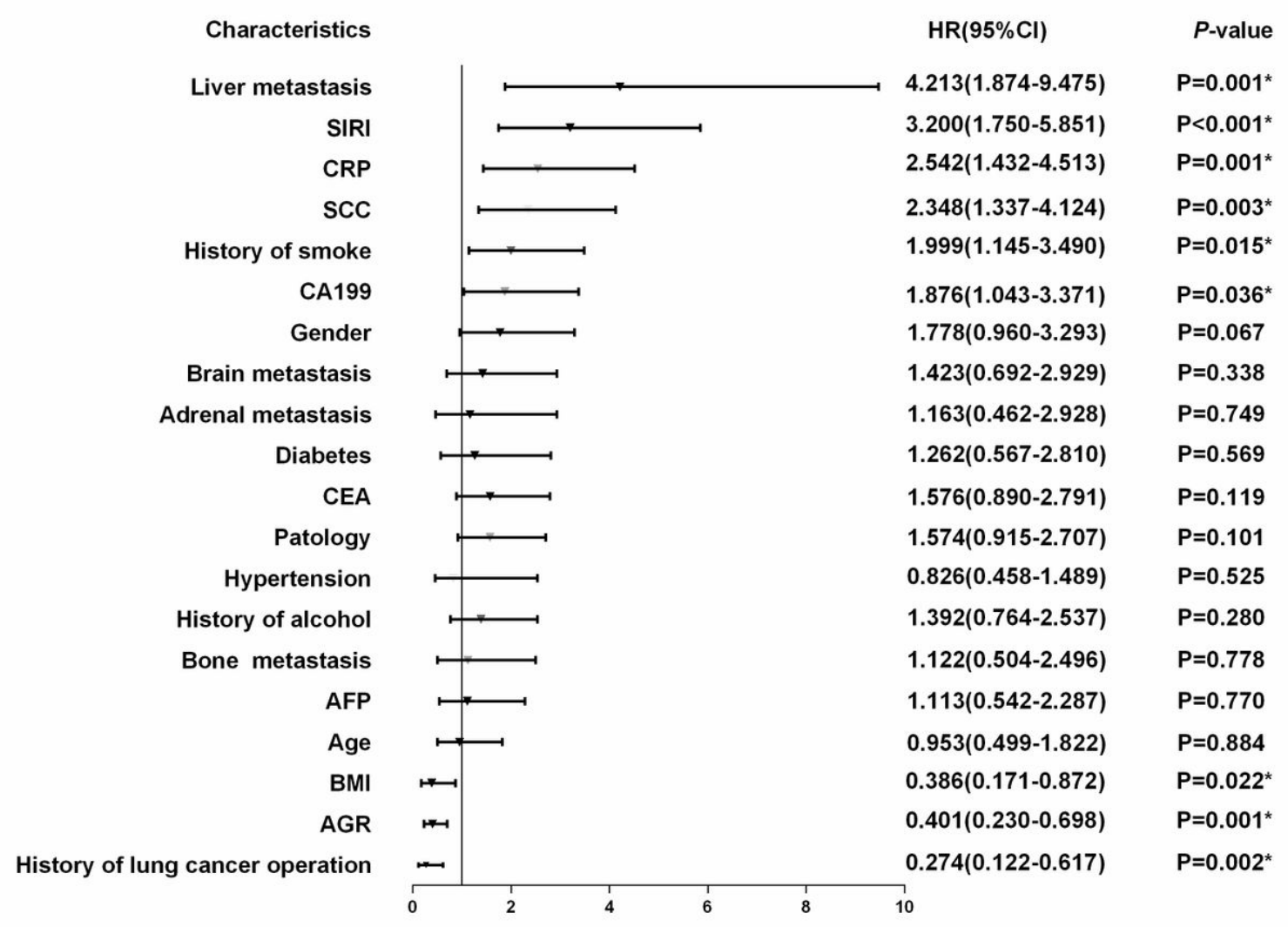


Figure 2

Forest of COX univariate regression analysis in training cohort.

