

A cuproptosis-related long non-coding RNA signature to predict the prognosis and immune microenvironment characterization for lung adenocarcinoma

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Background: Cuproptosis or copper-dependent cell death is a newly identified non-apoptotic cell death pathway which plays a critical role in the development of multiple cancers. Long non-coding RNAs (lncRNAs) are increasingly recognized as crucial regulators of programmed cell death and lung adenocarcinoma (LUAD) development, and a comprehensive understanding of cuproptosis-related lncRNAs may improve prognosis prediction of LUAD. However, few studies have explored the association of cuproptosis-related lncRNAs with the prognosis of LUAD.

Methods: The RNA sequencing data and corresponding clinical information of patients were extracted from The Cancer Genome Atlas (TCGA) database. Five hundred LUAD patients were randomly divided into a training (n=250) and a testing cohort (n=250). Pearson correlations were performed to identify cuproptosis-related lncRNAs, and univariate Cox regression was performed to screen prognostic lncRNAs. A cuproptosis-related lncRNAs prognostic signature (CLPS) was constructed by the least absolute shrinkage and selection operator Cox regression. Kaplan-Meier analysis, receiver operating characteristic curves, and multivariate Cox regression were performed to verify the prognostic performance of CLPS. Additionally, immune cell infiltration was estimated using the single-sample gene-set enrichment analysis. pRRophetic algorithm and Tumor Immune Dysfunction and Exclusion algorithm were used to assess the immunotherapy and chemotherapy response, respectively.

Results: CLPS was established based on 61 cuproptosis-related prognostic lncRNAs and exhibited a satisfactory performance predicting LUAD patients' survival (area under the curve at 1, 3, 5 years was 0.784, 0.749, 0.775, respectively). multivariate Cox analysis confirmed the independent prognostic effect of CLPS (hazard ratio: 1.128; 95% confidence interval: 1.071–1.189; P<0.001), and a nomogram containing it exhibited robust validity in prognostic prediction. We further demonstrated a higher CLPS-risk score was associated with lower levels of signatures including immune cell infiltration, immune activation, and immune checkpoints.

Conclusions: The CLPS serves as an effective predictor for the prognosis and therapeutic responses of LUAD patients. Our findings provide promising novel biomarkers and therapeutic targets for LUAD.

Keywords: Lung adenocarcinoma (LUAD); cuproptosis; long non-coding RNAs (lncRNAs); prognostic signature; tumor microenvironment (TME)

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Introduction

Lung cancer is the leading cause of cancer-related mortality and the second most common cancer worldwide (1). Lung adenocarcinoma (LUAD) is the most prevalent histologic sub-type and accounts for 40–50% of lung cancer (2). Despite the great success of molecular targeted therapy and immunotherapy in cancer treatment, as well as increasingly abundant prediction models, both diagnostic and prognostic, the prognosis for LAUD remains poor due to the heterogeneity of tumors and complexity of molecular mechanisms (3,4). Indeed, it is estimated that the 5-year survival rates vary from 4–17% depending on stage differences (5). Therefore, there is a continued need to develop novel sensitive and effective biomarkers for prognosis prediction and providing individualized therapy for LUAD.

Cuproptosis is a novel form of programmed cell death (PCD) distinguished from others, such as apoptosis, necrosis, pyroptosis, and ferroptosis (6,7). As a copperinduced cell death, cuproptosis is characterized by intracellular copper accumulation-triggered aggregation of mitochondrial lipoylated proteins [lipoylated dihydrolipoamide S-acetyltransferase (DLAT)] and the instability of Fe-S proteins, resulting in proteotoxic stress (8). The induction of PCD has been known to be a reliable approach for cancer therapy (9-11), making cuproptosis a novel promising strategy to inhibit tumor progression by triggering tumor cell death (7). However, the specific mechanisms of cuproptosis underlying the tumorigenesis, progression, and tumor microenvironment (TME) remodeling remain unclear.

With the rapid development of high throughput sequencing, long non-coding RNAs (lncRNAs) have become a major focus of PCD (12,13), which plays a critical role in the development of multiple cancers including LUAD (14,15). LncRNAs participate in complex biological processes by interacting with DNA, RNA, and proteins. Cumulative evidence has demonstrated that the dysregulation of lncRNAs in LUAD is widely involved in tumor cell proliferation, invasion, and metastasis, as well as shaping the TME (16-18). Studying cuproptosisrelated lncRNAs may provide further insight into the role of this pathway in cancer, potentially serve as prognostic/ predictive biomarker and help identify novel therapeutic targets for LUAD. This formed the basis of our Cancer Genome Atlas (TCGA)-based investigation, where we mined potential cuproptosis-related lncRNAs based on a TCGA-LUAD cohort to construct a cuproptosisrelated lncRNAs prognostic signature (CLPS). We also explored the mechanism of cuproptosis-related lncRNAs in tumor progression and the TME heterogeneity through functional analysis and immune infiltration analysis. Additionally, we assessed the potential role of CLPS in predicting therapeutic response to cytotoxic chemotherapy and immunotherapy. We present the following article in accordance with the TRIPOD reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-660/rc).

Methods

Data extraction and preprocessing

The design and implementation of this study are shown in detail in *Figure 1*. The RNA sequencing data and corresponding clinical information of 522 LUAD patients were extracted from TCGA database. Twentytwo patients were excluded due to the lack of available survival information, and 500 patients with corresponding clinicopathological information were eventually included for further analysis. These patients were randomly divided (conservative random 1:1 split) into a training (n=250) and a testing cohort (n=250) at a 1:1 ratio using the "caret" R package (19). The somatic mutation profiles of LUAD samples were downloaded from TCGA database. The



Figure 1 Overview of the study design and analytical flow. TCGA, The Cancer Genome Atlas; LUAD, lung adenocarcinoma; lncRNAs, long non-coding RNAs; LASSO, least absolute shrinkage and selection operator; OS, overall survival; PFS, progression-free survival; ROC, receiver operator characteristic; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.

study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Identification of cuproptosis-related lncRNAs

We retrieved 19 cuproptosis-related genes from previous studies (6-8,20) as shown in Table S1. The mRNA and lncRNA expression profiles were classified, and Pearson correlation analysis was then performed to reveal the correlation between the expression of cuproptosis-related genes and corresponding lncRNAs. A total of 1,227 cuproptosis-related lncRNAs were identified based on the standard that the P value <0.001 and the absolute value of Pearson correlation coefficient >0.4.

Construction and validation of the CLPS

In the training cohort, univariate analyses for overall survival (OS) were performed using a Cox proportional hazards regression model to screen cuproptosis-related prognostic lncRNAs with a P value filter of <0.05. A least absolute shrinkage and selection operator (LASSO) Cox regression (21) was then conducted using the "glmnet" R package to identify the robust prognostic lncRNAs and fitted a multivariable Cox

regression model. Finally, a CLPS including seven lncRNAs was constructed: Risk score = $\sum_{i}^{n} \alpha i \times \beta i$, where αi means the coefficients, and βi represents the expression value of each cuproptosis-related lncRNAs.

The median risk score from the training cohort was used as the cut-off point to define CLPS-based high-risk or low-risk scores. Kaplan-Meier curves were performed to estimate OS and progression-free survival (PFS) through the "survival" and "survminer" R package, and log-rank tests were used to compare the curves. Time-dependent receiver operating characteristic (ROC) analyses and the area under the curve (AUC) calculation were performed using the "timeROC" R package to evaluate the predictive capacity of the CLPS. The Harrell's concordance index (C-index) was calculated using the "survival" R package to quantify the performance of CLPS, and the Principal Components Analysis (PCA) was performed and visualized with the "scatterplot3d" R package. The same analyses were performed on the testing cohort for validation.

Independent prognostic analysis and nomogram construction

To confirm whether the CLPS was independent of other clinical characteristics in predicting the OS of LUAD patients, univariate and multivariate analyses were performed with a Cox proportional hazards regression model which included the CLPS and several clinical characteristics. Further, a novel nomogram which included age, gender, stage, and the CLPS was established to predict patient survival.

Functional enrichment analysis

Differentially expressed genes (DEGs) between the high and low-risk groups were identified with a significance threshold of $|\log_2 FC| > 1$ and false discovery rate (FDR) <0.05 using the "limma" R package. To explore the difference in biological pathways between the two groups, the "clusterProfiler" R package was used to perform Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses for these DEGs. Significant enrichment pathways (P value <0.05) are displayed in the bar plot and bubble plot.

Analysis of the TME characterization

The Estimation of Stromal and Immune cells in Malignant

Tumor tissues using Expression data (ESTIMATE) algorithm (22) was conducted to infer the fraction of stromal and immune cells (defined as the stromal and immune scores) in each sample using the "ESTIMATE" R package (v1.1.0, https://bioinformatics.mdanderson.org/estimate/ rpackage.html). The ESTIMATE score is a composite score summarizing the immune score and the stromal score, while the tumor purity, defined as the percentage of malignant cells in a solid tumor, is inversely proportional to the ESTIMATE score. The single-sample gene-set enrichment analysis (ssGSEA) algorithm (23) was conducted to estimate the immune cell infiltration, implemented in the "GSVA" R package, and 29 immune signature-specific gene sets were referred to the published literature (24,25). The gene sets of immune activation and immune-checkpoints were derived from Mariathasan et al. (26,27).

Prediction of response to immunotherapy and chemotherapy

We further investigated whether the CLPS could predict the clinical response to immunotherapy and chemotherapy. The gene signatures of T cell dysfunction and prediction of cancer immunotherapy response on cancer was inferred by Tumor Immune Dysfunction and Exclusion (TIDE, http://tide.dfci.harvard.edu/), a novel but effective algorithm as Jiang *et al.* described (28). Generally, a higher TIDE score predicts a poor response to immunotherapy. The pRRophetic algorithm was used to estimate the 50% inhibiting concentration (IC₅₀) values of five common first-line chemotherapy drugs (including cisplatin, paclitaxel, etoposide, gemcitabine, and doxorubicin) for LUAD (29).

