

# Construction of a Novel Prognostic Immune-Related LncRNA Risk Model for Gastric Cancer

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## Research

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# Abstract

## Background and Aim

Studies have recently shown that immune-related lncRNAs play a vital role in the occurrence and development of human malignancies. However, the study in gastric cancer (GC) remains unclear. Here, we aimed to identify immune-related lncRNAs and construct a risk score model to predict the prognosis of GC patients.

## Methods:

RNA expression data and clinical characteristics of GC were download from The Cancer Genome Atlas (TCGA) database. Immune genes were obtained from the Molecular Signatures Database (MSigDB). Immune-related lncRNAs were acquired by correlation coefficient between the immune genes and lncRNAs using "*limma R*" package and Cytoscape 3.6.1. The risk score model was constructed by univariate and multivariate Cox regression, and its prognostic value was verified in TCGA cohort.

## Results:

A total of 146 immune-related lncRNAs were obtained compared 375 GC samples with 32 normal samples. A five immune-related lncRNA (AP001528.2, LINC02542, LINC02526, PVT1 and LINC01094) risk score model was constructed to predict prognosis of GC patients by Cox regression analysis. Moreover, GC patients with higher risk score had a poorer overall survival than that with lower risk score ( $P < 0.001$ ). Furthermore, ROC analysis revealed that the risk score model had the best predictive effect compared with clinicopathological features during 5 years followed-up (AUC = 0.679). Indeed, PCA analysis showed that the patients in the low- and high- group were significantly distinguished in different directions based on the risk score model.

## Conclusion:

This study indicated that a five immune-related lncRNA risk score model possessed a satisfactory predictive prognosis, which might be potential prognostic biomarkers and immunotherapy targets for GC patients in future.

## Introduction

Gastric cancer (GC) is the fourth commonly diagnosed cancers, and the second leading cause of cancer-related deaths worldwide (Sung et al., 2021). In 2020, the number of new cases of GC are as many as 1,033,701 new cases, and the case of GC related death as many as 782,685, which contribute to a dramatic impact on global health (Sung et al., 2021). Although the combination treatment of surgery, chemotherapy, radiotherapy and immunotherapy has improved survival in GC patients, the survival rates of GC patients remain unsatisfactory (Akshatha et al., 2021). Therefore, it is crucial to explore the

molecular mechanism of GC to develop new diagnostic and prognostic biomarkers to improve clinical outcomes.

Long non-coding RNAs (lncRNAs) are defined as a class of non-protein-coding RNA transcripts, and more than 200 nucleotides in length (Geisler and Coller, 2013). LncRNAs account for a large part of the human genome, and are once considered transcriptional noise (Derrien et al., 2012). However, increasing studies recently reported that lncRNAs played vital role in transcriptional, post-transcriptional, and epigenetic levels (Lee, 2012; Ponting et al., 2009). Moreover, Dysregulation and mutation of lncRNAs is closely associated with the occurrence and development of human disease, including human malignancies (Fatica and Bozzoni, 2014; Gibb et al., 2011; Mercer et al., 2009). For instance, Xu M *et al.* reported that linc00941 was up-regulated in pancreatic ductal adenocarcinoma (PDAC), and contributed to poor prognosis for the patients with PDAC (Xu et al., 2021a). Mechanistically, linc00941 promoted PDAC cancer cell growth by activating the Hippo pathway and enhancing aerobic glycolysis (Xu et al., 2021a). Xu ZL *et al.* found that lncRNA PSMA3-AS1 promoted ovarian cancer (OC) cell proliferation, migration, invasion, and xenograft tumor growth through activating the PI3K/Akt pathway (Xu et al., 2021b). O'Brien SJ *et al.* discovered that lncRNA H19 expression was associated with advanced stage of colon cancer, and H19 over-expression was related with reduced recurrence-free survival of colon cancer (O'Brien et al., 2021). Notably, lncRNAs play a crucial role in the occurrence and development of human malignancies.

In addition, lncRNAs have been shown important regulatory effects of immune system in human malignancies, including immune activation, immune escape, immune surveillance, and immune infiltration (Atianand and Fitzgerald, 2014; Chen et al., 2017). For instance, Wang CJ *et al.* reported that lncRNA overexpression contributed to the gastric cancer (GC) cells immune escape, then promoted GC cells proliferation and migration, and inhibited apoptosis by up-regulating the expression of PDL1 (Wang et al., 2019). LncRNA SOX2-OT promoted the malignant progression and immune escape of non-small cell lung cancer (NSCLC) cells by up-regulating the expression of PD-L1 and activating the mTOR signaling pathway (Chen et al., 2021c). Furthermore, many of prognostic value of the immune-related lncRNAs were determined in human malignancies (Chen et al., 2021b; Liu et al., 2021; Qi et al., 2021). However, prognostic signatures of the immune-related lncRNAs for GC remained unclear.

In present study, we constructed a novel prognostic model according to comprehensive analysis of the immune-related lncRNA based on the data of 375 GC samples and 32 normal samples, which were downloaded from The Cancer Genome Atlas (TCGA). And, we identified 5 immune-related lncRNA associated with the prognosis of GC patients, which might be a potential prognostic markers and immune therapeutic targets for GC patients in future.

## Methods

### Data download

The RNA-seq FPKM (reads per kilobase per million) data of 375 GC samples and 32 normal samples, and corresponding clinical characteristics were downloaded from TCGA (<https://portal.gdc.cancer.gov>). The patients with a survival time less than 30 days were excluded. The immune-related genes list was downloaded from the Molecular Signature Database (MSigDB).