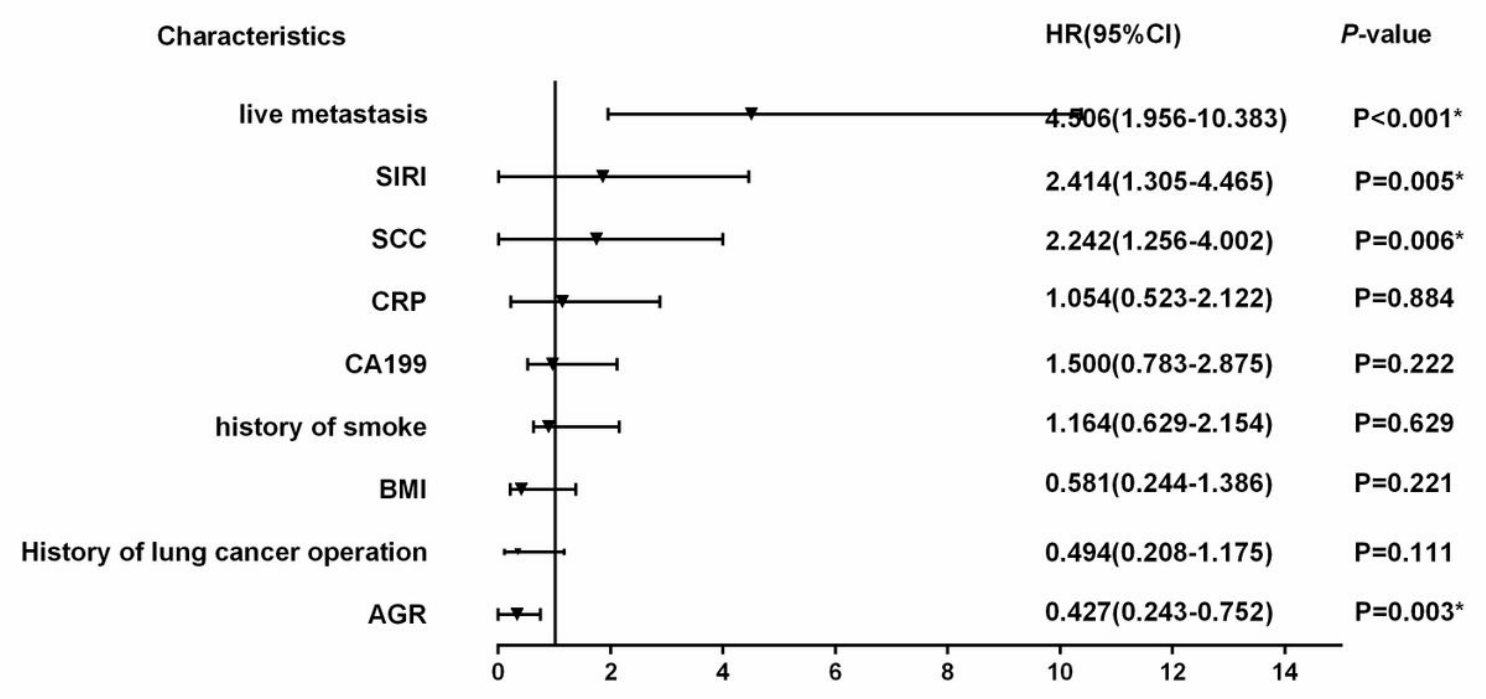


Figure 3

Forest of COX multivariate regression analysis in training cohort.

