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# Construction of a Nomogram Based on lncRNA and Patient's Clinical Characteristics to Improve the Prognosis of Non-Small Cell Lung Cancer

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**Abstract**

Although the American Joint Commission on Cancer (AJCC) staging has been widely used to predict the survival of cancer patients, there are still some limitations. The high accuracy of lncRNA-based signature prediction has attracted widespread attention. The data were obtained from the RNA sequencing data of nonsmall cell lung cancer (NSCLC) in the Cancer Genome Atlas (TCGA) database. Differentially expressed lncRNAs (DELs) and differentially expressed mRNAs (DEMs) were identified. Using univariate Cox proportional hazard regression (CPHR) analysis, least absolute shrinkage and selection operator method, and multivariate CPHR, 5 lncRNAs (LINC00460, LINC00857, LINC01116, RP11-253E3.3, and RP11-359E19.2) related to patient survival were successfully screened. Combined with age, gender, AJCC staging, and 5 lncRNAs, a nomogram with a better prognosis prediction ability than traditional parameters was constructed. Prognostic accuracy was evaluated using the receiver operating characteristic (ROC) curve and area under the ROC value. In addition, through co-expression analysis, we found that 5 lncRNA target genes have 34 DEMs. Gene ontology function analysis showed that these DEMs were mainly enriched in enzyme inhibitor activity and other aspects. Finally, these DEMs were found to be involved in the formation of the tumor immune microenvironment. In short, the nomogram based on 5 lncRNAs can effectively predict the overall survival rate of NSCLC and may guide the formulation of treatment plans for NSCLC.

**Keywords**

long noncoding RNAs, nomogram, prognosis, NSCLC, immune cell infiltration

**Abbreviations**

AJCC, American Joint Commission on Cancer; AUC, area under the ROC curve; CPHR, Cox proportional hazard regression; DELs, differentially expressed lncRNAs; DEMs, differentially expressed mRNAs; GO, gene ontology; GEPIA, Gene Expression Profiling Interactive Analysis; HNSCC, head and neck squamous cell carcinoma; K-M, Kaplan-Meier; LASSO, least absolute shrinkage and selection operator; lncRNAs, long noncoding RNAs; MDSCs, myeloid-derived suppressor cells; MMP12, matrix metalloproteinase 12; NSCLC, nonsmall cell lung cancer; OS, overall survival; RNASeq, RNA sequencing; ROC, receiver operating characteristic; TCGA, the Cancer Genome Atlas; TIMER, Tumor Immunity Assessment Resource.

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## Introduction

Nonsmall cell lung cancer (NSCLC) is one of the most common and deadly cancers worldwide. Although targeted therapies and immunotherapy have made great progress, the 5-year survival rate of patients with NSCLC is only 19%.[1] To make matters worse, most of the patients are already in a late-stage when they consult a doctor, and the best time for radical surgery has been lost.[2] Therefore, there is an urgent need to establish

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a prognostic risk scoring model for patients with NSCLC to guide the treatment of NSCLC.

With the development of sequencing technology, more and more long noncoding RNAs (lncRNAs) have been found to be involved in the occurrence and development of tumors.[3] lncRNAs are prognostic biomarkers for many types of cancers, such as prostate cancer, bladder cancer, kidney cancer, pancreatic cancer, hepatocellular carcinoma, lung cancer, colorectal cancer, and gastric cancer.[3–8] Since lncRNA as a biomarker has good stability, high tissue specificity, and is easily detected in body fluids, the high accuracy of signature prediction based on lncRNA has attracted widespread attention.[9,10]

The American Joint Commission on Cancer (AJCC) staging has been widely used to predict the survival of cancer patients for a long time. But, there are still some limitations. Although patients may have similar pathology, anatomical location, and AJCC staging, they will have different responses to treatment and different survival outcomes. Therefore, a new staging system must be established.

In this study, we conducted a large sample analysis, hoping to identify survival-related lncRNAs, and used univariate Cox proportional hazard regression (CPHR) analysis, least absolute shrinkage and selection operator (LASSO) method, and multivariate CPHR analysis to verify it. In addition, combined with gender, age, and AJCC staging, a new staging system based on lncRNAs combined with clinical characteristics and genes was constructed and its effectiveness in predicting the prognosis of NSCLC was evaluated.

## Materials and Methods

### Data Collection and Processing

The RNA sequencing (RNASeq) data of 108 normal tissues and 1037 cancer tissues and their corresponding clinical data were obtained from the Cancer Genome Atlas (TCGA) database (https://cancergenome.nih.gov/). The R software package (version 4.1.0) was used to process the downloaded files and convert and eliminate the unqualified data. All data were calibrated, normalized, and $\log_2$ converted. All data were divided into a training group (54 normal tissues and 518 cancer tissues) and a test group (54 normal tissues and 519 cancer tissues). This study was approved by the ethics committee of the First Affiliated Hospital of Xinxiang Medical University.

### Screening of Differentially Expressed Genes

Use the "limma" R package to analyze the differential expression of lncRNA and mRNA.[11] Differentially expressed genes were identified after the corrected standards of $P < .05$, and $|\log_2 FC| > 1.0$. The list of significantly upregulated or downregulated genes was saved as an XLS file. In addition, the "edgeR" package (version 3.34.0) and the "bioconductor" package (http://bioconductor.org) were used to identify differentially expressed lncRNAs (DELs) and mRNAs (DEMs) based on the TCGA dataset.

### Construction of Prognostic Feature Model

To determine the DELs that affect the prognosis of NSCLC patients, univariate and multivariate CPHR analyses of DELs were performed to select the DEL related to the prognosis of NSCLC and construct a risk linear model based on the TCGA NSCLC dataset.

First, univariate CPHR was performed to select DELs with a significant prognostic correlation.[12] The LASSO method was used to perform further functional analysis and develop the predictors of potential risk signatures. The coefficients and partial likelihood deviance were calculated using "glmnet" package (version 4.1-3) and "survival" package (version 3.2-13).