### **Identification of immune-related differentially expressed lncRNAs**

The differentially expressed lncRNAs were obtained compared the GC samples with normal samples using the *limma* package in R 4.0 software based on the criteria of  $|\log_2 \text{fold change (FC)}| \geq 1$  and false discovery rate (FDR) < 0.05. We calculated the correlation coefficient between the immune-related genes and lncRNAs to identify immune-related lncRNAs according to the criteria of correlation-Filter > 0.6 and p value < 0.05.

### **A prognosis model construction**

The prognosis-related immune-related lncRNAs were identified through univariate and multivariate Cox regression analyses using the *survival* package in R software. Subsequently, a risk score model was constructed based on the expression quantity and coefficients of prognosis-related immune-related lncRNAs. The risk score was calculated for each GC patient as follows:  $\text{Risk scores} = \beta_1 * \text{Exp}_1 + \beta_2 * \text{Exp}_2 + \beta_i * \text{Exp}_i$ , where  $\beta$  represented the coefficient score,  $\text{Exp}$  represented the gene expression, and  $i$  represented  $i^{\text{th}}$  prognosis-related immune-related lncRNAs.

### **Prognostic and independent analysis**

A Kaplan-Meier survival curve was performed to evaluate the survival difference compared the low-risk group with the high-risk group based on the median risk score using *survival* package in R software. Subsequently, univariate and multivariate independence analysis was applied to explore the independence of the risk score model comparing with clinicopathological features (including age, gender, grade, stage, T stage, N stage and M stage). Moreover, the receiver operating characteristic (ROC) curve analysis were performed, and the values of the area under the curve (AUC) were calculated to evaluate the specificity and sensitivity of the risk score model and the clinicopathological features using *survival ROC* package.

### **Immune status analysis**

Principal components analysis (PCA) was performed to discriminate the different immune statuses of GC patients according to the whole gene expression profiles, all immune-related lncRNAs and the risk score model through *limma* package and *scatterplot3d* package.

### **Statistical analysis**

All analyses were performed by available packages in R software 4.1.0. Values of  $p < 0.05$  were considered statistical significance.

# Results

## Identification of immune-related lncRNA

The flow diagram of this study was shown in the Figure 1. A total of 14,142 lncRNAs were downloaded compared 375 GC samples with 32 normal samples from the TCGA database. Meanwhile, 331 immune genes were obtained from MSigDB. Immune-related lncRNAs were identified by constructing the co-expression network between lncRNAs and the immune genes using *limma* package in R and Cytoscape 3.6.1 (Figure 2). Therefore, 146 immune-related lncRNAs were obtained in GC as the criteria of correlation-Filter > 0.6 and p value < 0.05.

## Construction of the prognostic model

Univariable and multivariable Cox regression was performed to determine the prognosis-associated immune-related lncRNA from these 146 lncRNAs in GC. As Figure 3A showed, 8 prognosis-associated immune-related lncRNAs (SERPINB9P1, AP002954.1, MAGI2-AS3, AP001528.2, LINC02542, LINC02526, PVT1 and LINC01094) were obtained by univariable Cox regression. Indeed, 5 immune-related lncRNAs (AP001528.2, LINC02542, LINC02526, PVT1 and LINC01094) can act as independent prognosis-associated predictors for GC patients by multivariable Cox regression (Figure 3B). Therefore, the risk score of each GC patient was calculated as follows:  $Risk\ scores = 0.323 * \text{expression quantity of AP001528.2} + 0.186 * \text{expression quantity of LINC02542} + 0.367 * \text{expression quantity of LINC02526} + (-0.369) * \text{expression quantity of PVT1} + 0.439 * \text{expression quantity of LINC01094}$ .

## Prognosis analysis of the risk score model

Based on the above risk score model, there were 167 low-risk patients and 167 high-risk patients, respectively, based on median risk score. Survival analysis showed that the patients with higher risk score had a poorer overall survival (OS) compared with that with lower risk score (Figure 4A). Moreover, the distribution of risk score curve and the survival status ranked by the risk score, and revealed that the high-risk patient had a relatively poor clinical outcome (Figure 4B).

## The independence prognostic analysis of the risk score model

We further assessed that whether the five immune-related lncRNAs risk score model possessed an independent prognostic value compared with other clinical risk factors such as age, gender, grade, stage, T stage, N stage, and M stage through univariate and multivariate Cox regression analyses. The results showed that the risk score model was an independent prognostic factor for GC patients ( $P < 0.001$ ) (Figure 5A, Figure 5B). Furthermore, ROC analysis revealed that the AUC value of the five immune-related lncRNAs risk score model was 0.679, which has the best predictive effect compared with age, gender, grade, T stage, N stage and M stage for GC patients after 5 years followed-up (Figure 5C).

## The correlation between the five immune-related lncRNAs and clinicopathological characteristics

We estimated the correlation between the five immune-related lncRNAs and clinicopathological characteristics (T stage, N stage and M stage) for GC patients by using chi-square test. We found that the expression of AP001528.2, PVT1 and LINC01094 was significantly associated with the depth of GC invasion (Figure 6A). Moreover, the expression of LINC02542 was significantly correlated with the distant metastasis (Figure 6B). However, the expression of these 5 immune-related lncRNA was not significantly related with lymph node metastasis (Figure 6C).