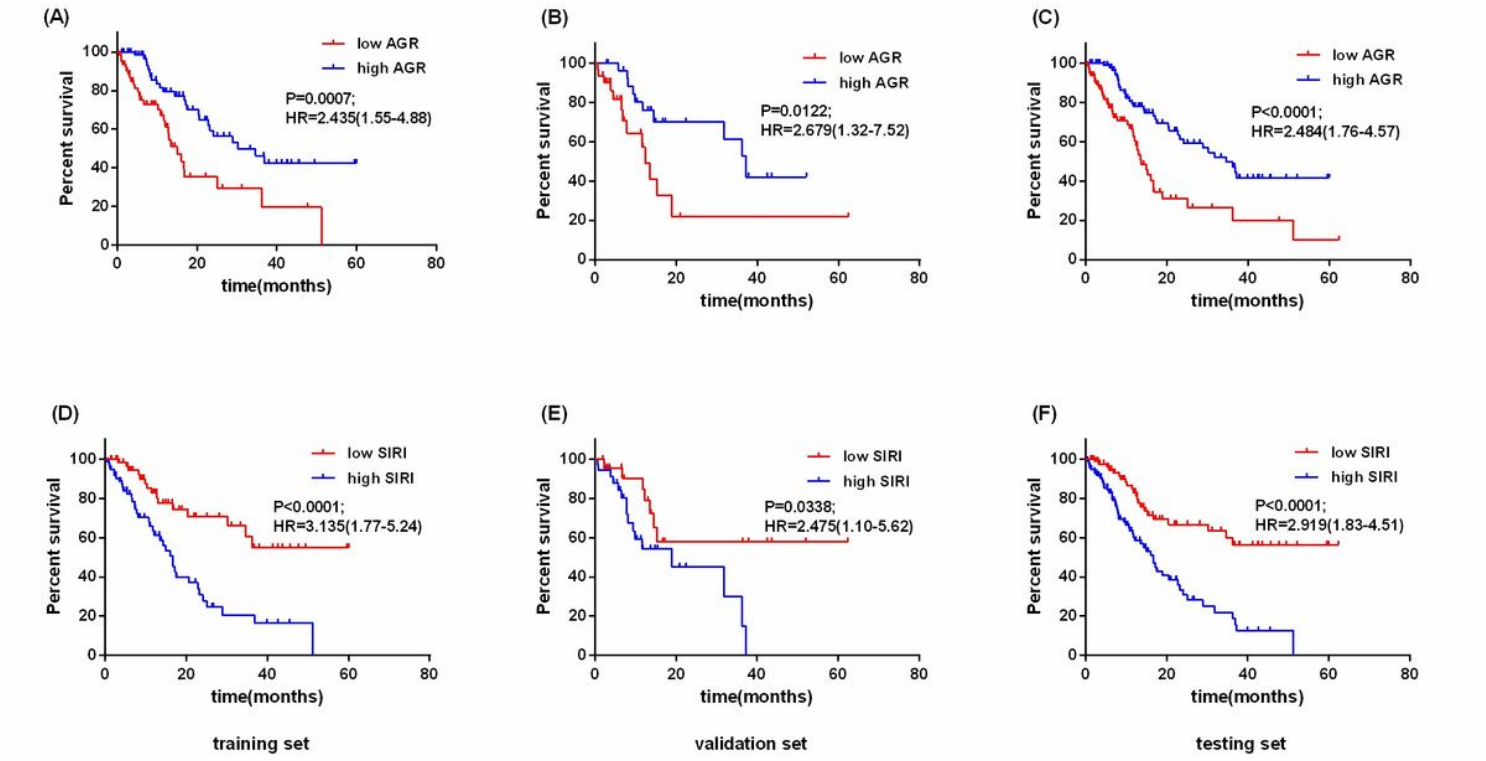
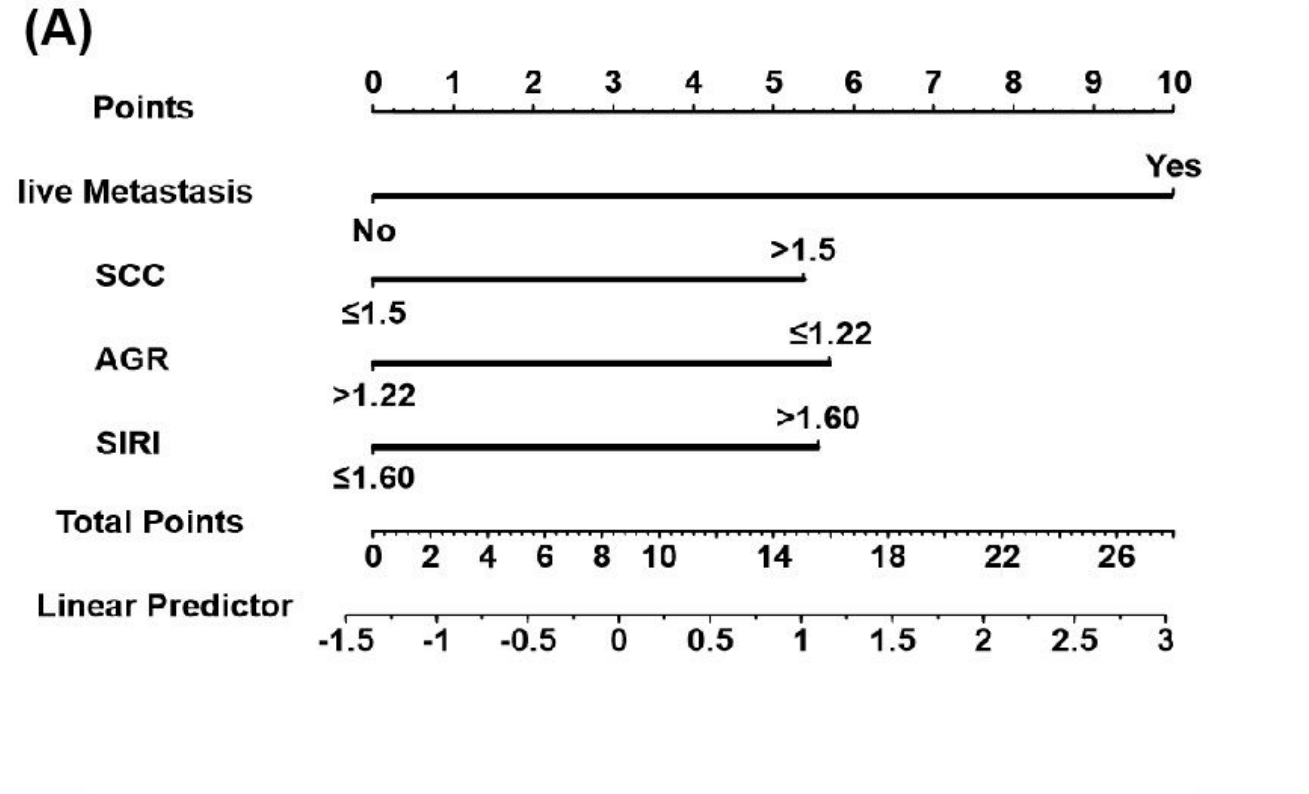