These genes were further studied by conducting multiple CPHR analyses to identify the candidate genes and construct a linear risk model. We used the following formula to calculate the risk score of NSCLC patients: Risk Score $= \Sigma\ \beta$lncRNAi $\times$ ExplncRNAi (where $\beta$ is the coefficient and Exp is the expression level of the lncRNA). In addition, according to the median risk score, patients were divided into high-risk and low-risk groups. The difference in survival time between the 2 groups was compared using Kaplan-Meier (K-M) curve analysis (http://kmplot.com/analysis/). The "timeROC" package of R software was used to predict the 3-year and 5-year survival rates and a time-dependent receiver operating characteristic (ROC) curve analysis was performed.[13] The area under the ROC curve (AUC) of sensitivity and specificity was used as an indicator of the predictive value. In addition, the Chi-square test was used to compare the results of the survival analysis of grade, age, gender, and pathological stage stratification between the 2 risk groups. A $P$-value of $<.05$ was used as the threshold in the analysis of prognostic characteristics. The same method was used in the test group to verify the reliability and validity of the model.

### Construction and Evaluation of Nomogram

We use R packages "hmisc" (version 4.6-0), "lattice" (version 0.20-44), "formula" (version 1.2-4), "foreign" (version 0.8-81), and "rms" (version 6.2-0) to construct a nomogram to predict the overall survival (OS) of NSCLC patients.[14] A calibration chart was created to evaluate the prediction accuracy of the nomogram. ROC curve analysis was used to evaluate the benefit of nomograms for predicting the survival of NSCLC patients during the clinical decision-making process.

### Construction of lncRNA and mRNA Co-Expression and Gene Enrichment

The R package "limma" was used to analyze the co-expression relationship between lncRNA and mRNA with independent prognostic significance. To obtain more accurate results, we only selected the data with |cor| of $>0.4$ and a $P$-value of $<.05$ for the next analysis. The intersection was then taken with the differentially expressed mRNAs to obtain the differentially co-expressed target genes.

We conducted a gene ontology (GO) term enrichment analysis to clarify the potential functions of lncRNAs in the nomogram. The R

package "clusterProfiler" (version 4.0.5) was used to perform a GO analysis to analyze the functions and pathways of the target genes.[15] In the enrichment analysis, a two-sided *P*-value of <.05 was considered significant. The differential expression of target genes in the NSCLC cohort was explored using the Gene Expression Profiling Interactive Analysis (GEPIA) database (http://http://gepia.cancer-pku.cn). We explored the correlation between target genes and prognosis in the K-M plotter database.

### *Relationship Between Immune Infiltrating Cells and Target Genes*

Data related to the target genes from NSCLC patients and immune infiltrating cells (CD8 + T cells, CD4 + T cells, macrophages, dendritic cells, and myeloid-derived suppressor cells [MDSCs]) were obtained from the Tumor Immunity Assessment Resource (TIMER) database (https://cistrome.shinyapps.io/timer/). The Spearman's test was used to measure the correlation between genes and the immune microenvironment. A two-tailed *P*-value of <.05 was considered significant.

## Results

### *Identification of Differentially Expressed Genes*

The RNASeq dataset of the training group was analyzed using the "limma" package. We identified 175 DELs (139 upregulated genes and 36 downregulated genes) and 2372 DEMs (1519 upregulated genes and 853 downregulated genes) in the training group (Figure 1).

### *Construction and Verification of the Prognostic Characteristics of lncRNA*

To identify the prognostic genes, 175 DELs in the training group were subjected to a univariate CPHR analysis, and 20 lncRNAs were significantly correlated with OS ($P < .05$) (Figure 2A). To determine the best prognostic genes, the LASSO-Cox regression algorithm was applied (Figure 2B and C) to 20 lncRNAs, and 8 lncRNAs were selected according to the minimum criteria to construct the risk characteristics. Multivariate CPHR analysis was used to evaluate the independent prognostic value of the 8 candidate prognostic genes (Figure 2D). The risk score was calculated as follows: [LINC00460 × (0.014444)] + [LINC00857 × (0.083816)] + [LINC01116 × (0.033358)] + [RP11-253E3.3 × (0.144383)] + [RP11-359E19.2 × (−0.037614)] + [RP11-10A14.5 × (0.013995)] + [RP11-114M1.1 × (−0.049818)] + [RP11-211G23.2 × (0.020163)]. LINC00460, LINC00857, LINC01116, and RP11-253E3.3 were selected as prognostic risk factors, while RP11359E19.2 was selected as a prognostic protective factor. According to the median risk score calculated using the abovementioned formula, the patients were divided into high-risk and low-risk groups. According to the Cox model, 5 candidate lncRNAs (LINC00460, LINC00857, LINC01116, RP11-253E3.3, and RP11-359E19.2) that retained their prognostic significance were selected as independent and significant prognostic factors.

Finally, 5 lncRNAs were selected to construct the model. The predictive ability of the 5 lncRNAs on OS is shown in Figure 3. The heat map of the prognostic marker scores of the training group, the test group, and the combination group (Figure 3A); the distribution of patients in the different risk groups (Figure 3B), and the OS status of the patients (Figure 3C) are shown in Figure 3. Results of the K-M analysis showed that the OS of the high-risk group was lower than that of the low-risk group ($P < .05$) (Figure 3D). In addition, we verified and analyzed the 5 lncRNAs signatures in the test and combined groups.

### *Predictive Risk Model Construction and Predictability Evaluation*

We constructed a prognostic nomogram using the "rms" package in the R software based on the patient's risk score to predict the 3-year and 5-year survival rates of NSCLC patients (Figure 4A). Each gene was used to obtain the corresponding score summary and total score of the individual samples. The sample with a higher score had a worse prognosis. The predicted AUC values of the 3-year and 5-year OS nomogram were 0.655 and 0.590, respectively (Figure 4D). A calibration curve was used to indicate the consistency between the predicted value of the actual observation and the predicted value of the nomogram. The calibration curves of the 3-year and 5-year survival rates were in good agreement with the nomogram (Figure 4B and C).

### *Construction and Evaluation of Predictive Nomogram*

As shown in Figure 5A, we constructed a new prognostic nomogram with the "rms" package based on the clinical characteristics and risk scores of lung cancer patients to predict the OS rate of NSCLC patients at 1, 3, and 5 years. For each factor (age, gender, clinical stage, and risk score), the corresponding score and the total score of the individual sample can be obtained. The predicted AUC value of the OS nomogram was 0.639, which was higher than that of the pathological stage (AUC = 0.612), age (AUC = 0.551), and gender (AUC = 0.457), indicating that the predictive ability of the nomogram constructed in this study was better than that of the pathological stage (Figure 5B). A calibration curve was used to indicate the consistency between the predicted value of the actual observation and the predicted value of the nomogram. The calibration curves of the 1-year, 3-year, and 5-year survival rates were in good agreement with the nomogram (Figure 5C and D).