### **The immune state of different risk groups**

Principal component analysis (PCA) was performed to distribute the low- and high- group using the total gene expression, all immune-related lncRNAs and 5 immune-related lncRNAs risk score model in GC. The results revealed that the low- and high- group was not differentiated by immune status of GC patients based on the total gene expression and all immune-related lncRNAs (Figure 7A and Figure 7B). However, the patients in the low- and high- group were significantly spread in different directions based on 5 immune-related lncRNAs risk score model (Figure 7C).

## **Discussion**

GC is a multifactorial disease with heterogeneity, and can be classified clinically as early or advanced GC (Waldum and Fossmark, 2018). Several risk factors are involved in the occurrence and development of GC, such as environmental factors, ethnicity, dietary habits, and host genetic factors (Poorolajal et al., 2020; Rawla and Barsouk, 2019). Recently, a lot of studies have reported that lncRNAs play a vital role in the occurrence and development of GC due to the progression of bioinformatics analysis and third-generation sequencing technology (Jin, 2021; Wang et al., 2021; Yousefi et al., 2021). Moreover, increased studies have found that lncRNAs are also involved in the regulation of immune system in GC (Nie et al., 2020; Sun et al., 2021). However, the underlying mechanisms of immune related lncRNAs associated with the occurrence and development of GC remain undetermined. Therefore, a comprehensive function analysis of immune-related lncRNAs will help us better investigate their role, and develop prognostic signatures and immune therapeutic targets for GC patients.

In present study, 146 immune-related lncRNAs were obtained by Pearson correlation analysis between the differentially expressed lncRNAs and the immune genes from MSigDB in GC. Then, 5 immune-related lncRNAs (AP001528.2, LINC02542, LINC02526, PVT1 and LINC01094) were identified as prognosis-related lncRNAs by using univariate and multivariate Cox regression analysis. Subsequently, a risk score model was constructed based on these 5 immune-related lncRNAs, which was significantly associated with OS by survival analysis and had a satisfactory predictive value of 5-year survival for GC patients by ROC analysis. Moreover, the expression of AP001528.2, PVT1, LINC01094, and LINC02542 was significantly correlated with the depth of invasion and the distant metastasis in GC. In addition, the 5 immune-related lncRNAs risk score model can clearly distinguish the high- or low- risk group compared with the total gene expression or all immune-related lncRNAs through PCA analysis. Therefore, the present study proved that the 5 immune-related lncRNAs risk score model were novel biomarkers, and had

a satisfactory predictive prognosis of GC patients. Furthermore, the 5 immune-related lncRNAs might be new immune therapeutic targets for GC patients in future.

Recently, several studies have discovered that immune-related lncRNAs are identified and have satisfactory capacity predict the prognosis of human malignancies. For instance, a seven immune-related lncRNAs prediction model was constructed in lung adenocarcinoma (LUAD), which had a satisfactorily predictive efficiency and guided the personalized treatment for LUAD patients(Li et al., 2020). Zhao K *et al.* have discovered that the signature of six immune-related lncRNAs are identified in bladder cancer, and closely associate with the prognosis for the patients with bladder cancer(Zhao et al., 2021). Therefore, these six immune-related lncRNAs might be immunotherapy targets for bladder cancer(Zhao et al., 2021). A nine immune-related lncRNAs prediction model was constructed in colon cancer, and closely related with overall survival for the patients with colon cancer, which could be defined as potential biomarkers affecting the prognosis of colon cancer(Lin et al., 2020). In present study, we firstly identified five immune-related lncRNAs (AP001528.2, LINC02542, LINC02526, PVT1 and LINC01094) in GC, and constructed a risk score model based on these immune-related lncRNAs. Furthermore, we found that GC patients with a higher risk score had a poorer overall survival than that with a lower risk score. Therefore, these five immune-related lncRNAs might be novel biomarkers to predict the prognosis, and immunotherapy targets for GC patients.

lncRNA PVT1 was found to be dysregulated in several human malignancies. For instance, PVT1 expression was significantly up-regulated in pancreatic ductal adenocarcinoma (PDAC) tissues compared with adjacent normal tissues. Meanwhile, patients with higher PVT1 expression level associated with shorter overall survival compared to those with lower PVT1 expression level(Huang et al., 2015). Similarly, the expression of PVT1 was higher in colon cancer tissues than that of adjacent tissues, and the higher PVT1 expression contributed to shorter disease-free survival and overall survival for the patients with colon cancer(Fan et al., 2018). In addition, PVT1 expression was dramatically increased in gastric cancer tissues compared with that in the normal control, and increased PVT1 expression resulted in poor overall survival and disease-free survival for the patients with gastric cancer(Yuan et al., 2016). However, we discovered that the overexpression of PVT1 was associated with a good prognosis for GC patients in present study. Therefore, it should be further verified potentially significant clinical implications of the PVT1 for GC patients in future.

Chen HY *et al.* have reported that the expression level of LINC01094 was prominently increased in ovarian cancer tissues compared with adjacent normal tissues, and LINC01094 overexpression promoted the viability, migration and invasion of ovarian cancer cells(Chen et al., 2021a). Consistently, LINC01094 was highly expressed in the clear cell renal cell carcinoma compared with adjacent normal tissues, and the LINC01094 overexpression was associated with a poor prognosis for the patients with clear cell renal cell carcinoma(Xu et al., 2020). In present study, we firstly found that the overexpression of LINC01094 was associated with a poor prognosis for GC patients.