Figure 4

Kaplan–Meier curves for OS according to the optime cut-off value about albumin to globulin (AGR) and neutrophil*monocyte/lymphocyte (SIRI). (A) AGR in the training cohort; (B) AGR in the validation cohort; (C) AGR in the testing cohort; (D)SIRI in the training cohort ; (E) SIRI in the validation cohort; (F) SIRI in the total cohort



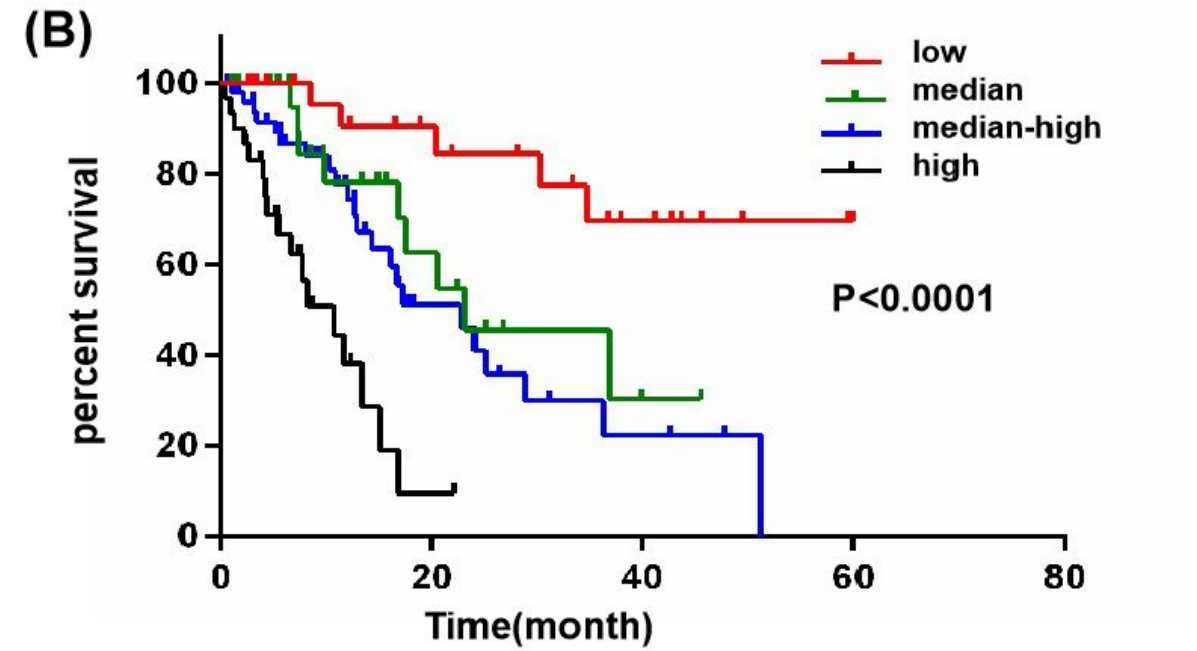


Figure 5

Nomogram model and Kaplan Meier curve about TNI in training cohort. (A)Nomogram to calculate risk score and predict survival probability. (B)Predicted patient survival probability curve corresponding to different risk

ranging from low risk to high risk according to the quarter of the TNI risk scores.