The OS time of the >60-year-old group was not significantly different from that of the ≤60-year-old group ($P > .05$) (Figure 5E). The OS time of the high-risk group was significantly shorter than that of the low-risk group ($P < .001$) (Figure 5F). The OS time of pathological stage I was significantly better than that of groups II, III, and IV ($P < .001$) (Figure 5G). The results showed that the use of the 5 lncRNAs risk characteristics to predict the survival of NSCLC is better than that of clinical factors.

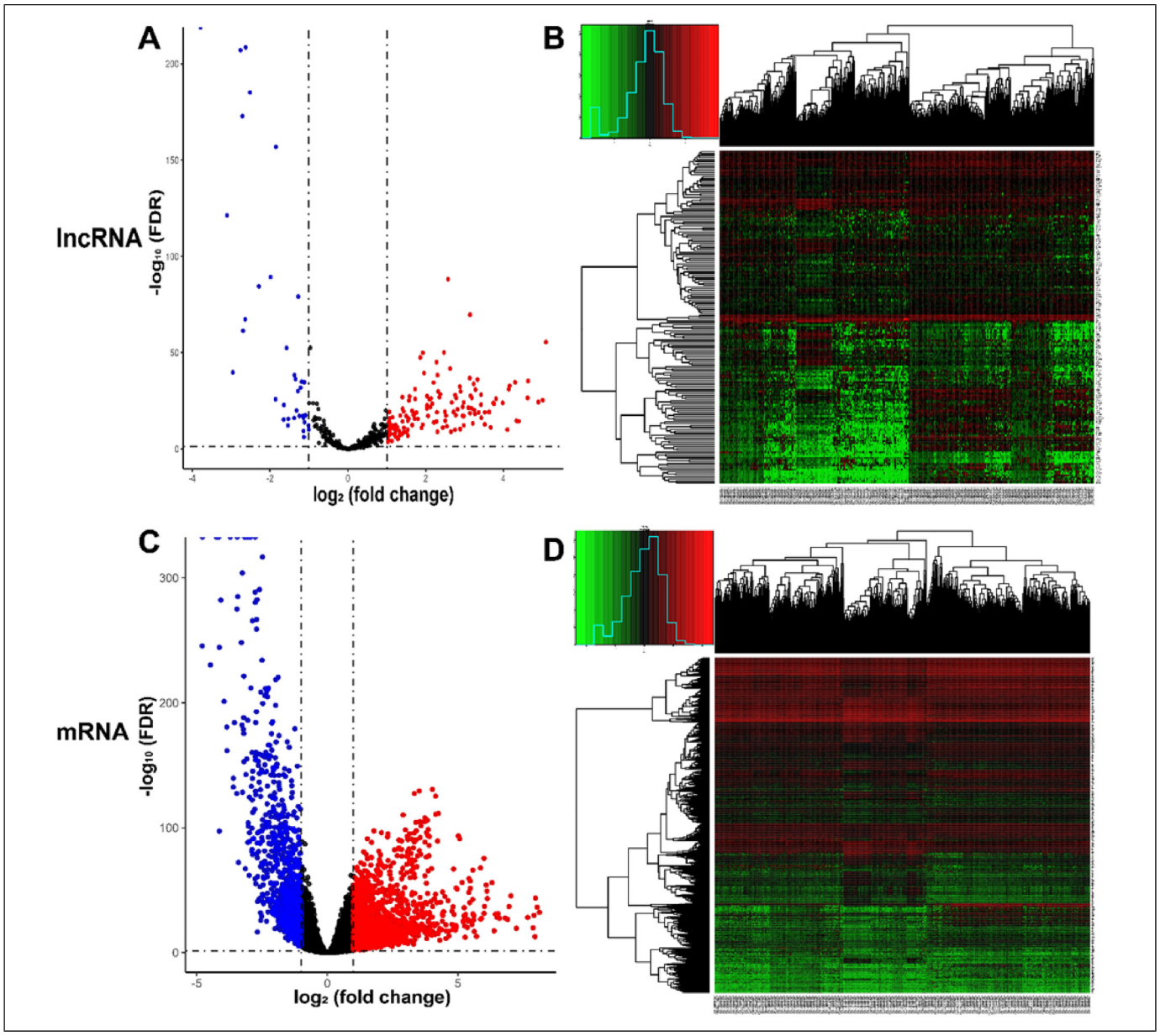


**Figure 1.** Identification of differentially expressed genes between long noncoding RNAs (lncRNA) and mRNA in the training group. (A and B) 175 differentially expressed lncRNAs (139 up-regulated genes and 36 down-regulated genes). (C and D) 2372 differentially expressed mRNAs (1519 up-regulated genes and 853 down-regulated genes).

Univariate and multivariate CPHR analyses of the clinical factors and risk scores were performed to evaluate whether the model was an independent predictor of NSCLC. The results showed that age, stage I, stage II, and risk score of the prognostic model can be used as independent prognostic indicators (Table 1).

## *Target Gene Prediction, Gene Enrichment Analysis, and Verification*

Use the R package "limma" to analyze the co-expression relationship between lncRNAs and mRNAs with independent prognostic significance. A total of 63 mRNAs co-expressed 5 lncRNAs, 2338 DEMs, and 34 mRNAs at the intersection of the 2 gene sets (Figure 6A). GO gene function enrichment analysis was performed and enriched in 5 terms: serine-type endopeptidase inhibitor activity, endopeptidase inhibitor activity, enzyme inhibitor activity, peptide inhibitor activity, and endopeptidase regulator activity (Figure 6B). Four mRNAs were enriched (CRIM1, SPINK1, WFDC3, and ITPRIP). After exploring the expression of these genes in the GEPIA database, we found that the expressions of CRIM1 and ITPRIP were significantly lower in lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) than in normal tissues ($P < .05$). The expressions of WFDC3 and