Obviously, there were some shortcomings in present study. First, all the data were obtained based on online databases. Therefore, further studies should be performed to verify our findings. Second, we firstly discovered that the overexpression of AP001528.2, LINC02542 and LINC02526 was associated with a poor prognosis for GC patients. However, there was no report of these three immune-related lncRNAs involved in other human malignancies, nowadays. Therefore, the biological function and mechanisms of these immune-related lncRNA required further exploration in human malignancies. Third, it is important to explore the underlying mechanism of these five immune-related lncRNA involved in the occurrence and development of GC *in vivo* and *in vitro* in future.

In conclusion, we constructed a novel five immune-related lncRNAs risk score model which had a satisfactory predictive prognostic value for GC patients. Therefore, the five immune-related lncRNAs risk score model might be potential prognostic biomarkers and immunotherapy targets for GC patients in future.

## Abbreviations

TCGA: The Cancer Genome Atlas; MSigDB: Molecular Signatures Database; GC: Gastric cancer; lncRNAs: Long non-coding RNAs; FDR: false discovery rate; FC: fold change; PCA: Principal components analysis.

## Declarations

### Acknowledgements

None.

### Authors' contributions

G-H Y designed the study, searched databases, performed data analysis, and wrote the manuscript.

### Funding

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### Availability of data and materials

RNA sequencing data of 375 GC samples and 32 normal samples, and corresponding clinical characteristics were downloaded from TCGA (<https://portal.gdc.cancer.gov>).

### Declarations Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

## Competing interests

There were no competing interests.

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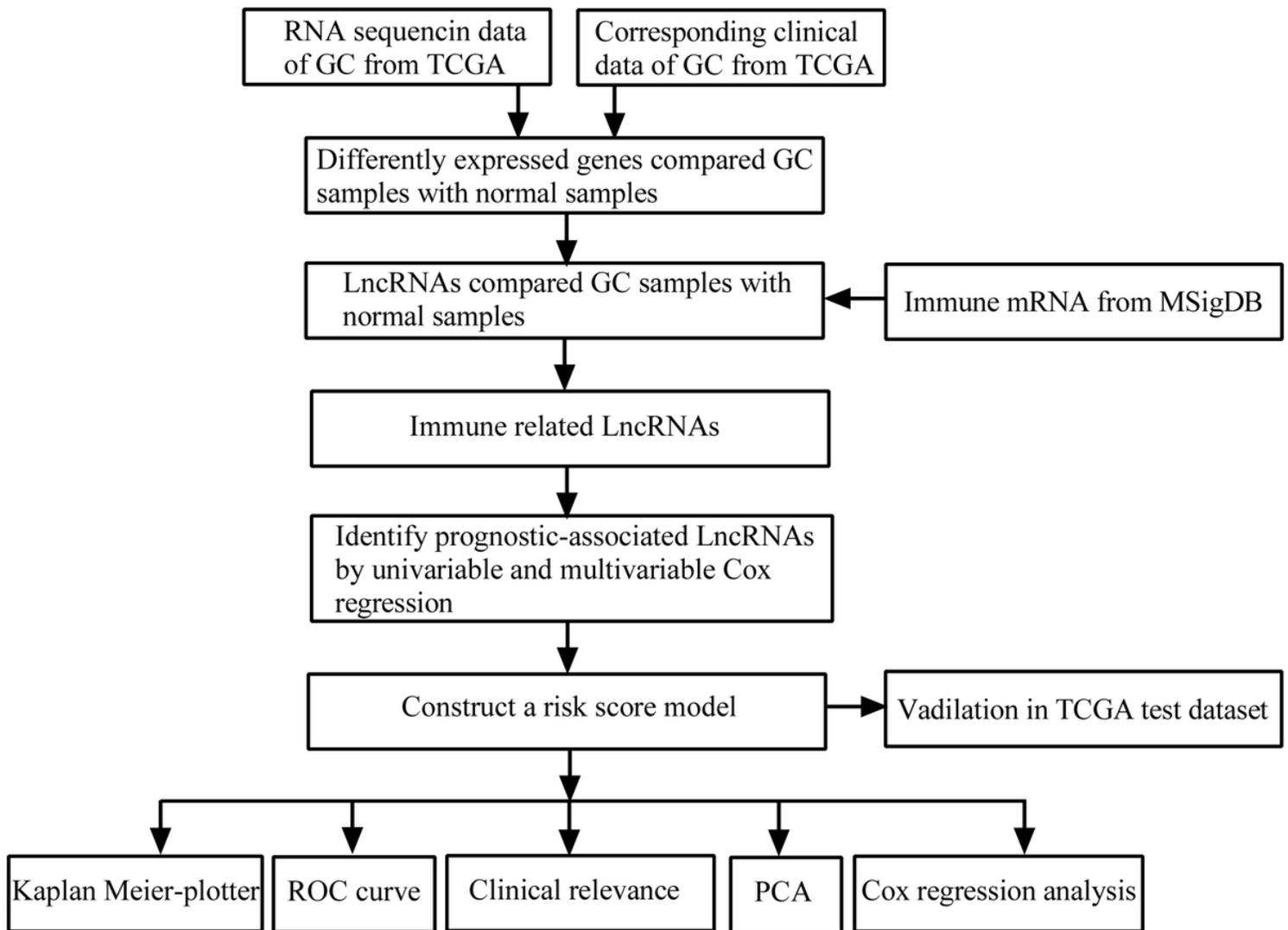
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## Figures



**Figure 1**

Flow chart.