Statistical analysis

All statistical analyses were performed using R software (version 4.1.1) and attached packages. Wilcox test was used to assess the differences between the high and low-risk groups, and Pearson correlation analysis was used to determine the correlation coefficient. Survival curves were performed using the Kaplan-Meier method, and the log-rank test was used to determine the statistical significance of differences. The waterfall plots of the mutational landscape were generated using the "maftools" R package (30). All reported P values were two-tailed, and statistically significant was defined as P value <0.05.

Results

Construction and validation of the CLPS

The 500 LUAD patients were randomly divided into a training (n=250) and a testing cohort (n=250), and no statistically significant difference was detected in clinical characteristics between the two (Table S2). Based on the identified 1,227 cuproptosis-related lncRNAs (available online: https://cdn.amegroups.cn/static/public/TLCR-22-660-1.xlsx, Figure S1), 61 cuproptosis-related prognostic lncRNAs (Figure 2A) were screened by univariate analysis in the training cohort, and a LASSO Cox regression analysis was performed based on them (Figure 2B,2C). Finally, seven lncRNAs were adopted to constitute the CLPS (Table S3, Figure 2D). Risk scores of patients in the training cohort and the testing cohort were calculated, respectively (Tables S4,S5), and there were significant correlations between the cuproptosis-related gene expressions and the expressions of the seven CLPS-lncRNAs (Figure 2E). As shown in Figure S1B-S1E, PCA based on the seven CLPSlncRNAs exhibited an absolute distribution difference of patients from the two groups.

Kaplan-Meier survival curves indicated patients with lower risk scores showed significantly better OS and PFS in both training (*Figure 3A*, 3B) testing cohorts (Figure 3C, 3D). As shown in Figure 3E, 3F, the AUC) of the risk score reached 0.784 at 1 year, 0.749 at 3 years, and 0.775 at 5 years in the training cohort, and were still greater than 0.6 in the testing cohort. C-index values further indicated the good prediction accuracy of the CLPS (Figure 3G, 3H). As shown in Figure 31,37, high-risk patients exhibited a higher probability of death than low-risk patients, and the heatmaps suggested AC090541.1 (a human DNA sequence from clone RP11-1105O14 on chromosome 8) and AC107021.2 (a human DNA sequence from clone RP11-274H2 on chromosome 3) were upregulated in the high-risk group, while LINC02390 (long intergenic non protein coding RNA 2390), NIFK-AS1 (NIFK antisense RNA 1), AC026355.2 (a human DNA sequence from clone RP11-114M1 on chromosome 3), MIR34AHG (MIR34A host gene), and LINC01215 (long intergenic non protein coding RNA 1215) were downregulated in the high-risk group. The above analysis performed in the entire LUAD cohort also showed consistent results (Figure S2A-S2E). Additionally, subsequent subgroup survival analyses (Figure S2F-S2K) demonstrated the prognostic value of the CLPS remained statistically significant for each subgroup based on gender (male, female), age (≤ 65 , >65 years), and

clinical stage (I–II, III–IV).

Analysis of clinical characteristics and construction of the nomogram

We next performed a series of analyses based on clinical characteristics, and ROC analysis suggested the CLPS had a stronger prognostic capacity than other clinical characteristics (*Figure 4A*). Univariate (*Figure 4B*) and multivariate (*Figure 4C*) Cox analyses confirmed the CLPS as an independent prognostic factor for predicting patient outcomes [HR: 1.128 (1.071–1.189), P<0.001]. Furthermore, a nomogram consisting of age, gender, clinical stage, and CLPS was constructed (*Figure 4D*) as a visualizing prognostic tool to quantify the survival probabilities at 1, 3, and 5 years. Calibration curves indicated that the observed and predicted survival proportions at 1, 3, and 5 years exhibited good concordance in the LUAD cohort (*Figure 4E*).

Functional enrichment analyses

A total of 224 DEGS were identified between the high and low-risk groups (Table S6). To reveal the biological pathways associated with the CLPS, GO functional enrichment and KEGG pathway enrichment analyses were performed based on the DEGs between the high and lowrisk groups. As expected, GO analysis suggested the DEGs were primarily enriched in pathways related to immune cell-infiltrating (e.g., lymphocyte, leukocyte, macrophage and mononuclear cell proliferation, and myeloid leukocyte migration), immune activation (e.g., antimicrobial humoral response, humoral immune response), extracellular matrix (ECM) remodeling (e.g., collagen-containing ECM, ECM structural constituent), and cytokine-cytokine receptor interactions (Figure 5A, 5B). Similarly, KEGG analysis revealed DEGs were mainly focused on critical pathways involved in cytokine signaling (cytokine-cytokine receptor interaction, chemokine signaling pathway), ECM remodeling (focal adhesion, ECM-receptor interaction), and immune-related pathways (primary immunodeficiency, B cell receptor signaling pathway) (Figure S3A, S3B).

TME characterization

The ESTIMATE analysis results indicated tumors with lower CLPS-risk scores were remarkably abundant in immune cells, while no significant difference in stromal cell abundance was observed in the two groups (*Figure 6A-6D*).



Figure 2 Construction of a CLPS. (A) Univariate Cox regression analysis for 61 cuproptosis-related prognostic lncRNAs. (B,C) LASSO Cox regression analysis based on 61 cuproptosis-related prognostic lncRNAs. (D) Coefficients of the LASSO Cox model with the minimum lambda criteria. (E) Correlation analyses of cuproptosis-related genes and the CLPS lncRNAs. CLPS, cuproptosis-related lncRNAs prognostic signature; lncRNAs, long non-coding RNAs; LASSO, least absolute shrinkage and selection operator.

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Figure 3 Survival analysis and validation of the CLPS in LUAD patients. (A,B) Kaplan-Meier curves of (A) OS and (B) PFS in the training cohort. (C,D) Kaplan-Meier curves of (C) OS and (D) PFS in the testing cohort. (E,F) ROC curves for the CLPS risk score at 1, 3, and 5 years in (E) training cohort and (F) testing cohort. (G,H) The C-index of the CLPS risk score and other clinical characteristics in (G) the training cohort and (H) testing cohort. (I,J) Survival state (the middle section) of the patients sorted according to the risk scores (the top section) and the differences in the CLPS lncRNAs between high-risk and low-risk groups (the bottom section) in (I) the training cohort and (J) testing cohort. AUC, area under the curve; CLPS, cuproptosis-related lncRNAs prognostic signature; LUAD, lung adenocarcinoma; OS, overall survival; PFS, progression-free survival; ROC, receiver operating characteristic; lncRNAs, long non-coding RNAs.

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Figure 4 Establishment of a novel nomogram for predicting prognosis of LUAD patients. (A) ROC curve for the risk signature and several clinical characteristics at 1-year in the entire cohort. (B) Univariate and (C) multivariate analyses for the risk score using the Cox regression model. (D) A nomogram for predicting OS of LUAD patients constructed based on the entire cohort. (E) The calibration curves of the nomogram predicted 1-, 3-, and 5-year OS in the entire cohort. ***, P<0.001. AUC, area under the curve; LUAD, lung adenocarcinoma; ROC, receiver operating characteristic; OS, overall survival.

In addition, the ssGSEA analysis demonstrated higher CLPS-risk scores were significantly associated with reduced levels of majority immune-related signatures (Figure 6E), including immune cell infiltration (e.g., dendritic cells, B cells, CD8⁺ T cells, mast cells, neutrophils, T helper cells, and tumor infiltrating lymphocyte), immune activation (cytolytic activity, human leucocyte antigen, inflammation promoting, T cell co-stimulation, and type II interferon response), and immune checkpoints. Furthermore, we analyzed the expression of chemokines and cytokines considered to be relevant to immune activation and immune checkpoints, respectively, and as expected, the mRNAs related to immune activation were significantly downregulated in the high-risk group (Figure 6F). There were also negative correlations between the CLPS-risk scores and the expression of most immune checkpointrelated mRNAs (Figure 6G, Figure S4A-S4I). The above results revealed a non-negligible association of the CLPS

with different TME immune landscapes, which might in turn affect tumor affect tumor progression and the therapeutic response.

Analysis of tumor somatic mutation and prediction of the therapeutic response

Accumulated evidence indicates the tumor mutational burden (TMB) is a predictive biomarker for response to immune checkpoint inhibitor therapy (31,32). We evaluated the intratumoral somatic mutation landscape to indirectly predict the immunotherapeutic outcomes. The waterfall plots suggested the high-risk group exhibited more extensive somatic mutation than the low-risk group (*Figure 7A*,7*B*), while subsequent Kaplan-Meier survival curves showed patients with higher TMB had better OS than lower TMB (*Figure 7C*). As shown in *Figure 7D*, combining the CLPS-risk score and TMB exhibited a

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Figure 5 Functional annotation for DEGs between the high and low-risk groups using GO enrichment analysis. (A) The bar plot and (B) bubble plot showing the significantly enriched GO pathways. The bubble color representing the P value, and the bubble size representing the number of genes in the relevant pathway. BP, biological process; CC, cellular component; MF, molecular function; DEGs, differentially expressed genes; GO, Gene Ontology.

greater prognostic value for LUAD patients.

To directly predict the response to immunotherapy, we estimated the TIDE score of all LUAD patients based on the TIDE algorithm. As shown in *Figure 8A*, the high-risk group showed a significantly lower TIDE score compared with the low-risk group, which indicated a better response to immunotherapy in patients with higher CLPS-risk scores. Moreover, there were significant negative correlations of the CLPS-risk score with the IC₅₀ to cisplatin (*Figure 8B,8C*), paclitaxel (*Figure 8D,8E*), etoposide (*Figure 8F,8G*), gencitabine (*Figure 8H,8I*), and doxorubicin (*Figure 8J,8K*), which indicated patients with higher CLPS-risk scores had a better response to these chemotherapy agents.