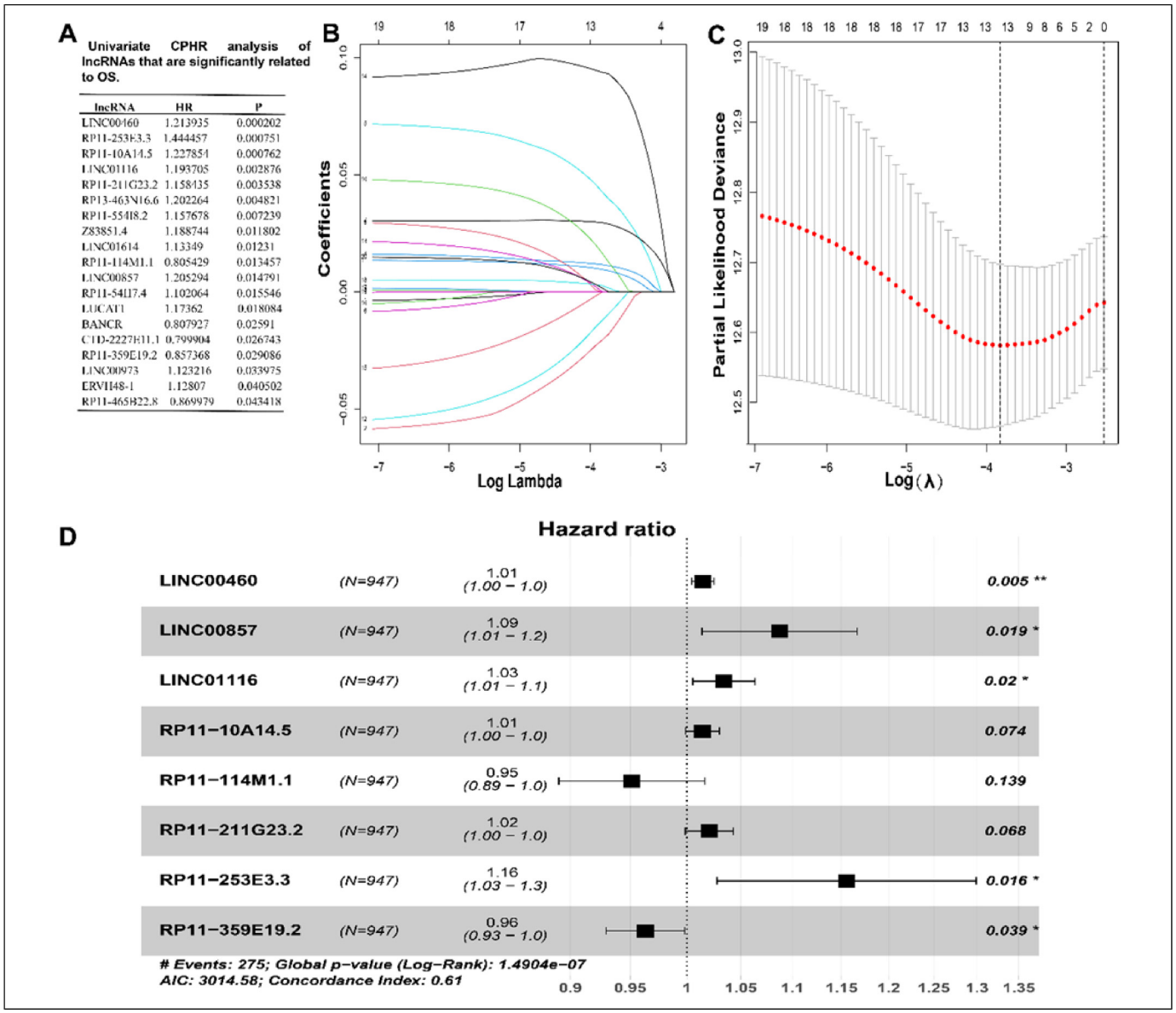


**Figure 2.** Identify lncRNAs related to survival and establish a risk scoring formula. (A) Univariate CPHR analysis of lncRNAs significantly related to OS. (B) LASSO coefficient curve of all predictors. (C) Verify the error rate of the predictor variables and calculate the best cut variables. (D) Identify and calculate the variables most relevant to survival.
Abbreviations: lncRNAs, long noncoding RNAs; OS, overall survival; LASSO, least absolute shrinkage and selection operator; CPHR, Cox proportional hazard regression.

SPINK1 were significantly higher in LUAD than in normal tissues ($P < .05$), but no significant difference was observed in the expression of LUSC (Figure 6C).

We verified the correlation between the expression levels of these 4 genes and survival in the external database K-M plotter. Among the 1925 lung cancer patients in the K-M plotter database, the 5-year OS rate of the high expression group of 3 genes (CRIM1, SPINK1, and WFDC3) was higher than that of the low expression group ($P < .05$) (Figure 6D). The 5-year OS rate of the ITPRIP high expression group was not significantly different from that of the low expression group ($P > .05$) (Figure 6D).

## *Relationship Between Target Genes and Immune Infiltration*

The correlation between these 3 genes (CRIM1, SPINK1, and WFDC3) and immune cells of lung cancer patients was evaluated using the TIMER website. The expression of CRIM1 was positively correlated with the degree of infiltration of CD8 + T cells, CD4 + T cells, macrophages, and dendritic cells, but negatively correlated with the degree of infiltration of MDSCs. The expression of SPINK1 was positively correlated with the degree of infiltration of CD4 + T cells but negatively correlated with the degree of infiltration of CD8 + T cells, macrophages,