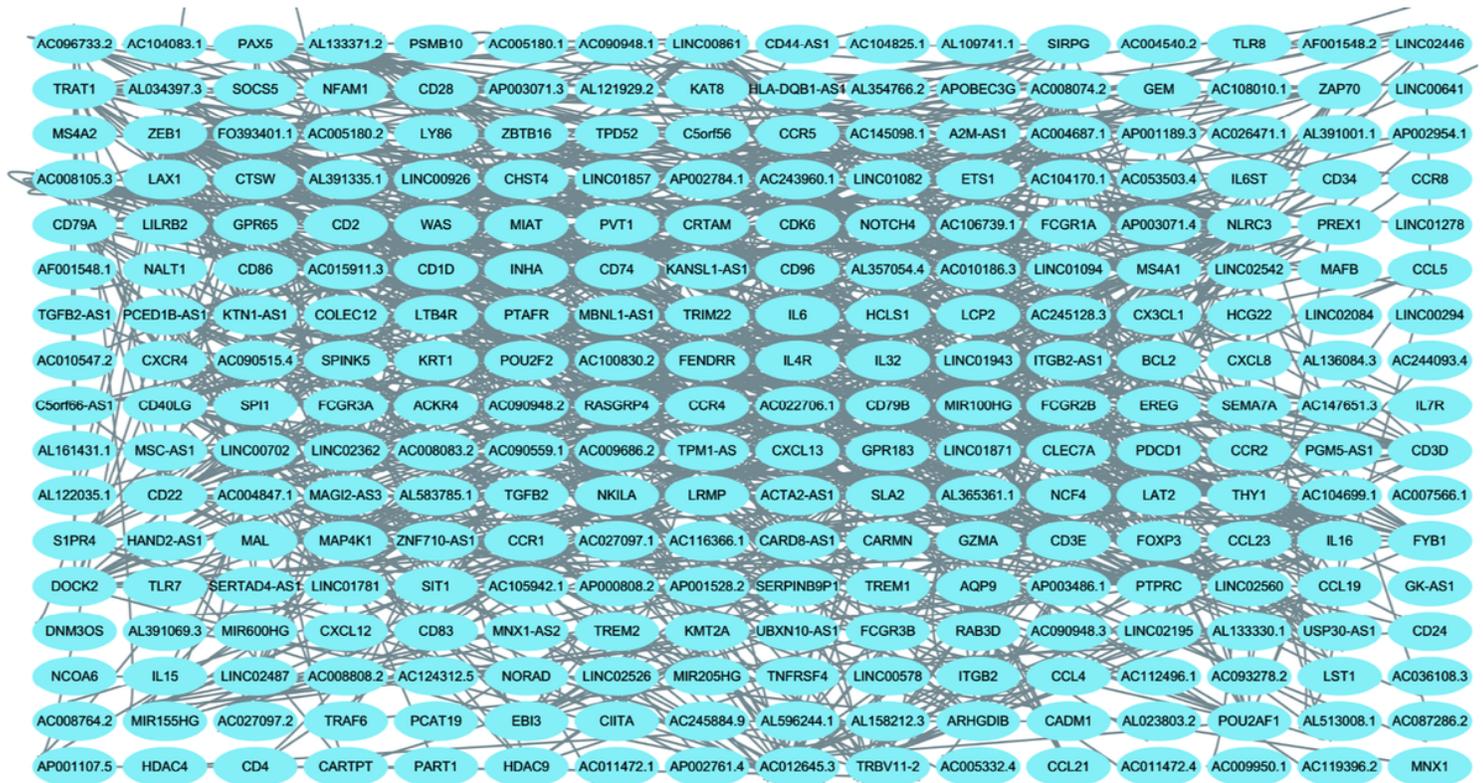


Figure 2

Co-expression network between immune gene and lincRNAs.