Discussion

LUAD is considered a highly heterogeneous tumor, where multiple genetic, epigenetic, and phenotypic alterations drive its development and progression (33,34). With growing understanding of the molecular mechanisms of LUAD, there has been a rapid evolution of personalized therapies for treatment of LUAD such as epidermal growth factor receptor (EGFR) inhibitors and programmed cell death 1 (PD1)/programmed cell death ligand 1 (PD-L1) inhibitors (35,36). Unfortunately, primary and secondary resistance and variable responses to currently available treatments present an ongoing challenge, highlighting the need for continued exploration of novel molecular biomarkers for individualized prognosis and treatment of LUAD. Several studies have emphasized the critical importance of PCD in battling cancer, including apoptosis, necrosis, pyroptosis, and ferroptosis (10,37). Cuproptosis is a newly discovered form of PCD, which has been shown to have antitumor potential (7) but the underlying mechanisms have not been clearly identified. With the development of next-generation sequencing technology (38), an increasing number of lncRNAs have been identified and confirmed to play critical roles in initiation and progression of LUAD (16,17). We hypothesized that cuproptosis-related lncRNAs may have a great potential as diagnostic biomarkers and help identify therapeutic targets in LUAD.

To the best of our knowledge, this study is the first to comprehensively explore the prognostic significance of cuproptosis-related lncRNAs in LUAD. First, we identified 61 cuproptosis-related prognostic lncRNAs and constructed a CLPS based on seven lncRNAs, including five protective factors (LINC02390, MIR34AHG, NIFK-AS1, LINC01215, AC026355.2) and two risk factors (AC107021.2, AC090541.1). MIR34AHG is the host gene of miR-34a and may have biological functions similar to the miR-34 family, which inhibits the progression of LUAD



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Figure 6 TME characteristics in the high- and low-risk groups. (A-D) Difference in the (A) stromal score, (B) immune score, (C) estimate score, and (D) tumor purity between the two groups. (E) Difference in the levels of 29 TME signatures between the two groups. (F) Difference in the immune-activation related gene expression between the two groups. The horizontal line indicates the median, the lower and upper boundaries of the boxes the interquartile range, and the dots the outliers. Asterisks indicate statistical significance, *, P<0.05; **, P<0.01; ***, P<0.001. (G) Correlations between the risk score and immune-checkpoint related gene expression. Positive correlation was marked with red and negative correlation with blue. The circle color represents Spearman coefficient value, the size of circle is inversely proportional to the P value, and the * stands for P<0.001. TME, tumor microenvironment.

(39,40). Importantly, the CLPS exhibited a satisfactory performance in predicting OS and PFS in LUAD, which provided an effective prognostic tool to complement traditional clinical indices. MIR34AHG, NIFK-AS1, LINC01215, and AC026355.2 have been confirmed to be associated with progression or prognosis of tumors. NIFK-

AS1, LINC01215, AC026355.2 have also been previously shown to have a positive effect on prognosis (41-44). Expression of MIR34AHG, NIFK-AS1, and LINC01215 have also been associated with the heterogeneity of immune cell infiltration (41,42,45), suggesting that the CLPS may be beneficial in predicting survival outcomes as well as



Figure 7 Analysis of tumor somatic mutation in LUAD patients with different risk scores. (A,B) The top barplot depicts TMB and mutation frequency in each gene is given on the right. The right barplot depicts the proportion of each variant type. The stacked barplot below depicts fraction of conversions in each sample. (C) Kaplan-Meier curve of OS for high and low-TMB groups. (D) Kaplan-Meier curve of OS for subgroup patients stratified by the risk score and TMB. TMB, tumor mutational burden; H, high; L, low; LUAD, lung adenocarcinoma; OS, overall survival.

assessing immune regulation in cancer.

Our CLPS exhibited a satisfactory performance in predicting OS and PFS in LUAD, providing an effective prognostic tool to complement traditional clinical indices. In addition, our analysis validated previously observed survival protective effect of MIR34AHG, NIFK-AS1, LINC01215, and AC026355 (41-44). Furthermore, our study demonstrated for the first time that three lncRNAs, namely LINC02390, AC107021.2, and AC090541.1 are prognostic in LUAD, with LINC02390 having a positive effect and the others a negative effect on prognosis. These findings warrant further exploration.

The TME plays a crucial role in tumorigenesis and development (46,47), and is an important determinant of prognosis and treatment response for LUAD patients (48,49). In particular, tumor infiltrating CD8⁺ T cells, which are key to an effective anti - tumor response, and high CD8⁺ T cell infiltration has been linked with favorable

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Figure 8 Sensitivity of immunotherapy and chemotherapy in LUAD patients. (A) Difference in TIDE score between low- and high-risk groups. (B-K) The correlation of risk score and the IC50 of (B,C) cisplatin, (D,E) paclitaxel, (F,G) etoposide, (H,I) gemcitabine, and (J,K) doxorubicin. TIDE was negatively correlated with immunotherapy sensitivity. TIDE, Tumor Immune Dysfunction and Exclusion; LUAD, lung adenocarcinoma; IC50, 50% inhibitory concentration, which was negatively correlated with drug responsiveness.

prognosis in LUAD (50,51). Dendritic cells and T follicular helper cells are considered to play important roles in antitumor immunity (51,52). In our study, we explored the association between the CLPS and TME heterogeneity in LUAD. DEGs between the high and low-risk groups were identified and demonstrated to be significantly enriched in biological pathways related to immune cell-infiltrating, ECM remodeling, and cytokine signaling. Combining results from the ESTIMATE and ssGSEA analyses, the high-risk group was characterized by a lower level of immune cell-infiltration (e.g., dendritic, B, CD8⁺ T, and T helper cells) and immune activation. Moreover, significant negative correlations between the CLPS-risk score and the expression of immune checkpoint-related genes indirectly suggested the differences in the immunotherapeutic response rates of patients with different risk score (53). To further explore whether the CLPS could be used to predict the efficacy to immunotherapy, we evaluated differences in the TMB and TIDE score between high and lowrisk groups. Cumulative evidence has indicated a higher TMB and lower TIDE were associated with a greater clinical response to immunotherapy (28,31). Significant differences in the TMB and TIDE score between the two groups demonstrated the ability of the CLPS to predict an immunotherapeutic response. Recent studies have revealed the interplay between immunotherapy and chemotherapy, and differences in immune infiltration have been shown to influence the resistance to adjuvant chemotherapy (54-56). In our results, patients with a higher CLPS-risk score exhibited better efficacy to five first-line chemotherapy drugs (including cisplatin, paclitaxel, etoposide, gemcitabine, and doxorubicin) in LUAD, suggesting additional potential of the CLPS to predict chemotherapy efficacy.

Despite the strengths and provocative observations as detailed above, our study had several limitations. First, there may be potential bias as the multivariate analysis was performed with limited clinical parameters available in a public dataset. Secondly, we could not directly analyze the association of cuproptosis-related lncRNAs and response to therapy due to the lack of detailed treatment information. Finally, the above findings were carried out mainly based on the bioinformatics analysis.

In conclusion, we successfully constructed a robust CLPS, which can potentially serve as a clinically effective tool to predict prognosis and predict response to immunotherapy and chemotherapy. Our findings also provide new insights into the role of cuproptosis in tumor progression and TME heterogeneity. CLPS contributes to further understand the regulatory mechanisms of cuproptosis on cancer development and offers a promising avenue for future targeted cancer therapy.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-660/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Supplementary

Table S1 Cuproptosis-related genes Genes NFE2L2 NLRP3 ATP7B ATP7A SLC31A1 FDX1 LIAS LIPT1 LIPT2 DLD DLAT PDHA1 PDHB MTF1 GLS CDKN2A DBT GCSH DLST

Characteristics		Total	Train	Test	P-value*
Age, years					0.1464
	<=65	237 (47.4%)	128 (51.2%)	109 (43.6%)	
	>65	253 (50.6%)	119 (47.6%)	134 (53.6%)	
	unknow	10 (2%)	3 (1.2%)	7 (2.8%)	
Gender					0.2434
	Female	270 (54%)	128 (51.2%)	142 (56.8%)	
	Male	230 (46%)	122 (48.8%)	108 (43.2%)	
Stage					0.2969
	Stage I	268 (53.6%)	124 (49.6%)	144 (57.6%)	
	Stage II	119 (23.8%)	66 (26.4%)	53 (21.2%)	
	Stage III	80 (16%)	43 (17.2%)	37 (14.8%)	
	Stage IV	25 (5%)	11 (4.4%)	14 (5.6%)	
	unknow	8 (1.6%)	6 (2.4%)	2 (0.8%)	

Table S2 Demographic and clinical characteristics between the training and testing cohort

*Chi-square test.



Figure S1 Identification of cuproptosis-related lncRNAs and principal component analysis (PCA) in the entire LUAD cohort. (A) Sankey diagram for cuproptosis-related genes and lncRNAs. (B-E) PCA analysis based on (B) all gene, (C) cuproptosis-related gene, (D) cuproptosis-related lncRNAs and (E) signature lncRNAs, respectively.