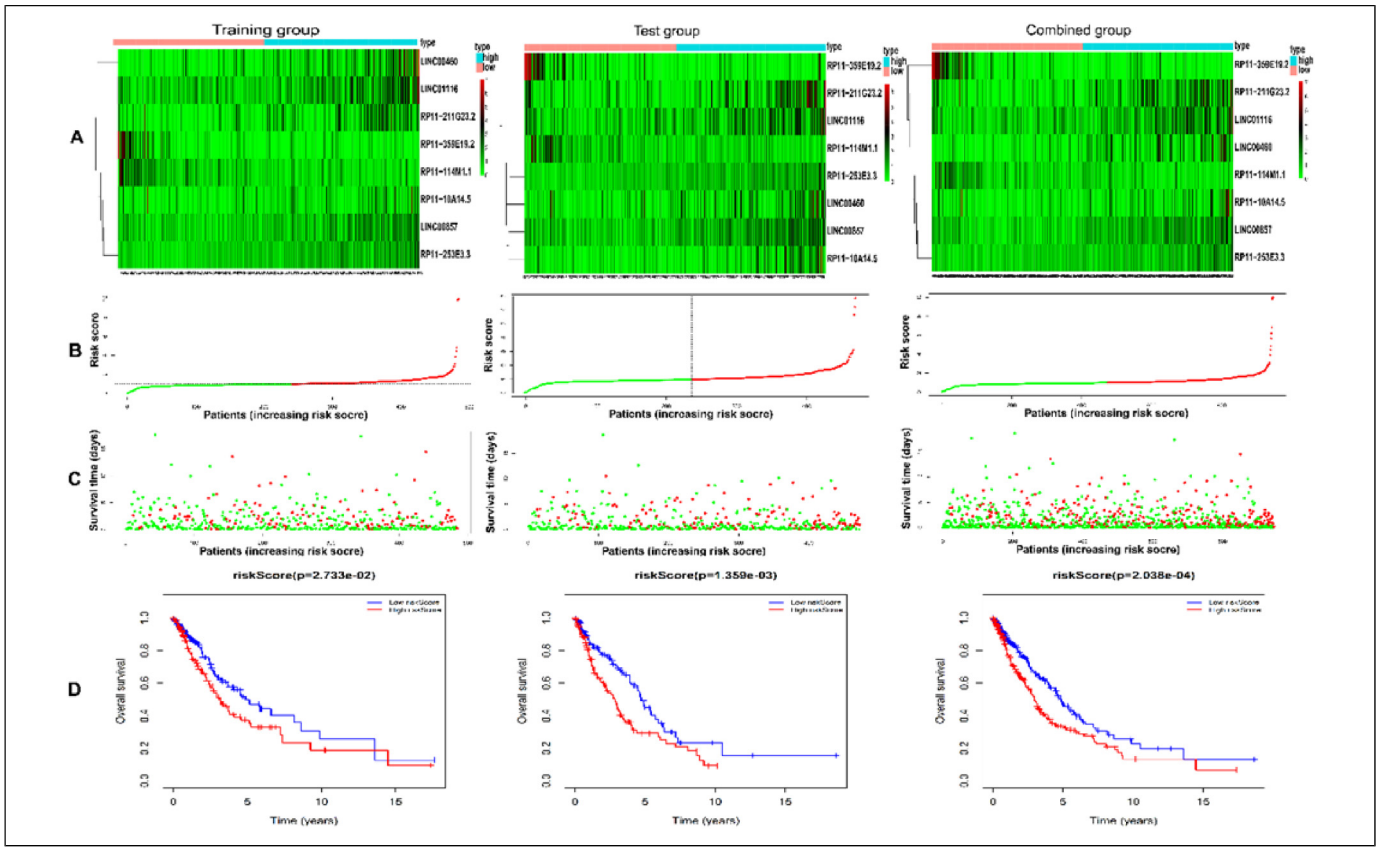


**Figure 3.** The OS risk score of the prognostic marker consisting of 5 lncRNAs in the 3 groups. (A) Heat map of the prognostic marker scores of the training group, test group and combination group. (B) The distribution of patients with different risk scores in the training group, test group and combination group. (C) OS status of patients with different risk scores in training group, test group and combination group. (D) K-M analysis was performed on patients in the high-risk group and the low-risk group in the training group, test group, and combination group.
Abbreviations: OS, overall survival; K-M, Kaplan-Meier; lncRNAs, long noncoding RNAs.

dendritic cells, and MDSCs. The expression of WFDC3 was positively correlated with the degree of infiltration of dendritic cells and MDSCs, but negatively correlated with the degree of infiltration of CD8 + T cells, CD4 + T cells, and macrophages ($P < .05$) (Figure 7). The above results indicate that these lncRNAs target genes may be related to the formation of the tumor immune microenvironment (TIME).

## Discussion

Nomograms have been widely used to evaluate the prognosis of tumors,[16] such as cervical cancer, renal cell carcinoma, lung cancer, and prostate cancer.[17–20] Its main advantage is that it is used to conduct a personalized risk assessment based on the characteristics of the patient or disease. In this study, we successfully constructed a survival nomogram based on the lncRNAs and patients' clinical characteristics of NSCLC. We combined age, gender, AJCC staging, and 5 lncRNAs in a risk formula and quantified the OS probability of each variable to detect their relationship with OS. Based on the total risk points in the nomogram, we calculated the survival probability of patients at 1, 3, or 5 years, and its predictive performance was better than that of traditional parameters and AJCC staging. In addition, both doctors and patients will be able to use the scoring system to understand personalized survival expectations. This prognostic model can be used as a tool for studies and clinical decision-making, including patient stratification and treatment recommendations. In addition, with the improvement of the treatment level of lung cancer, more and more treatment methods are applied in the clinic to improve the survival rate of patients. The study reported that gefitinib combined with pemetrexed and carboplatin chemotherapy significantly prolonged the survival time of patients with EGFR-mutant NSCLC.[21] Adding pembrolizumab to standard chemotherapy can significantly prolong survival.[22] Therefore, according to the nomogram, for patients with a shorter survival period, a combination of multiple treatment modes, including targeted therapy or immunotherapy, may be an option.