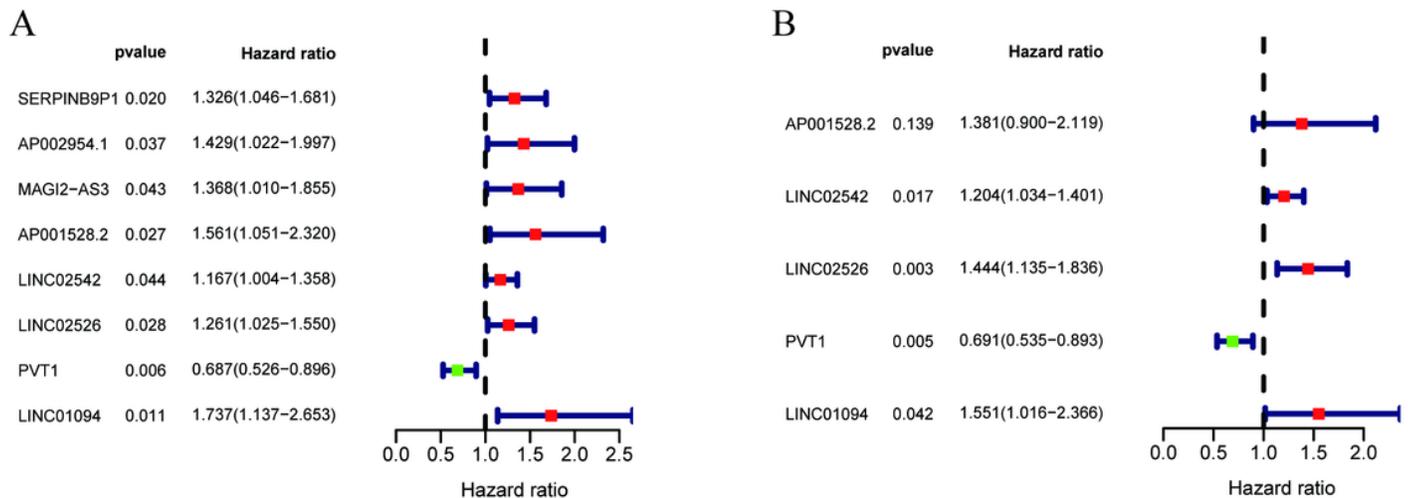
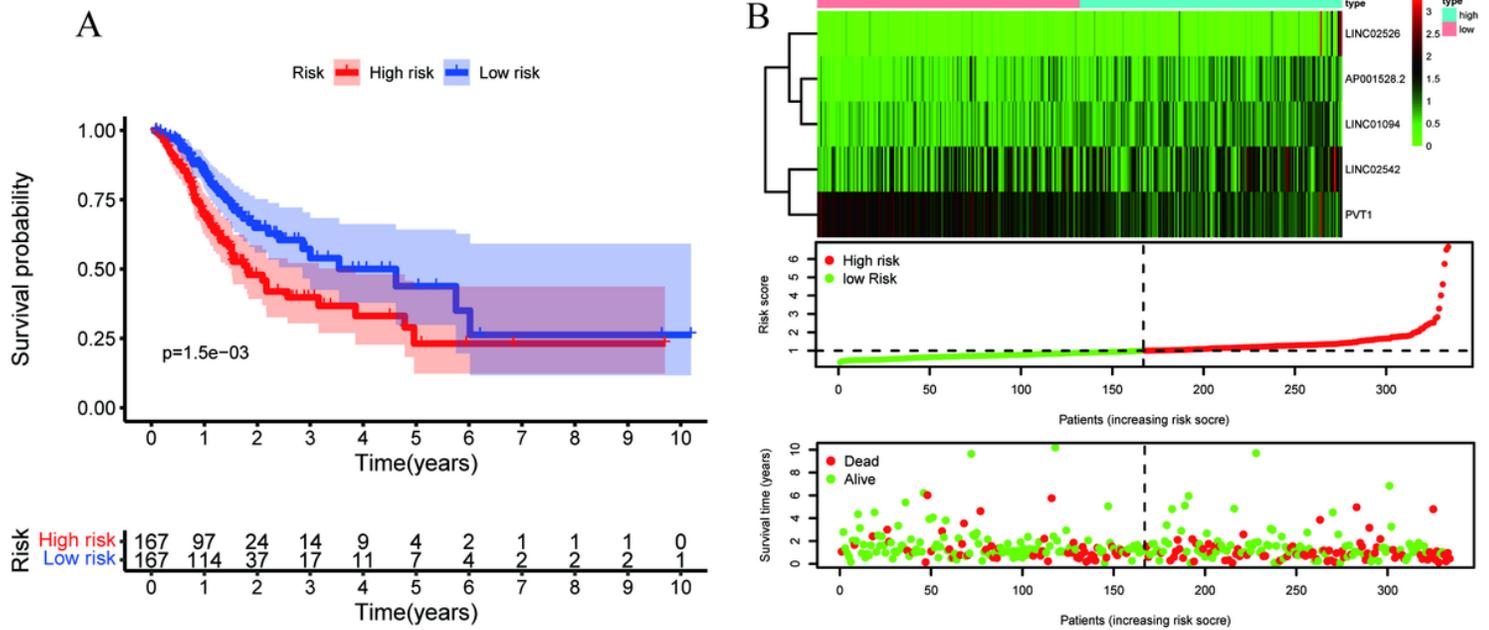