Table S3 The cuproptosis-related lncRNAs risk signature

LncRNAs	coefficent
AC090541.1	0.425683724
LINC02390	-1.102861115
NIFK-AS1	-0.766522002
AC026355.2	-0.40311251
AC107021.2	1.174579099
MIR34AHG	-0.944282562
LINC01215	-0.560092802

Table S4 Risk score for patients in the training cohort

ld TCGA-MP-A4T6 TCGA-49-4510	AC090541.1 0.05407954 0.35329687	LINC02390 0.1730156 0.1714833	NIFK-AS1 2.030406 2.05645971	AC026355.2 1.02374717 0.48683555	AC107021.2 0.12916287 0.2039159	MIR34AHG 1.65100897 0.10907205	LINC01215 0.56728239 0.20729754	Risk score 0.12979256 1.02959086	Risk group* low high
TCGA-67-3772 TCGA-69-7763	0.11499889 0.97346191	0.0490693	1.83188413 1.49093153	1.5594179 0.95376318	0.25605317 0.22287342	0.2292404 0.3536205	0.57853456 0.44025964	0.63276106	low high
TCGA-MP-A4TC TCGA-95-A4VK	0.1230606	0 0.31071831	1.12260186 2.22427093	1.61086748 0.10624599	0.43012655	0.18727354	0.07881453	1.90943537 0.3477966	high Iow
TCGA-49-AARO TCGA-55-7994 TCGA-78-7149	0 0 0.86662008	0.37533578 0.15632011	1.34517512 2.25959549	1.25457879 2.57861971 1.98104086	0.42155365 0.15337058	0.36916063 0.18201083 0.06691136	0.94214184 1.11584708 0.20987866	0.37031593 0.38053565 0.59771172	low low
TCGA-44-7660 TCGA-44-2656	0 1.19054778	0 0.74689559	2.23494489 1.52150475	0.24470728 3.45490649	0.37127899 0.57105857	0.26416569	0.63337844 0.82573633	0.85228634 0.15018754	low
TCGA-78-7153 TCGA-55-6987	0.13393286	0.21692117 0.19218331	1.29034655 1.33222483	0.25517983	0.23079375	0.3816907	0.12119496	1.47500681 0.52035532	high Iow
TCGA-78-7539 TCGA-83-5908 TCGA-95-7567	0 0 0	0.3211262 0.04463584 0.03443009	1.84495844 1.11016175 1.51819217	0.58444323 0.59418236 1.50756633	0.00958224 0.16039329 0.05482862	0.20804686 0.20966012 0.34540126	0.4273043 0.45773947 0.10871971	0.54420041 1.5134234 0.73196715	low high low
TCGA-44-7667 TCGA-69-8254	0.09666357 0.0670508	0 0.16223258	1.93891167 1.29749968	0.07742243 0.48274587	0.35394518 0.1863225	0.28184279 0.2600026	0.06170532 0.5360419	1.58218034 1.1660341	high high
TCGA-44-A47G TCGA-44-2668	0.14679883	0.39245811	1.40427916 1.33544857	1.21463028 1.92943182	0.45426003	0.35376546	1.1727256 2.77767563	0.56346032	low high
TCGA-44-6775 TCGA-55-5899 TCGA-J2-A4AD	1.83067314 0 0	0.86223612 0.13874567 0	1.44579493 1.91340526 2.11547969	2.50184635 0.13264825 2.15024963	1.02708867 0.16533457 0.53690214	1.45097757 0.39402993 0.31838999	0.84149423 0.12066856 0.06056101	0.33174077 0.90613065 0.689187	low low low
TCGA-69-7974 TCGA-05-4403	0	0.06778981 0.05170461	1.27806209 1.03842213	1.07143662 0.18807424	0.15799958	0.12406986 0.49433901	0.44211641	1.16708865 1.58166909	high
TCGA-97-7938 TCGA-62-A46P	0 0.18386123	0.06848124 0	1.57712836 1.3563664	0.8756006 0.21685948	0.10831055 0.12551152	0.16477389 0.27689217	0.58892596 0.03490403	0.83897535 1.89197267	low high
TCGA-62-8399 TCGA-64-5775 TCGA-86-8672	0.11302346 0 0.19118235	0.09485599 0 0.08281622	1.36666856 0.90479289 1.26835774	3.82385939 0.05104006 0.22539501	0.12542361 0.96979318 0.98490071	0.05975047 0.06622705 0.28756461	0.17905505 0.02334163 0.26812175	0.43393126 8.75318123 4.4023599	low high high
TCGA-93-A4JO TCGA-NJ-A4YP	0 0.49484126	0.17271165 0.04840569	1.85011331 1.33721441	0.40439591 0.37068679	0.24037894 0.26382431	0.14470973 0.27776044	1.13736581 0.23502398	0.64215069 2.05204896	low high
TCGA-97-8171 TCGA-44-6147	0 1.78832632	0 0.52513295	1.60156721 1.59460326	0.46650027 3.93548085	0.72020219 0.72391442	0.63263564 1.23231452	0.1376411 1.64151997	1.778579 0.13011433	high Iow
TCGA-55-1592 TCGA-69-7760 TCGA-64-5778	0.0393526 0 0	0.06504908 0.0601484 0.17051196	2.22098243 1.20022034 2.4191659	0.50384929 2.05933913 0.67666089	0.26713388 1.14903088 0.20976265	0.54513364 0.39821726 0.50216162	0.24408307 0.03926983 1.16789354	0.61991049 2.5991248 0.25232274	low high low
TCGA-55-8620 TCGA-53-7813	0 0.44775056	0 0.20381294	2.62599259 1.85244836	0.13354105	0.3621323 0.55231942	0 0.13015984	0.33749417 0.52864143	0.98971257	high
TCGA-78-7542 TCGA-86-8073	0.03878278 0.03885779	0.03241383 0.21333454	1.10851844 0.96866443	0.17639988 1.55238217	0.70095731 0.24932563	0.04022768 0.11768778	0.11563754 0.24121859	4.95586494 1.32265401	high high
TCGA-91-6848 TCGA-05-4424 TCGA-86-A4P7	0 0 0	0 0.11483771 0.26584858	1.43017417 1.60737153 1.63185361	0.32256835 1.57340191 1.64311526	0.29649899 0.06252772 0.30799088	0.21836885 0.20746729 0.32400947	1.61207109 0.56008912 0.68102824	0.8461204 0.54383354 0.49066461	low low low
TCGA-05-4405 TCGA-97-7553	0 0	0.23290562 0.04868405	1.5046815 1.53523405	0.58633011 0.51162096	0.20927183 0.08979486	0.52210795 0.46925635	0.13873316 0.75668067	0.85945389 0.68514377	low low
TCGA-49-6761 TCGA-NJ-A4YG	0	0 0.28260432	0.75870007	0.75232009	0.37302161 0.23084747	0.49784614 0.14758479	0.37640986 0.28101924	1.99856426 1.14735436	high high
TCGA-44-7672 TCGA-55-8619 TCGA-50-5939	0 0 1.12311391	0.0869396 0.34131877 0	1.38878575 1.43032008 1.14250885	1.06782219 0.32727003 0.28752501	0.11505627 0.20737455 1.30312141	0.20738892 0.41376719 0.1002	0.96555092 1.13210115 0.49779465	0.68913967 0.56785157 11.7478066	low low hiah
TCGA-55-7726 TCGA-L9-A5IP	0 0.2173573	0.34787164 0.09464041	1.55776003 1.40146974	0.72277044 0.4390846	0.93440954 1.42027885	0.22609983 0.22495988	0.1982198 0.04165787	2.06265199 7.3112314	high high
TCGA-55-7995 TCGA-64-1681	0 0.14071739	0.31848414 0.0405131	1.2389299 1.76314899	3.34917318 0.40711886	0.79320755	0.66363062	0.89055938	0.35889599	low high
TCGA-50-5066 TCGA-78-7146	0	0.04322229	1.40914433 0.91370745	0.98958174	0.37377142	0.39274247	0.52015951	1.07267229 6.16371666	high high
TCGA-62-A472 TCGA-44-7659	0 0	0.31720634 0.3138374	1.58253722 1.96248967	2.07253769 1.65280566	0.28583233 0.17621351	0.38518616 0.53964804	0.37969803 0.4376421	0.4408897 0.28812713	low low
TCGA-38-6178 TCGA-78-8640	0	0 0.86904155	1.50151048 1.60578256	0.61954438	0.37915869	0.12096413	0.36569366	1.72575691 0.1406259	high Iow
TCGA-55-8614 TCGA-97-8547	0 0.0980349	0.07133254	1.80407793 1.627675	0.56905637	0.23405158 0.35854367	0.64864132	0.24630361	0.70721324 0.7051739	low
TCGA-01-A52J TCGA-44-6145	0 0.82161371	0.20182592 0.21410664	2.10864489 1.44915615	1.92345652 0.8591813	0.45550382 1.14513188	0.55300949 0.33965877	0.62609163 0.87149193	0.32236465 2.75304102	low high
TCGA-49-4505 TCGA-44-7671 TCGA-44-2665	0 0 0.10600721	0.08614451 0 0.28988356	1.47236247 1.16929649 1.61137637	0.66629649 0.32781657 1.44825239	0.43973206 0.30326652 0.67343024	0.32795588 0.08475203 0.52124416	0.28347829 0.04476235 0.22013874	1.45629319 2.836919 0.90665327	high high Iow
TCGA-55-8097 TCGA-78-7537	0 0	0.26132077 0.07141234	1.92861872 1.64761522	0.71313771	0.07461482	0.48703737 0.21147677	0.7073535 0.10667488	0.36699762	low
TCGA-86-8358 TCGA-78-7167	0 0.18210608	0 0	1.83574866 2.24656284	0.23513264	0.56505818 0.15570144	0.20656502	0.35683696	1.79842054 0.43553211	high Iow
TCGA-55-8513 TCGA-05-5429 TCGA-55-6978	0.5868623 0 0	0.08379448 0 0.22842678	1.56327559 1.08623998 1.13416988	0.97809973 0.35148923 0.52249955	0.32856456 0.08656447 0.45891116	0.29073114 0.28204797 0.23623012	0.625407 0.03561083 0.31857499	1.15718337 1.93697872 1.86947961	high high bigh
TCGA-71-6725 TCGA-50-7109	0	0	1.01683534 1.54391007	2.35967934 1.01526562	0.02757652 0.48605828	0.37793803	0.01492472	0.78392325	low high
TCGA-86-7953 TCGA-78-7150	0.13247559 2.27179326	0.18099962	1.06415614 1.34576209	0.79877267	0.36271265	0.41433859	0.69422352	1.20331564 5.84517387	high high