In addition, results of the functional analysis showed that 5 lncRNAs were also involved in several cancer pathways. LINC00460 promotes the entry of PRDX1 into the nucleus and promotes EMT in the head and neck squamous cell carcinoma (HNSCC) cells. It is a promising candidate for predicting the patient's prognosis and a potential target for HNSCC treatment.[23] LINC00857 mainly regulates the proliferation, glycolysis, and apoptosis of LUAD cells by targeting the miR-1179/

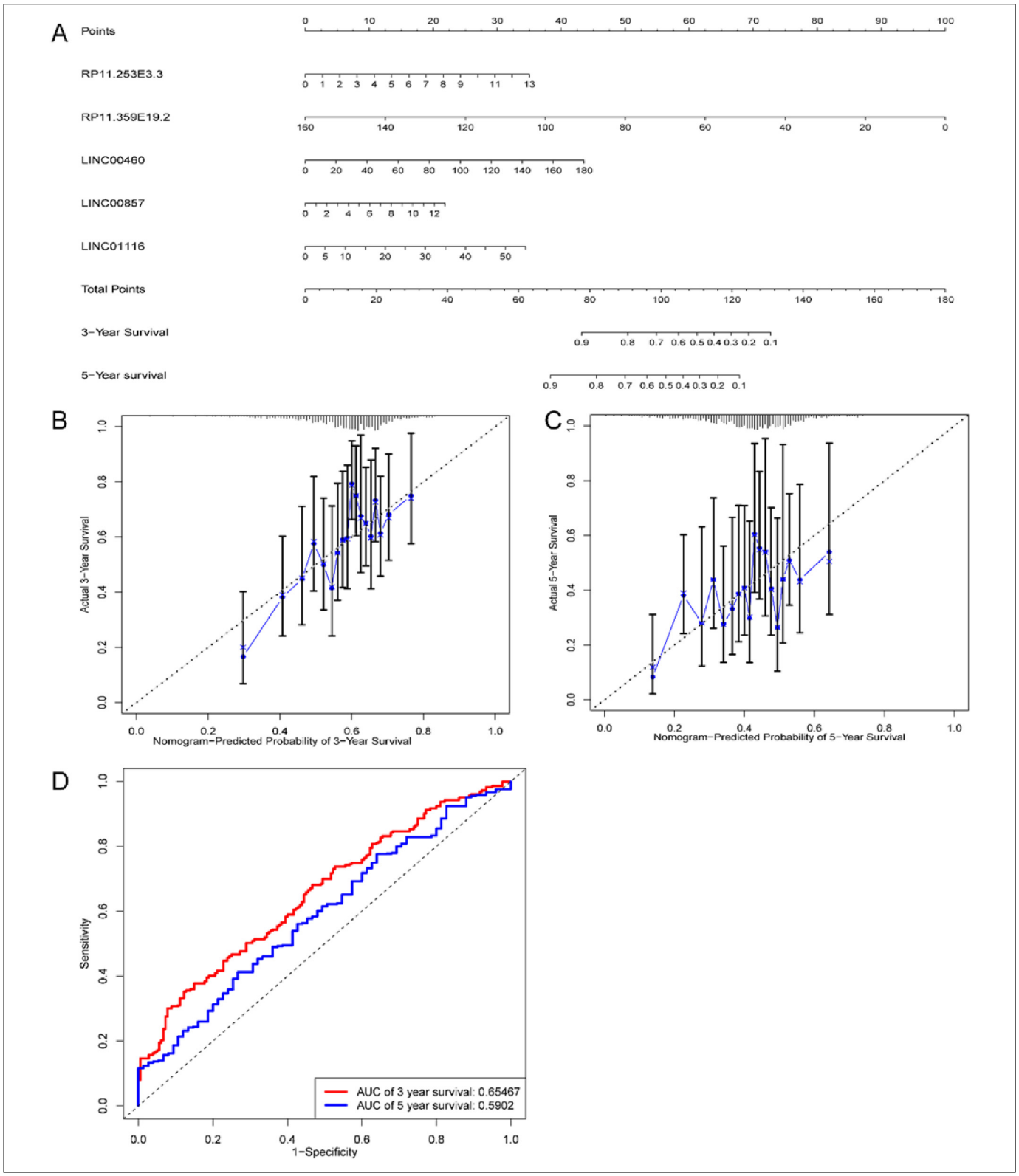


**Figure 4.** Construction and evaluation of nomogram. (A) Nomograph predicts OS in patients with NSCLC. (B and C) The calibration curve of nomogram to evaluate the prediction effect of 3 and 5 years in the NSCLC. (D) ROC curve analysis of OS prediction formula for NSCLC.
Abbreviations: NSCLC, non-small cell lung cancer; OS, overall survival; ROC, receiver operating characteristic.