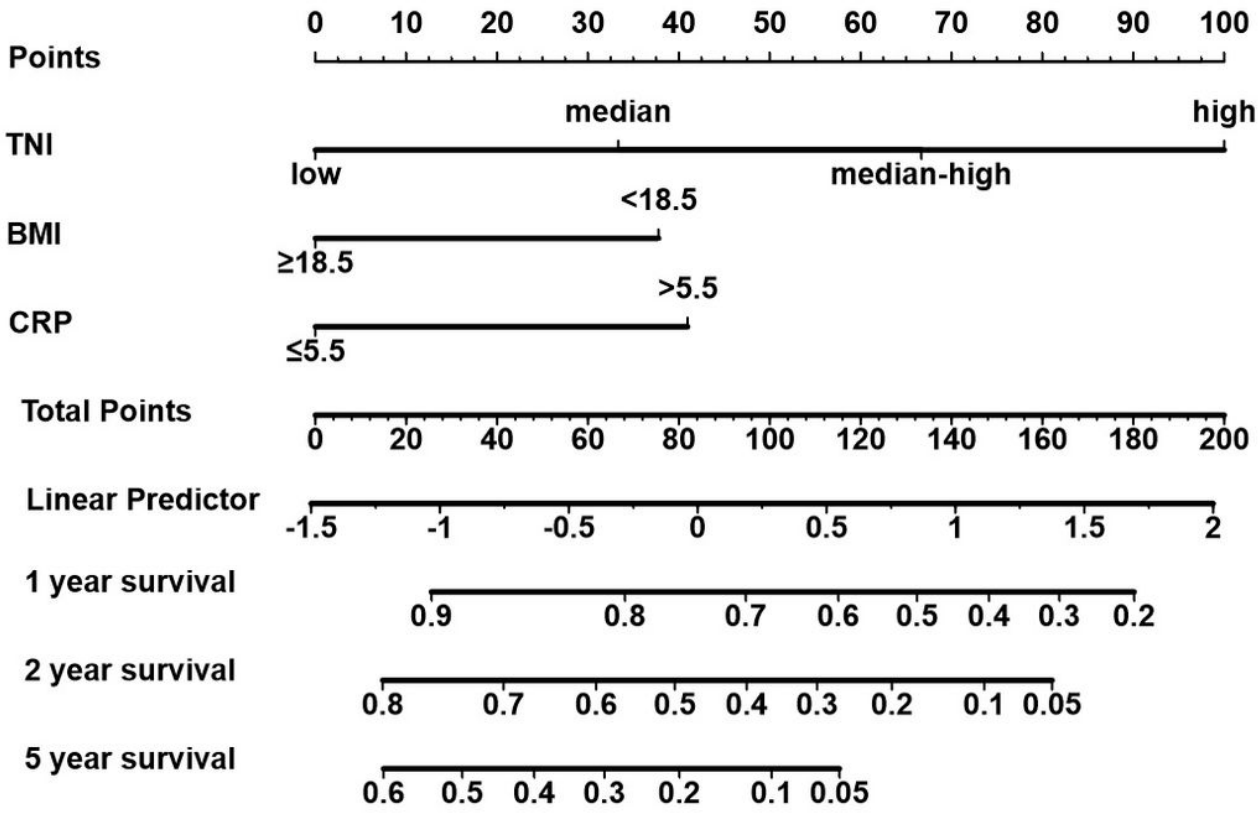


Figure 6

The nomogram prognostic model was built based on the TNI in patients with advanced lung cancer in total population.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplementaryfigure1.tif
- supplementaryfigure2.tif
- supplementaryfigure3.tif
- supplementarytable1.docx
- supplementarytable2.docx

- supplementarytable3.docx