ICGA-55-A4DF TCGA-50-5068 TCGA-49-4514	0 0	0.78491979 0 0	1.67448445 2.25509279 1.6501152	0.5074227 2.29664212 0.48539303	2.60878462 0.11511634 0.11643192	0.13746403 0.38886313 0	0.83269947 1.01468522 0.56124274	6.91949213 0.1950231 1.1995425	high Iow high
TCGA-97-8177 TCGA-91-6829	0 0.07441273	0.07137436 0	1.47981345 1.36977285	1.23558092 0.41888219	0.42835655 0.54613657	- 0.49594626 0.07715001	0.76661571	0.75155798	low high
TCGA-44-4112 TCGA-53-7624	2.01391885 3.48435213	0.6885698	1.53982062 1.57405596	4.97237883 0.05129866	2.09101234 0.51194363	1.39066227 0.19112283	0.53755252	0.65377669 9.37783433	low high
TCGA-55-8208 TCGA-55-6543 TCGA-49-44P4	0 0.0763691 0.09048867	0.26017977 0 0.34471057	1.50901006 1.09539517 1.7550354	1.1943021 0.51851631 1.58900502	0.36798165 0.28465532 0.19445575	0.61622919 0.59238097 0.41779128	1.13923582 0.09566742 0.64136226	0.40951944 1.69093933 0.35602167	low high Iow
TCGA-49-AAA4 TCGA-05-4432 TCGA-55-8512	0.45670892 0	0.13166494 0	2.02553383 1.6508151	0.42423147	0.3857217	0.72599116	0.83969754	0.5728307 0.75682415	low low
TCGA-55-7911 TCGA-99-7458	0.06986727 0	0.41255068 0.14834816	2.29758792 1.54112907	2.74083864 0.23977333	0.04709541 0.19502542	0.33052765 0.52407615	0.61113696 0.72185146	0.12614756 0.74704347	low low
TCGA-97-A4M3 TCGA-55-8205 TCGA-86-A456	0.06414189 0.04739304 0.08049061	0 0.11576484 0.36411595	1.47515702 1.26101657 1.23432029	1.10929837 0.14571023 0.96982713	0.05732809 0.49512028 0.23763932	0.19098293 0.4659562 0.56204572	0.14598207 0.6522415 0.24619961	1.07752883 1.58956863 0.76045387	high high
TCGA-64-5774 TCGA-05-4427	0.07057083 0	0.18519796	2.21993362 1.35622102	0.44249524	0.13825786	0.20923874 0.59585285	0.1127543	0.8796303 1.10885477	low high
TCGA-50-6591 TCGA-05-4397	0 0.09063541	0 0.05109006	1.39180236 2.07157151	0.06729017 0.92153063	1.09568817 0.19476019	0.0871683 0.4892668	0.04605671 0.54546788	6.71900265 0.49864597	high Iow
TCGA-44-8117 TCGA-MP-A4SY	0 0	0.0325675	1.18881044 1.25179967	0.83519931	0.08546193 0.92976101	0.3607761	0.16141292 0.13491487	1.22814194 2.70478599	high high
TCGA-86-7955 TCGA-L9-A8F4 TCGA-49-4507	0.1166048	0.39605192 0	1.64853677	0.52270311 0.95427087 0.55398522	0.72465071 0.34720012 1.18832622	0.62099481 1.43484444 0.38441281	0.06205118 0.93929338 0.02276198	2.13853268 0.14918955 5.92341735	nign Iow high
TCGA-55-8511 TCGA-55-A494	0 0	0.13064619 0	0.85109891 1.66117542	0.89455007 0.35986971	0.20416109 0.13648816	0.16086 0.24462053	0.9189919 0.10054726	1.26637415 1.31608502	high high
TCGA-69-7979 TCGA-L9-A743 TCGA-50-5049	0 0 0	0.07131104 0.43670742 0.12892112	1.402859 1.32557665 1.46357049	0.4966085 0.74373282 1.42993515	0.08535717 0.39504374 0.12095196	0.78672923 0.37103893 0.15875746	0.02349833 1.39935751 0.8542466	0.82703582 0.52330158 0.60246845	low low low
TCGA-62-A46Y TCGA-05-5428	0	0.15555185 0.07768706	1.64047841 1.94714209	0.32587636	0.30253618 0.4382115	0.24963065 0.27088268	0.47876187 0.06737926	1.11755972 0.90420007	high
TCGA-67-6217 TCGA-MN-A4N5	0 0	0.44975362 0.17385877	1.42552187 1.32839072	1.78361078 1.1517348	0.13459072 0.09554362	0.93391472 0.87714365	0.84815943 0.41363502	0.18516686 0.44845994	low low
TCGA-55-7724 TCGA-69-A59K TCGA-99-8028	0 0 0 10990012	0 0.48315135 0.09221878	1.6290115 1.60629487 1.68480118	0.67957036 1.5175191 0.55806351	0.11675095 0.31227297 0.48232741	0.37218688 0.81970864	0.72003045 0.23841893 0.94633381	0.72602617 0.33401257	low low
TCGA-38-4627 TCGA-55-8616	0	0.03789979	1.39828893 1.71218299	0.56801631	0.41620349	0.30085513 0.45783382	0.24370231 0.84527317	1.7258701 0.42211703	high
TCGA-NJ-A7XG TCGA-49-AAQV	0 0.04615098	0.18957663 0.07617094	1.86771226 1.41106498	1.48984655 1.6298294	0.60930053 0.39130812	0.87191562 0.68457003	0.04311993 0.82148818	0.57518603 0.53267459	low low
TCGA-44-6777 TCGA-55-8092 TCGA-73-4675	0 2.35390813 0 50992949	0.10851845 0.30625614 0.03153366	0.9780632 2.11865955 1.58975198	0.74049165 0.50896764 0.34943492	0.6736766 0.73445234 0.2134854	0.42251099 0.19805695 0.70707999	0.29613608 0.533142 0.11258371	2.40755401 2.80718199 1.17693349	high high bigh
TCGA-55-A4DG TCGA-MP-A4TF	0.0760416	0.23944069	1.96604095 1.78477118	0.92919441 1.31413263	0.17977625 0.74228782	0.53538752	0.11256571 1.22398037 0.17565878	0.27994154	low high
TCGA-35-5375 TCGA-78-7158	0 0	0.10307373 0.09161653	1.67939002 1.68894482	1.09115548 0.88314758	0.30749334 0.17815995	0.12718787 0.26780568	0.27262786 0.04030316	1.06993801 1.00219359	high high
TCGA-91-6840 TCGA-55-8299	0 0.05795161	0 0.09539777 0.0715366	1.62727858 1.4626345	0.08414528	0.265362	0.10881791 0.27819336 0.17187741	0.65192257 0.87535176	1.46606112 0.93323321	high Iow
TCGA-38-A44F TCGA-78-7155	0	0.24375194 0	1.39209097 1.77911429 1.45981401	0.19596638 0.17849297 0.06696604	0.18645323 0.42697704 0.11086259	0.08033785	1.07283023 0.16138093	0.94205855 2.04194269	low high
TCGA-78-7147 TCGA-86-7711	0 0.29495534	0.04543227 0	1.89880416 1.33847559	0.12639463 0.49166211	0.30969575 1.0960959	0.309032 0.23457806	0.22995474 0.20572547	1.22957454 5.32363875	high high
TCGA-35-3615 TCGA-50-5946	0.18236711 0	0 0.01924249	1.57959918 1.51284834	3.63544911 0.45092907	0.05108427 0.66478218	0.15298513 0.36205605	0.15902046	0.38591457 2.24063371	low high
TCGA-86-7713 TCGA-50-5051	0.5864897 0.11119803 0.7309304	0.18831192 0.06287545 0.35058222	1.76708778 1.50553936	0.55144947 0.1456665 1.83662787	0.34245382 0.42032695	0.35295339	0.18339974 0.51912116 0.68363726	1.17704078 0.60177644	high low
TCGA-86-8585 TCGA-64-5781	1.17144448 0.31536138	0.28672883 0	1.52520093 1.24938587	2.73627214 1.75749738	0.37168297 1.08166822	0.18498963 0.70830485	0.97227842 0.10706434	0.57561691 2.29295123	low high
TCGA-05-4415 TCGA-97-7937 TCGA-99-8032	1.72795247 0 0	0.05253685 0.09314336 0.16122547	1.18674776 1.75234227 1.40967117	0.09863804 1.69012473 0.22551828	0.33084501 0.30070935 0.57519381	0.24441286 0.27200586 0.37214719	0.04551349 0.13863232 0.48782877	5.3685316 0.74939695 1.68498071	high Iow bigh
TCGA-50-5072 TCGA-55-6970	1.7432267 1.63553664	0	1.53087429 1.334451	0.63546801 0.55011657	0.32422027 0.06123046	0.23937788	0.11924768 0.45200759	3.38884454 2.40748936	high
TCGA-38-4625 TCGA-55-7283	0 0	0.07719879 0.10866785	2.04786744 1.54753817	0.29541412 0.86470811	0.58454213 0.02985809	0.21363943 0.3142776	0.48931161 0.10575724	1.29289312 0.85596584	high Iow
TCGA-55-6975 TCGA-50-6594 TCGA-55-8203	0.87625617 0	0.18823264 0 0.17483309	1.43076593 1.54970613 1.91382194	0.262355 0.75294619 0.2883399	0.26890492 0.34709141 0.31956164	0 0.20034653 0.21453082	0.31136522 0.15883607 0.92316417	2.52047038 1.58119557 0.74061521	high high
TCGA-49-AAR0 TCGA-L9-A7SV	0.18528593 0	0.34103115 0.04456485	2.0777482 1.75503796	1.08855616 0.08387111	0.30358076 0.03584563	0.3068834 0.15978714	0.87930591 0.26704121	0.39284601 1.14278172	low high
TCGA-05-4250 TCGA-97-A4M1	0	0.03856445 0.05415896	1.47413956 2.14502998	0.33165019 0.44883887	0.2311844 0.18005771	0.09413775 0.65191709	0.36378773 0.26105215	1.63682821 0.54056363	high Iow
TCGA-S2-AA1A TCGA-38-4628 TCGA-86-A4D0	0.08912265 0 0	0.51108755 0 0.15349122	1.4179902 1.2155587 1.57866488	0.542274 0.25685209 0.14677811	0.63596821 0.0431115 0.63238512	0.67371362 0.50960363 0	1.64867757 0.04868848 0.07941682	0.43876792 1.38668038 2.94416157	low high hiah
TCGA-49-AARQ TCGA-86-A4JF	0 0	0 0.05001732	1.95042511 1.20215627	1.53957276 1.8172565	0.5851937 0.30537943	1.00407706 0.2862939	0.37189637 0.21419283	0.46547822 1.08245257	low high
TCGA-78-7154 TCGA-91-8496 TCGA-99-8022	1.5935689 0	0.16752955	1.32969482 1.40369583	0.51674418 1.53411391	0.17843548 0.05927565	0.2056839 0.54163348 0.50234094	0.1688307 0.26711818 0.18170255	2.73709631 0.57874408 3.46715400	high Iow