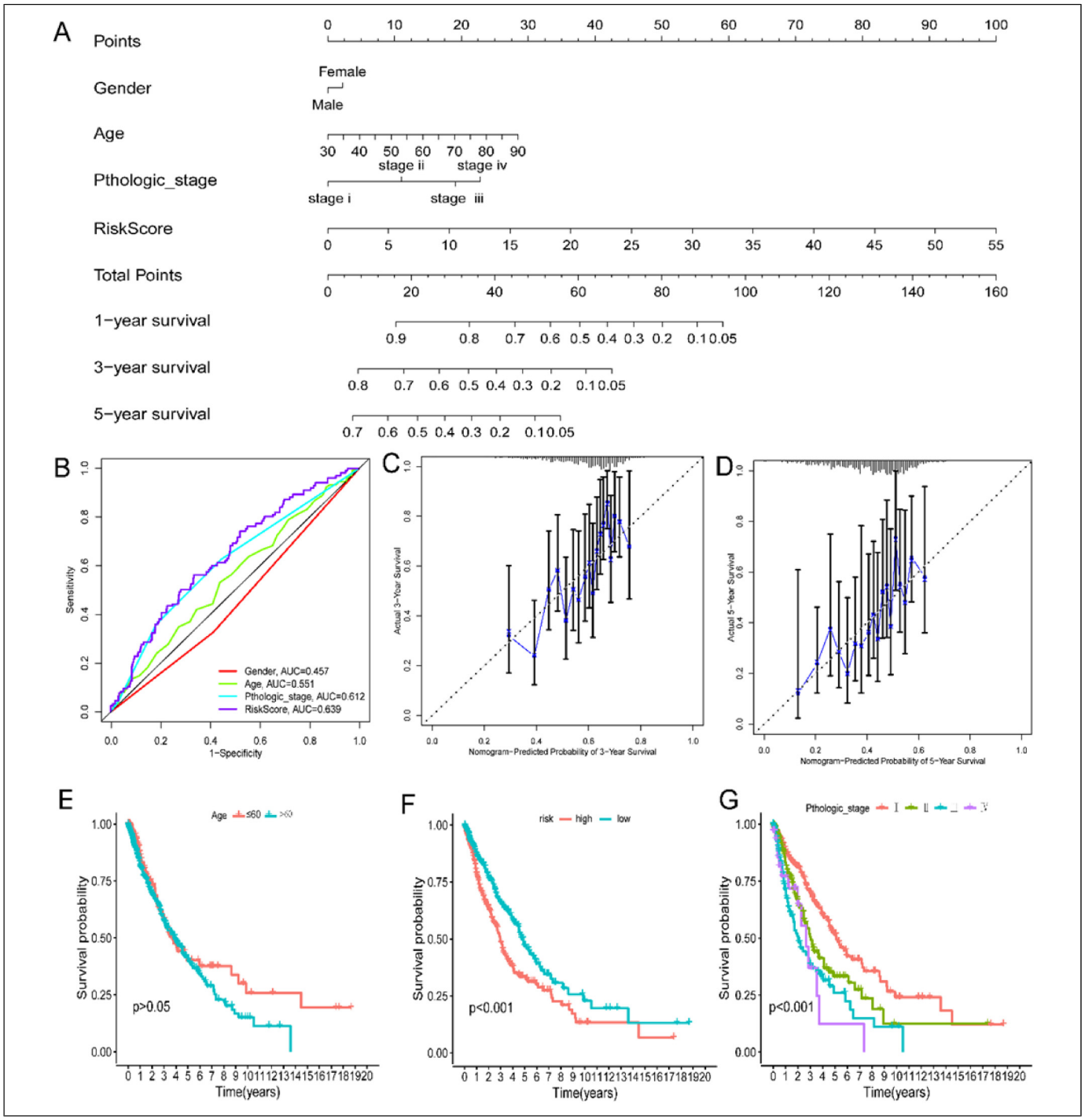


**Figure 5.** The nomogram is used to predict the OS prognosis of NSCLC patients at 1, 3, and 5 years. (A) A nomogram based on characteristics and clinical information. (B) ROC analysis of nomogram, gender, age and pathological stage predicting OS. (C and D) Calibration curve. (E-G) K-M analysis of age, risk score, and pathological stage.
Abbreviations: NSCLC, non-small cell lung cancer; OS, overall survival; K-M, Kaplan-Meier; ROC, receiver operating characteristic.

SPAG5 axis, providing a potential target for the clinical treatment of LUAD patients.[24] The dysregulation of LINC01116 expression leads to the resistance of LUAD to cisplatin through the epithelial-mesenchymal transition process, which may be a new predictor of cisplatin adverse reactions.[25] Therefore, lncRNAs in the nomogram can not only be used as biomarkers for predicting prognosis, but also play a regulatory role in the occurrence and development of tumors and can be used as potential therapeutic targets for NSCLC.

In addition, we explored the relationship between target genes and immune infiltrating cells. It was found that these

**Table 1.** Univariate and Multivariate CPHR Analysis of Survival-Related Risk Factors.

| | Univariate analysis | | | | Multivariate analysis | | | |
|---|---|---|---|---|---|---|---|---|
| Variables | HR | HR.95L | HR.95H | *P*-value | HR | HR.95L | HR.95H | *P*-value |
| Gender | 1.007 | 0.789 | 1.286 | .949 | 1.098 | 0.858 | 1.407 | .454 |
| Age | 1.015 | 1.002 | 1.029 | .019 | 1.020 | 1.006 | 1.034 | .003 |
| Stage I | 1.561 | 1.168 | 2.088 | .002 | 0.442 | 0.326 | 0.599 | <.001 |
| Stage II | 2.409 | 1.378 | 4.210 | .002 | 0.709 | 0.511 | 0.984 | .040 |
| Stage IV | 2.278 | 1.689 | 3.073 | <.001 | 1.173 | 0.657 | 2.094 | .588 |
| RiskScore | 1.092 | 1.063 | 1.122 | <.001 | 1.080 | 1.050 | 1.111 | <.001 |