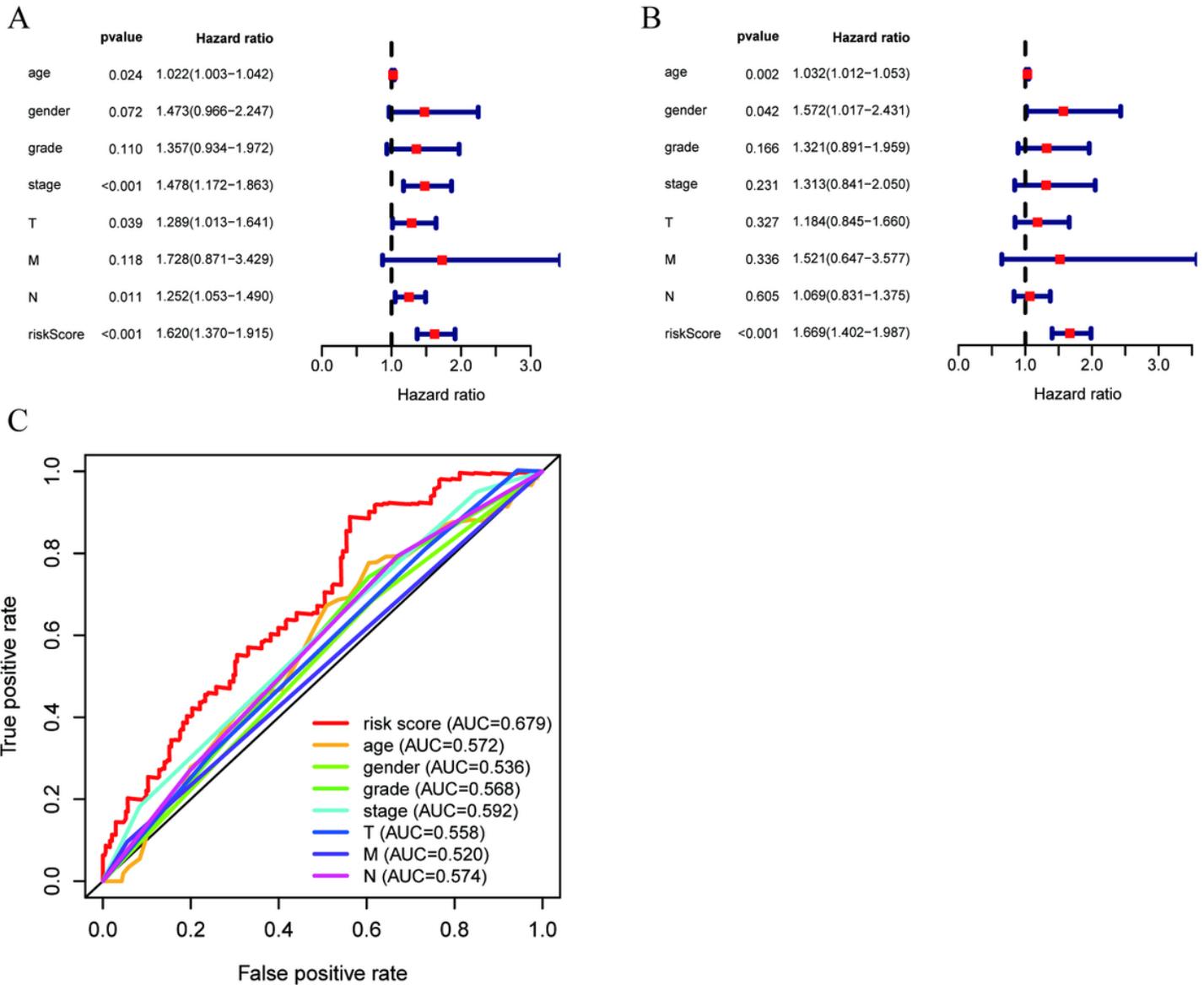
Figure 3

Cox regression analysis. A, The forest plot of univariate Cox regression showed 8 immune-related lincRNAs associated with overall survival; B, The forest plot of multivariate Cox regression showed 5 immune-related lincRNAs associated with overall survival.



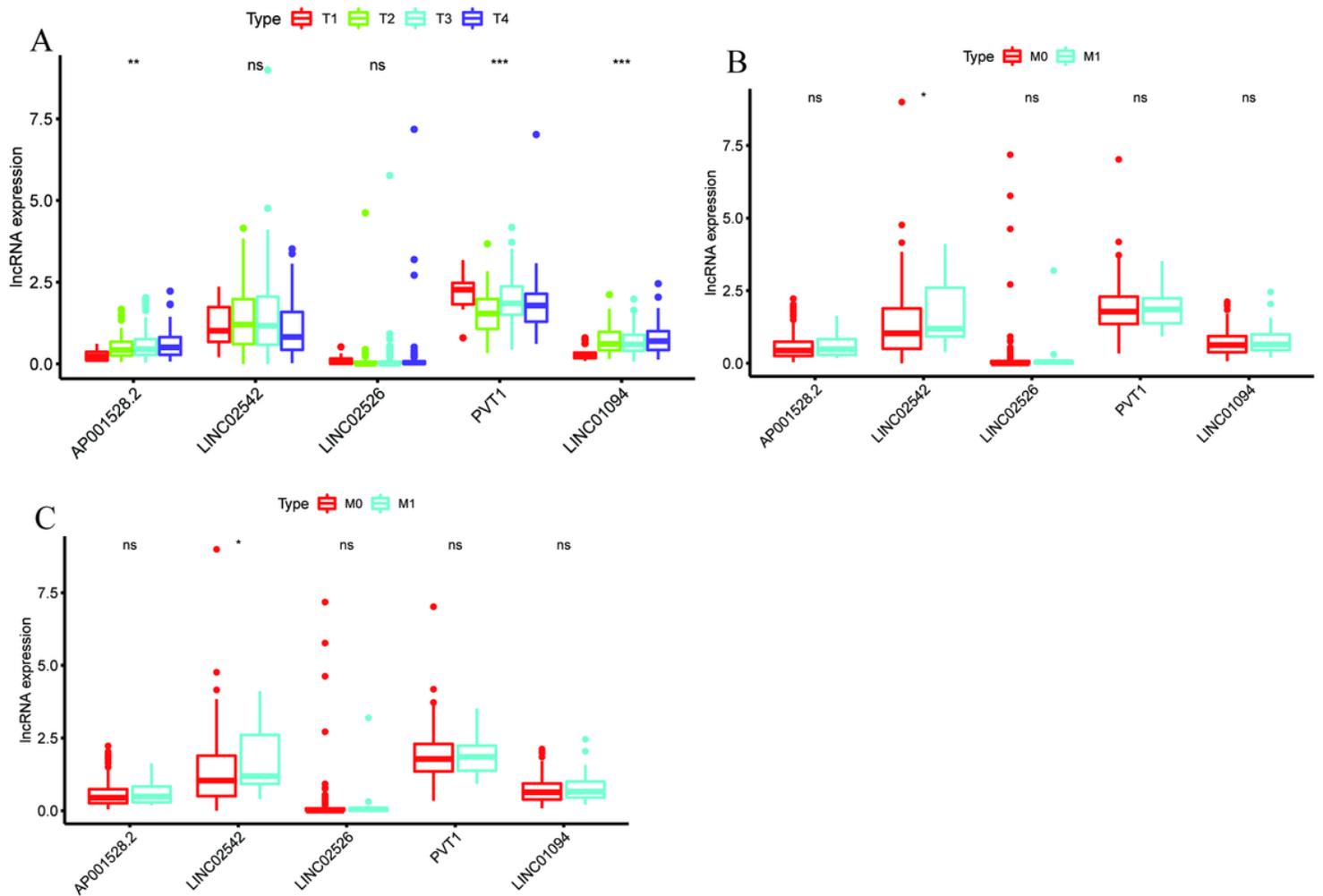
**Figure 4**

Validation of risk scores model of the five immune-related lncRNAs in TCGA cohort. A, The higher risk score group had a poorer overall survival compared with the lower risk score group; B, The overexpression of the five immune-related lncRNAs contributed to high-risk scores and poorer OS.