TCGA-86-7714	2029/112 0.28274577 0	0.00408468 0.16397284 0.20348171		1.69564475 0.51956183	0.25465285 0.46952104	0.37804864 0.35924149	0.72258533 0.25864555	0.66341122 1.3570398	low high
TCGA-95-7944 TCGA-55-8301	0.09178488 0.05926797	0 0.18889417	1.49808897 1.47489398	0.42189436 1.26380341	0.2690286 0.45830785	0.14045671 0.23153673	0.39355503 0.89635522	1.65477817 0.83077176	high Iow
тода-44-8120 TCGA-55-6981 TCGA-97-8174	U O 0.25477228	0.10369306 0.19185311 0.02875851	∠.∠4401905 1.01003924 1.85924961	0.53630629 0.80428752 0.65648182	u.27795548 0.02716715 0.09756236	0.28260064 0.69553993 0.56174628	0.48247267 0.45285295 0.49456113	0.043266 0.69177712 0.61516721	iow Iow Iow
TCGA-73-4658 TCGA-67-3771	0.07689321 0	0.06440388 0.22712529	1.10079371 1.97085765	0.17716355 1.93334711	0.1971578 0.48025019	0.36071461 0.58022493	0.18660905 0.38622679	1.92128498 0.3982682	high Iow
тода-75-5147 ТСДА-J2-8192 ТСДА-69-7973	0.08471069 0 0.22062627	0.03592781 0.06308298 0.0327586	1.54064182 1.57156422 1.58157589	1.17051286 1.36607298 0.23300377	0.165205 0.25958114 0.08595433	U.39374391 0.93941822 0.26310882	0.75862878 0.61001947 0.20641493	0.64470536 0.39507126 1.36137664	low low high
TCGA-44-6779 TCGA-86-8074	1.03043762 0	0.09340316 0	1.4028336 1.32910809	0.87144691 1.15295114	0.3222694	0.22214493 0.4633771	0.13901303 0.51341636	2.27046905 2.28074885	high high
TCGA-55-1596 TCGA-55-7914 TCGA-62-64614	0.43668647 0	0.06919511 0.06023447 0	1.42809253 1.83928443	2.27603475 0.53347903 2.41805174	0.17801879 0.07995163 0.6012046	0.68832397 0.45564932 0.37952140	0.13163278 0.44280128 0.1319527	0.55038405 0.63403645 0.66264000	low low
TCGA-91-6831 TCGA-05-5420	0.18794557 0.30531779	0 0	1.95641542 1.59900446	0.47242143	0.33758129	0.36602135	0.18634715	1.16940497 0.73896745	high Iow
TCGA-J2-A4AE TCGA-50-6673	0 0.07632058 0	0.06481546 0.29456923	1.20104286 1.78199079	0.9082371	0.34508225	0.59898703 0.22544029	0.84335455	0.84296832	low low
TCGA-49-AAR2 TCGA-55-8090	0.53587758 0	0 0.22245887 0.03228161	2.31187566 1.41619095	1.13283279 0.62263312	0.13785891 0.44027777	0.65127382 0.45003438	0.75990746 0.25176504	0.27127532 1.49045625	low high
TCGA-49-4486 TCGA-97-8176	1.22857737 1.03395018	0.02962342 0.13365746	1.63280657 1.28201403	2.05887995 1.44000587	0.0549424 0.07299068	0.38934841 0.56871313	0.15902744 0.33588654	0.84927613 0.91409671	low low
тСGA-55-8508 ТСGA-73-4662	υ 0.51618503 0	0.1772028 0.09996297 0.20541704	∠96569 1.63172687 1.57738485	0.00874513 1.36415497 0.57791131	0.04016449 0.67311803 0.04359223	0.40028816 0.53248573 0.46555534	0.53557464 0.90135504	1.12379705 0.47624721	nigh high Iow
TCGA-55-8206 TCGA-49-4512	0.04291288 0	0.13843573 0.07630156	1.83035188 1.31150922	0.06769284 0.78692305	0.0383243 0.23169348	0.58622863	0.84333034 0.35796475	0.48405961 1.17237792	low high
TCGA-MP-A4TE TCGA-91-6828 TCGA-50-6590	0.11194456 0 0.1557240	0 0 0.1922040	1.27648892 1.29868529 1.67125995	0.25407298 0.09754542 0.49372699	0.2386081 0.25821474 0.75365100	0.54648765 0.44889186 0.16130081	0.19581108 0.57636821 0.46460600	1.5548461 1.40754639 1.9480977	high high high
TCGA-86-8279 TCGA-38-4632	0 0.78654384	0.24045331	1.9783538 1.29656313	0.97281262 0.8992594	0.0682981	0.48353122 0.20221684	0.07474285 0.39338127	0.76853916 1.22418409	low high
TCGA-50-5044 TCGA-95-A4VP	0	0	1.08475236 1.61860704	0.44628839	1.23534083 0.34317765	0.39535586	0.13196383	6.12526723 1.18361649	high high
тсда-ө9-7978 ТСДА-48-А93V ТСДА-44-А479	u 0.72204128 0	0.29947936 0.19464132 0.1362951	າ.ຂວອອຮ453 1.54029018 1.49914021	0.53389879 0.24980137	∠.v∠438351 0.5008514 0.14526855	+ <i>1</i>	0.19941027 1.61115916		nigh high Iow
TCGA-05-4430 TCGA-38-4626	0 0.08355556	0.03573182	1.46305112 1.27863484	0.87759742	0.12053765 0.27817798	0.32152662 0.38889957	0.24391909 0.23323362	1.00678346 1.21612132	high high
това-78-7535 TCGA-55-6712 TCGA-MP-А4TD	0 0 0.06736673	0.03506578 0.08342553 0.16297244	2.2368425 1.02789372 1.26972619	1.08858194 0 1.7475481	0.20321594 0.34541577 0.40017907	0.24331129 0 0.13647572	0.03784309 0.71640246 0.94226541	0.6809324 2.5717943 0.82256409	low high low
TCGA-86-6562 TCGA-05-4418	0	0.06636109	1.13977356 1.13779269	0.34419552 0.18440675	0.13836969	0.08212878	0.12635113 0.49217899	2.11415327 5.22370774	high high
TCGA-MP-A4T9 TCGA-69-8255	0	0.09924376	1.35503415 1.57084371	0.98919452	0.1058665	0.48417536	0.53223986	0.6992281	low high
TCGA-05-4384 TCGA-86-8075 TCGA-NJ-A4YO	U.087678 0 0.08633733	0.14340047 0.13465965 0.64683094	1.67070213 1.40460671 1.38862655	3.10048742 0.91584271 1.68161972	0.09739037 0.50428519 0.58005101	0.77844519 0.27865127 0.25338871	0.32003589 0.15866418 1.0238607	0.19569758 1.5936351 0.48177825	low high Iow
TCGA-62-8398 TCGA-73-4677	0.33058925	0.04359629	1.20462249 1.23980006	0.90924375	0.25920587	0.10615903	0.22938795 0.30238492	2.01079717 1.34547922	high high
TCGA-86-8673 TCGA-71-8520	0.16076723	0	1.96791723 1.92983719	2.19022158 0.43660428	0.47939343	0.31576276	0.13168699	0.73219032	low high
тсса-44-7669 ТССА-78-7161 ТССА-53-А4F7	บ.04614762 1.44170284 ด	0.46413113 0.11039039 0.25323851	1.78750268 1.64050479 1.83622632	0.07274895 0.75083269 0.71430109	u.63961032 0.22656796 0.62156673	0.49034976 0.17880361 0.39876407	0.50756785 0.11889332 0.39815902	0.93453383 2.18703809 0.97612593	low high Iow
TCGA-62-8397 TCGA-67-4679	0 0	0.13108289 0.28704835	1.19283803 1.43257624	0.44674492 1.74509747	0.03622147 0.16051868	0.77416075 0.9496788	0.16774033 0.26274331	0.81760539 0.31553594	low low
TCGA-38-7271 TCGA-50-5944 TCGA-91-7774	0 0 0.07450700	0.0846421 0 0.28812045	1.3972327 1.76924364 1.4305427	0.65668227 0.44680673 0.32546202	0.09032065 0.20485738	0.37937746 0.37402353 0.07726946	2.51418513 0.41017479 0.88761464	0.28101276 0.94315114	low low
TCGA-44-7661	0.04336819	0.10967163 0.10614297	1.71857863 1.18268505	0.87093407 0.57101393	0.33386449 0.58821999	0.47835878 0.25098419	0.43579819 0.52040693	0.76112257 2.11096551	low high
TCGA-J2-8194 TCGA-50-5932	0.08939861 0.52544431	0.0379516 0	1.41023906 1.45205505	1.24681484 0.1726296	0.1557491 0.05048825	0.61422238 0.27173833	0.34558316 0.10025891	0.69910332 1.83611086	low high
I UGA-55-8087 TCGA-55-8621 TCGA-55-8085	0 0.07106406 0.40813869	0 0 0.03881147	1.90876603 1.73057693 1.80192182	0.52478895 0.44522219 0.97267847	0.14210859 0.22506036 0.30244809	0.85858119 0.3357041 0.42150609	0.16385022 0.38879293 0.65208058	0.55421119 1.07668826 0.7942738	low high Iow
- TCGA-97-7552 TCGA-80-5611	0	0.19417154 0.1356261	1.56831667 2.20111564	0.14153783 0.92093217	0.14522261 0.30699864	0.39368627 0.57594823	1.32297197 0.32832002	0.55130649 0.46995164	low
TCGA-78-8648 TCGA-91-A4BD TCGA-78-7162	0 0	0.08043304 0 0.08023004	1.2258917 1.72713585 1.84549447	0.28545257 0.58321116 0.49485212	0.5757281 0.2462428 0.09597620	0.77695188 0.19460489 0.09918257	1.37737802 0.08770488 0.25278702	0.8587436 1.37356136 0.99497464	low high
TCGA-86-8359	0 0.08949453 0	0.14631425 0		0. 106 17623 0.36676748	0.42000705	0.94845889 0.08804773	0.24577964	0.59264126 2.69576238	low high
TCGA-55-6983 TCGA-75-6212	0.32170694 0	0.07324522 0	1.63212115 1.70848604	0.4037617 1.47614617	0.16134738 0.47860758	0.25632738 0.64481104	1.38040087 1.06241451	0.69538657 0.48366163	low low
тСGA-55-7284 ТСGA-93-А4.IP	0 0.6942871 0	0 0 0.26302871	1.72953885 1.30071024 1.53248835	1.91293416 0.06925259 0.32699158	0.19933908 0.14186923 0.29012629	0.53701729 0.50277098 0.32063832	0.10874969 0.27024941 0.16661915	0.52418341 1.87980607 1.18310676	ıow high hiah