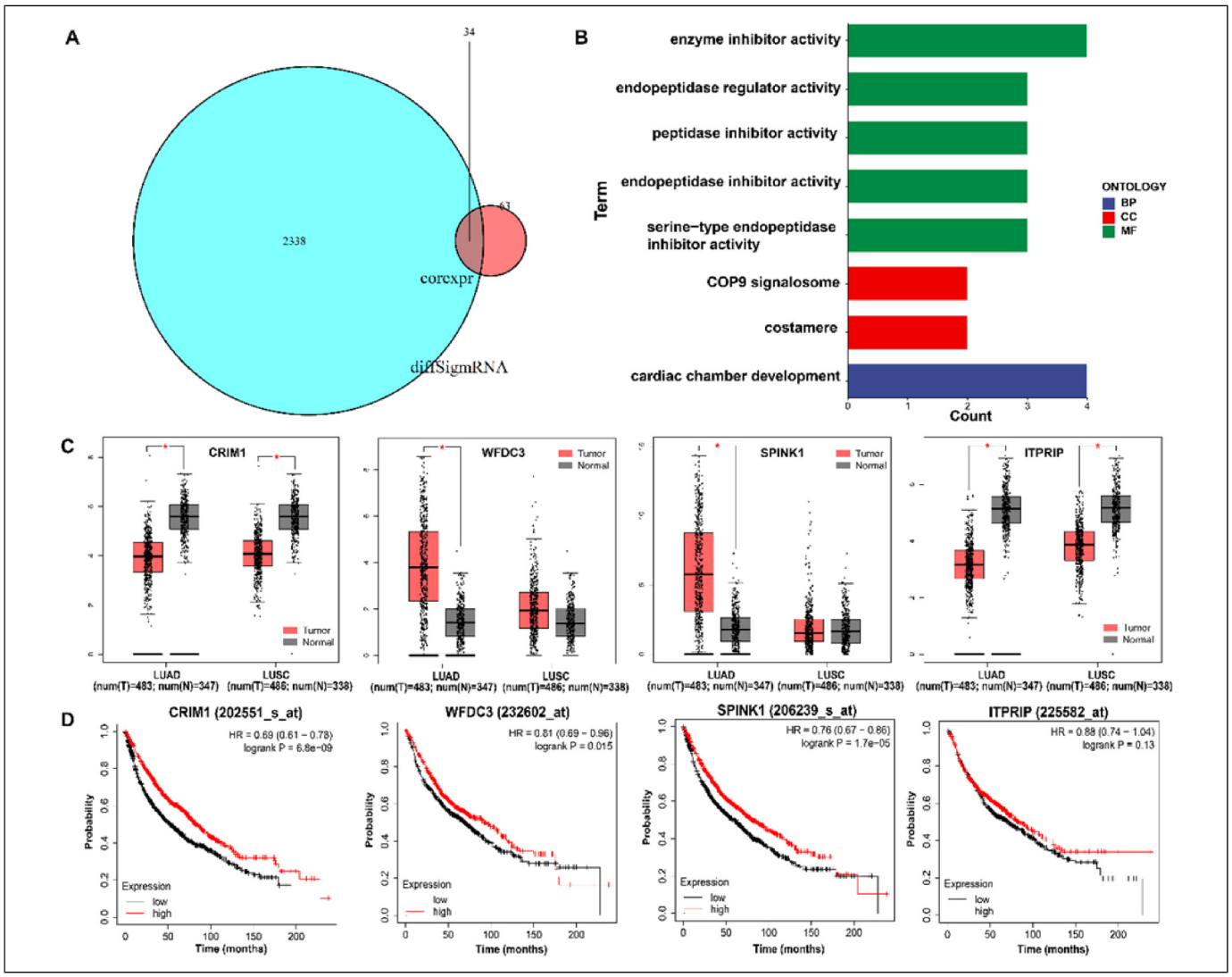


**Figure 6.** The prediction and functional enrichment analysis of target genes are correlated with the prognosis of these genes in the K-M plotter database. (A) The intersection of differentially expressed mRNA and co-expressed genes. (B) GO enrichment analysis of target gene function. (C) The expression of the target gene in the GEPIA database. (D) The prognostic correlation of the target gene in the cohort in the K-M plotter database. *Represents a statistically significant difference ($P < .05$).

Abbreviations: GO, gene ontology; GEPIA, Gene Expression Profiling Interactive Analysis; K-M, Kaplan-Meier.

target genes may be related to the formation of TIME. Moreover, these target genes are involved in the occurrence and development of cancer. CRIM1 plays a role in cancer cells by enhancing the migration and adhesion of cancer cells and increasing the expression of N-CAD and E-CAD.[26] SPINK1 promotes the migration and invasion of LUAD cells by upregulating

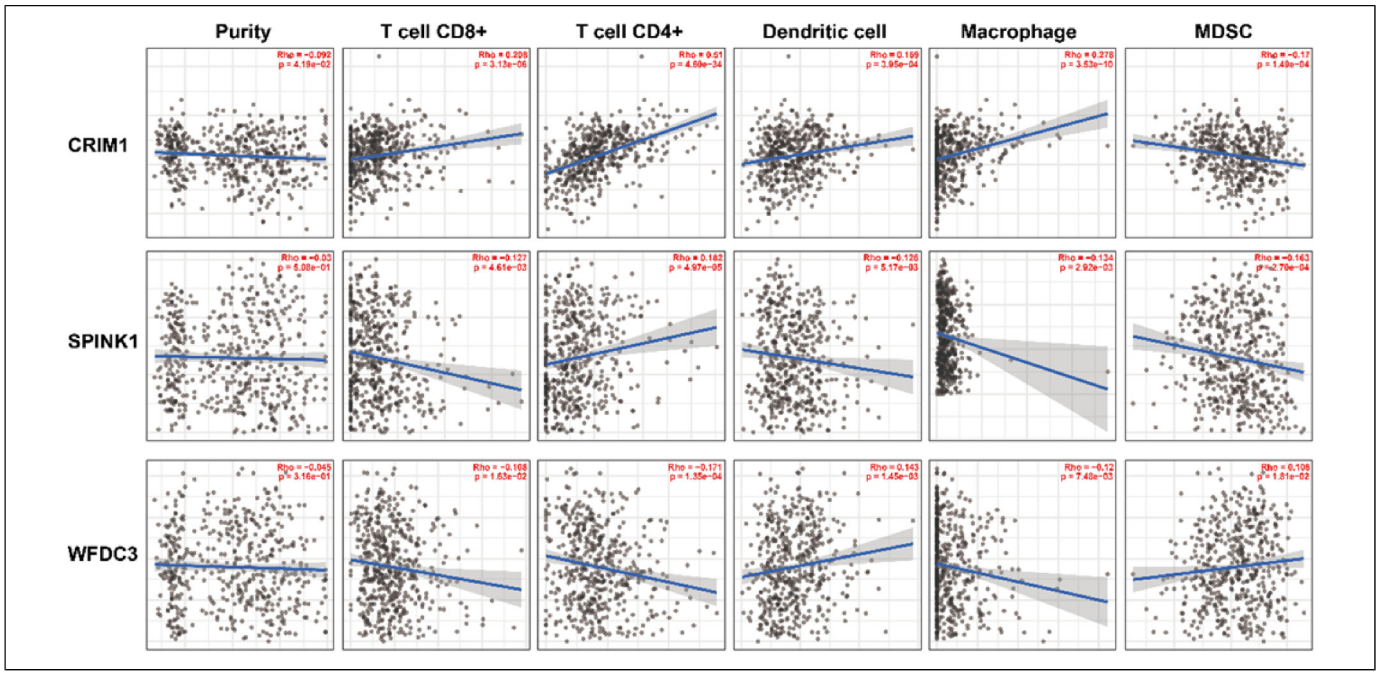


**Figure 7.** The correlation between immune cell infiltration and the expression of genes CRIM1, SPINK1, and WFDC3.

matrix metalloproteinase 12 (MMP12), which may be a biomarker for MMP12 to promote LUAD progression.[27]

Although our lncRNA-related nomogram is effective in predicting the survival of NSCLC, it also has some limitations. First, this was a retrospective study. It used a large sample of 1145 patients, and the results were reliable. However, our data lacked detailed clinical information, such as chemotherapy and radiotherapy history, smoking history, and patient medical history. Therefore, when our results are applied in clinical practice, further clinical studies are needed. Finally, we may overlook some valuable information when constructing survival-related lncRNA nomograms. In summary, despite these limitations, we believe that our unremitting efforts will eventually establish an ideal prognostic model in clinical practice.

## Conclusion

In short, the nomogram based on 5 lncRNAs can effectively predict the OS rate of NSCLC and may guide the formulation of treatment plans for NSCLC.

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### Data Availability

The RNASeq data were deposited in the TCGA database.

### Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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