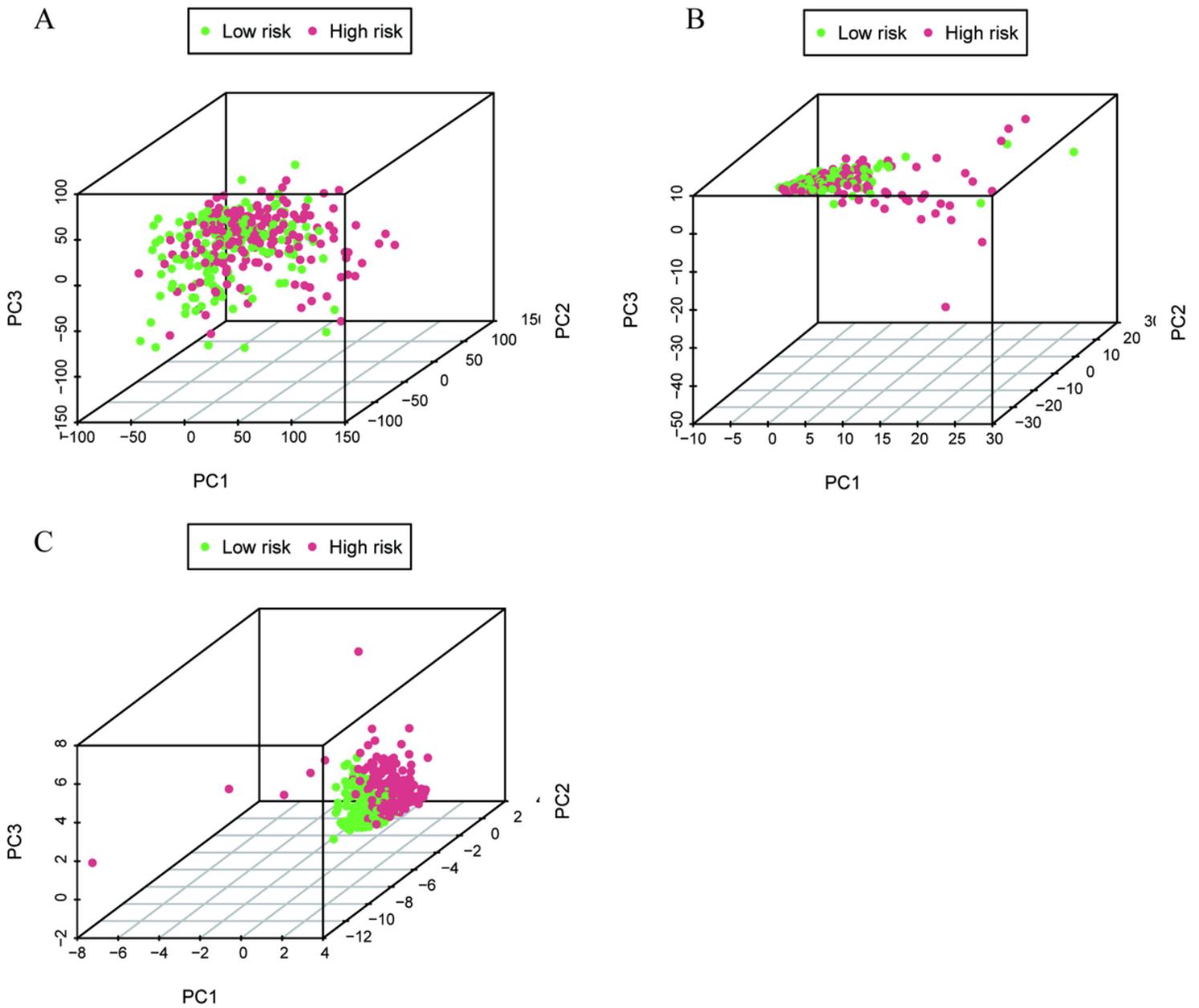
**Figure 5**

Stratification analysis of clinicopathological features. A, The forest plot of univariate Cox regression showed age, T stage, N stage and risk score model were associated with overall survival; B, The forest plot of multivariate Cox regression showed age and risk score model were associated with overall survival; C, ROC analysis showed that risk score model had an effective predictive prognosis for GC.



**Figure 6**

The relationship between five immune-related lncRNA and clinicopathological features. A, The expression of AP001528.2, PVT1 and LINC01094 was associated with the depth of GC invasion; B, The expression of LINC02542 was correlated with the distant metastasis; C, The expression of five immune-related lncRNA was not related with lymph node metastasis.



**Figure 7**

Identification of immune status in high- and low-risk group. A, Principal component analysis (PCA) of high- and low- risk group based on all expression genes; B, PCA of high- and low- risk group based on all immune-related lncRNAs; C, PCA of high- and low- risk group based on five immune-related lncRNAs.