* The training cohort patients were divided into high-risk and low-risk groups using the median risk score as the cut-off.

Table S5 Risk score	for	patients	in	the	testing	cohort
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Id	AC090541.1	LINC02390	NIFK-AS1	AC026355.2	AC107021.2	MIR34AHG	LINC01215	Risk score	Risk group*
TCGA-MP-A4T8	0.462189093	0.049617916	0.827135635	1.849496129	0.281101526	0.686717537	0.184058334	1.174838073	high
TCGA-95-7039	0	0.079439228	0.864753818	0.767269774	0.240711939	0.098210119	0.228011479	2.276360042	high
TCGA-62-A46S	0.115275337	0.096757925	1.408224903	0.581425682	0.164173807	0.33224677	0.292549133	1.17802352	high
TCGA-49-6743	0.075822907	0	1.119435863	3.664156263	0.469803371	0.356147304	0.369237309	0.622441881	Iow
TCGA-53-7626	0.04163676	0.257427551	1.854866588	2.026779879	0.168660005	1.001998911	0.919580353	0.142549274	Iow
TCGA-55-7574 TCGA-78-7163 TCGA-91-A4BC	0 0 0 0	0.258279664 0 0.344056392	1.509689153 2.056734817 1.578315141	0.642564582 0.772845466 0.443294529	0.120805799 0.214585076 0.473783899	0.492238376 0.236051443 0.181499261	0.270307147 2.081761687 0.111353277 0.368413791	0.254124551 0.903708009 1.25967579	low low high
TCGA-69-7980	0	0.036889572	1.99496831	0.603002936	0.329011939	0.330954242	0.423665696	0.855338823	low
TCGA-05-4417	0.246293812	0	1.109430839	0.135841537	0.186907694	0.402701446	0.640616115	1.649047122	high
TCGA-05-5425	0.076928936	0.126112717	1.418458218	0.431451377	0.118310125	0.360866871	0.634691675	0.900527345	low
TCGA-44-6146	2.553693899	0.114651138	1.416562163	2.167833018	1.055850418	0.904188521	0.189599334	3.007591549	high
TCGA-67-3770	0	0.090389553	1.424838802	2.135074145	0.164763499	0.111649415	0.519085323	0.647185823	Iow
TCGA-MP-A4T4	0	0.318326776	1.260567797	0.594844888	0.36285539	0.441949138	0.448354931	1.020907578	high
TCGA-NJ-A4YF TCGA-50-5055 TCGA-44-6776 TCGA-64-1677	0 0.112304036 0.260497241 0	0.06751282 0 0.077255484 0	1.359738739 1.666322128 1.41322253 1.595419159	1.37832961 0.536876295 1.27317569 2.744073024	0.971190587 0.194545136 0.062276931 0.542285987	0.237390682 0.324273971 0.349165053 0.471159777	0.100916159 2.709824158 0.083279334 0.435123429	2.739437251 0.294849196 0.947460711 0.570805791	high Iow Iow
TCGA-05-4389 TCGA-05-4425 TCGA-91-6835	0 0 0	0 0 0.486396563	1.595419159 1.532233662 1.669927699 1.81689458	2.744073024 1.147397882 0.12571854 1.153155579	0.052426662 0.052478184 0.075308675	0.389704247 0.307477423 0.484560323	0.435123429 0.486268703 0.128015952 1.891926192	0.673181002 1.210365793 0.134972855	low high low
TCGA-55-6982	0	0	1.001427643	1.511789428	0.292567706	0.312125541	0.188752221	1.471379467	high
TCGA-55-A491	0	0.059177313	1.085400365	0.309959802	0.465233445	0.143019066	0.336103809	2.775983044	high
TCGA-55-8094	1.380228518	0.322692636	1.451877862	0.563905795	0.392515374	0.553757129	0.076087697	1.834937301	high
TCGA-62-A46R	0	0.22515613	1.616215212	0.056977006	0.168845281	0.275235146	0.604075666	0.913915495	low
TCGA-49-AAR9	0	0	0.809622046	0	0.29816666	0.188289632	0.034502394	3.867280461	high
TCGA-55-7227	0	0.066558218	1.63805715	0.782994331	0.310102405	0.234220234	0.483192527	1.049001141	high
TCGA-55-A48Z	0.067498429	0.355698693	1.362380795	0.543274011	0.576419695	0.376563206	0.197496056	1.497880545	high
TCGA-MN-A4N4	0.128217753	0.15867478	1.21082647	2.361986993	0.733767695	0.613999463	0.138123487	1.024369245	high
TCGA-49-6744	0	0.222243956	1.501902245	0.811231526	0.638287346	0.390543341	0.736104701	1.067514806	high
TCGA-73-4676	0	0	0.699367607	2.623946189	0.197816377	0.275625174	0.126141474	1.136159018	high
TCGA-38-4630	0	0.104742187	2.293165211	0.050911597	0.386214832	0.459261303	1.264957302	0.466601668	Iow
TCGA-75-7027	0.5161239	0.093901339	1.694842315	0.513719638	0.378081747	0.188383706	0.08150231	1.916542465	high
TCGA-05-4382	0	0.082491564	1.741347035	2.808758394	0.907358184	0.197184636	0.640983453	0.804608066	Iow
TCGA-78-8662	0	0	1.783156979	1.386279562	0.041490659	0.094799266	0.175942515	0.782754961	low
TCGA-97-8552	0	0	1.845035141	0.615298391	0.086911959	0.808688098	0.776248798	0.391189379	low
TCGA-91-6847	0	0.198921556	1.863358085	0.040132114	0.316159879	0.19809555	0.009186839	1.398406026	high
TCGA-73-4659	0	0	1.209138902	0.650065188	0.110694404	0.411445879	0.080377706	1.387697208	high
TCGA-86-A4P8	0	0.195900043	1.665393357	0.353320711	0.120977441	0.492855987	0.784674691	0.561142668	Iow
TCGA-44-5643	0	0	1.733174698	1.623773706	0.055038421	0.508353194	0.546936725	0.412817384	Iow
TCGA-97-A4M7 TCGA-86-8056 TCGA-L4-A4E5	0 0 0	0.265988294 0.134599671 0 0.163817121	1.472565577 1.420474856 1.294971805	0.504351165 0.879401514 0.840389189	0.545971757 0.073516104 0.111759863	0.505805568 0.349146479 0.459415041	0.825998907 0.679983561 0.176581668	0.900921411 0.67306283 1.091117904	low low high
TCGA-86-8671 TCGA-78-7152 TCGA-05-5715	0 0 0	0.163817121 0.487332122 0.103624423 0	1.88938398 1.573245446 1.130892661 1.138725007	0.821083854 1.27553276 0.488590132	0.436766194 0.147196994 0.028436065 0.111925482	0.415095323 0.245308362 0.293178623	0.362635512 1.536242822 0.926749425 0.108681047	0.263463643 0.675313082 1.722855885	low low low hiah
TCGA-55-A48Y	0.837831373	0	1.144434083	2.739149263	0.106732268	0.328084712	0.180138311	0.913881895	low
TCGA-86-8054	0.047454016	0	1.146251159	0.246377318	0.368163436	0.353461738	0.10878853	2.459704003	high
TCGA-44-2655	0.756654843	0.083367275	1.720696983	3.069813509	0.067231181	0.103033674	0.838570627	0.370006889	low
TCGA-78-7220	0.605983146	0.10989509	1.596250594	0.294579463	0.374285779	0	0.095453272	2.720080065	high
TCGA-91-6836	0	0.055707526	1.465397401	0.104492002	0.158023047	0.371785209	0.226646241	1.350973959	high
TCGA-05-4420	1.254069716	0.028943837	1.525121732	0.27817642	0.127087792	0.324448876	0.336504717	2.004144195	high
TCGA-67-3774	0.220947024	0.29868541	1.633910092	0.804140895	0.213954781	0.156397134	1.621668847	0.450879075	low
TCGA-86-7701	0.397142511	0.526518582	1.632521363	0.224134145	1.074980776	0.285988884	1.279400571	1.408781965	high
TCGA-44-A4SS	0.279176248	0.123033934	1.110946485	1.454713908	0.146762215	0.413974419	2.24222353	0.329836689	low
TCGA-64-1678 TCGA-49-AARR TCGA-97-7546	0 0 0.073116541 0.065218021	0.386407929 0.077543376 0 0.206960181	1.548595929 1.772428335 1.518567753 1.471325238	0.797026844 0.366827405 1.326752366	0.939123208 0.614826762 0.187845601 0.194482468	0.811725666 0.517940783	0.050732273 0.822157561 0.751198826	2.1135711 0.626842657 0.48458583	high Iow Iow
TCGA-55-7573	0	0.282419996	2.25924388	0.388939995	0.398239898	0.556707092	1.052758539	0.357887607	low
TCGA-97-A4M6	0	0.162622415	1.637810072	1.287984624	0.410967656	0.672604564	0.972630681	0.435569541	low
TCGA-75-6214	0	0	1.035468372	0.270212202	0.198486987	0.123752795	0.597540804	2.011770195	high
TCGA-50-5936	0.756348693	0	1.261357501	0.314633539	0.367589802	0.212810484	0.287773923	3.058583139	high
TCGA-75-5125	0	0.863500959	1.060436887	2.203127656	0.1812405	0.359820289	0.437315688	0.299674388	Iow
TCGA-NJ-A4YI	0	0.07725279	1.951120372	0.394911501	0.19791042	0.09552392	0.146601006	1.150535659	high
TCGA-44-5645 TCGA-86-8674 TCGA-78-7156	0.925304885 0.350557896 1.221839351	0.797518438 0 0 0 11634816	1.880165967 1.404088925 1.608179523	3.665424896 3.468052798 2.871080316 0.263408256	0.758759706 0.15103114 0.136198488	1.895522377 0.424957981 0.428350283	1.463530036 0.014228542 0.056598607	0.036780677 0.478615391 0.721720703	low low low
TCGA-44-5644 TCGA-97-A4M0 TCGA-44-A4SU	0 0.854302831 0 0	0 0 0.325133086 0.156593188	1.468120851 1.613307216 1.957635188	0.203406236 0.402028818 0.756176589 1.040768502	0.434623386 1.035980669 0.107315023 0.483785743	0.097431568 0.781585155 0.928750476	0.051565747 0.635922909 0.731657444	7.33206516 0.350585042 0.371084816	high Iow Iow
TCGA-78-7145	0	0	0.789905564	0.762969011	1.785272201	0	0.234393192	17.68411195	high
TCGA-44-7670	0.211693313	0	2.602618108	0.170870133	0.350267984	0.091675331	0.91718485	0.70996426	Iow
TCGA-05-4396	1.528510309	0	1.321503303	0.378412629	0.30485024	0.209748799	0.113038374	4.062919585	high
TCGA-95-8039	0.040951848	0.132304557	1.491641229	0.714907785	0.166001954	0.504184289	0.834561317	0.613521836	low
TCGA-64-1676	0	0	2.410082449	2.226922166	0.575875066	0.082106138	0.071536584	0.693349115	low
TCGA-95-8494	0	0.215567649	1.332675285	0.780301699	1.275959985	0.416039067	0.143335945	3.567296623	high
TCGA-50-8459	0.066109126	0.257629003	1.327210084	0.246735718	0.370344967	0.314179356	0.954371315	1.05237649	high
TCGA-78-7148	0.831067808	0	1.402699259	0.241571384	0.304436627	0.131075106	0.136286399	3.185850096	high
TCGA-44-3917	1.058971085	0.743633963	1.585745912	3.760665345	1.544453658	0.655068666	0.725066607	0.61179217	Iow
TCGA-35-4122 TCGA-50-8460 TCGA-J2-A4AG TCGA-93-7348	0 0 0	0.046261803 0.117618704 0.368596717 0.067178482	1.306814593 2.377724307 1.429530158 1.43245671	0.284051402 0.490752484 0.799544809 0.348050637	0.321650609 0.317768762 0.569651978	0.276690441 0.240163664 0.161738995	2.738632098 0.632783584 1.321297121 0.454948057	0.394237135 0.566678314 0.549842635 2.158053496	iow Iow Iow hiah
TCGA-49-4501 TCGA-55-6642 TCGA-05-5423	0 0 0	0.217049211 0	1.962930977 1.441583842 1.481455501	1.109459522 0.498791512 2.233555871	0.216835022 0.41436874 0.07872235	0.435472423 0.265485179 0	1.141414479 0.144345696 0.678620115	0.39548735 1.536898411 0.604399615	low high low
TCGA-05-4398	0.196649468	0.165791953	1.169170114	0.96054003	0.290681542	0.429108368	0.533348548	1.077901799	high
TCGA-05-4433	0	0	1.334867278	0.145951285	0.083599054	0.187604525	0.532094601	1.434802512	high
TCGA-62-8394	0.06101177	0	1.350344085	0.27046687	0.218713448	0.291774425	0.19896356	1.771564143	high
TCGA-50-5942	0.079623627	0.066700991	2.017100585	0.124705384	0.280985999	0.613506476	0.280586153	0.800531245	low
TCGA-44-7662	0	0.034716162	1.364374083	0.301412171	0.318911557	0.241050237	0.123603959	1.998051053	high
TCGA-55-A490	0	0	1.026136492	0.420458729	0.463846127	0.372107209	0.195016194	2.581115215	high
TCGA-97-7941	0.090660435	0.038496979	1.493091359	0.331124812	0.17647278	0.771235691	0.323353235	0.848847615	low
TCGA-97-8175	0.045928415	0.147829491	1.128959817	1.225397103	0.332944359	0.264735662	0.274778344	1.355811899	high
TCGA-55-8507	0.21914237	0	2.335344331	0.762165772	0.487727327	0.360342812	1.994610497	0.34350396	low
TCGA-38-4629	0.112607731	0.083686036	0.974719971	0.090291171	0.318824381	0.258914082	0.23329393	2.755322478	nign
TCGA-86-7954	0	0.187722239	1.372121561	1.103637991	0.16043943	0.518366606	1.214756769	0.421031346	Iow
TCGA-55-6984	0.096922806	0.081270873	1.144625127	0.221385016	0.207769219	0.282552605	0.446869348	1.702326119	high
TCGA-55-7816	0	0.085989579	1.726812785	0.717646379	0.444841356	0.341984389	0.1368685	1.265153038	hiah
TCGA-99-AA5R	0	0.118978321	1.913954913	0.76306906	0.325118583	0.513912472	1.21906336	0.418093567	low
TCGA-55-7727	0	0.473598972	1.164647279	2.344163511	0.169461854	0.471803538	1.299087541	0.220020425	low
TCGA-69-7765	0	0.130059144	1.346086626	0.992762934	0.527367991	0	0.350671653	1.949624685	high
TCGA-93-7347	0	0.242673638	1.377752587	1.226389962	0.197735104	0.340226196	0.857042441	0.567181403	low
TCGA-49-6742	0.347645135	0	1.760439836	0.814529916	0.145734705	0.359268817	0.017598779	1.118893219	high
TCGA-86-8280	0.100766862	0.202665821	1.549910907	1.26908007	0.312540363	0.86855964	0.752139733	0.392773088	low
TCGA-55-7725	0	0.611552484	1.904501439	0	0.215701704	0.248168894	1.007327563	0.42340251	low
TCGA-L9-A50W	0	0.086971181	1.559544673	1.294168394	0.475424543	0.587487056	0.164559533	0.921742766	low
TCGA-44-3919	0	0.037005221	1.55350544	1.029307861	0.481161265	0.29434826	0.93309295	0.93998466	low
TCGA-55-1594	0.058585764	0	1.813482824	0.178730829	0.321278967	0.229021931	0.309111795	1.448948646	high
TCGA-55-8514	0.08525749	0.071442972	1.636511495	1.294523916	0.148689049	0.590161203	0.19230362	0.613207391	Iow
TCGA-91-6849	0.8501354	0.200063336	1.536787494	1.612422939	0.136719703	0.127705642	0.503635801	0.896945687	Iow
TCGA-44-3918	1.128072888	0.558135393	1.81503869	3.710921275	2.162490565	0.868167744	0.67937299	1.147088143	high
TCGA-62-8395	0.066391068	0.305256822	1.584231335	0.896646467	0.262383352	0.370989056	0.336892079	0.744558609	low
TCGA-44-2662	1.265738826	0.31555024	1.445754067	3.89197983	3.385158901	1.843707361	0.888996459	2.918212908	high
TCGA-97-A4M5	0.310599433	0.18085121	1.432431926	0.290385121	0.099494495	0.32111765	0.389764811	1.142359963	high
TCGA-49-AARE	0.056987162	0.620677589	1.535934365	0.401131781	0.193710429	0.545913277	0.367783509	0.510071189	low
TCGA-78-7159	0.136633247	0	1.902659547	0.352309534	0.31449503	0.388760542	0.259268931	1.144358331	high
TCGA-55-7281	0.131946698	0.056490866	1.5087086	1.124982356	0.118219045	0.200484216	0.291976142	0.990020923	high
TCGA-MN-A4N1	0	0.530300416	1.264754395	0.509743365	0.253163094	0.511210649	0.09280909	0.837700072	low
TCGA-49-4506	3.468877821	0.123162682	0.89522552	0.145711101	0.099586084	0.353054151	0.344328465	7.438326639	high
TCGA-91-8497	0.092702466	0.68597426	1.858307522	0.508316801	0.199043731	0.63318373	1.450898135	0.182115034	low
TCGA-73-4670	0.397060015	0.026972691	1.315686208	0.462660793	0.324494846	0.435389209	0.046306805	2.03072703	high
TCGA-44-3396	0	0.205516823	1.26703181	0.760239853	0.369140376	0.716347657	0.651296153	0.746831786	Iow
TCGA-55-A57B	0	0.37530161	1.524611856	0.819913707	0.152100328	0.703591646	0.380392226	0.45302205	Iow
TCGA-55-8089 TCGA-55-8091 TCGA-64-5779 TCGA-86-8278	0.435081233 0.097601749 0 0.035526442	0.11110368 0.081843269 0.169972706	1.550216 1.300762763 1.953819857 1.463703244	0.036267446 0.689326627 1.209231875 2.31807665	0.354094953 0.538505783 0.723991065 0.552689839	0.221615165 0.627402419 0.552677581	0.981357244 0.17939907 1.02860239 0.130044065	1.400489873 1.546487268 0.548744116	high high Iow
TCGA-73-4666 TCGA-55-6980 TCGA-50-8457	0.033320442 0.037114661 0.220850453 0.061350319	0.309235687 0.271333853 0.148846153	1.313346866 1.518613089 1.721457125	0.542120535 1.037613388 0.924927906	0.406323869 0.472153399 0.068214819	0.314287583 0.425823642 0.665465497	0.213671653 1.281300628 1.359175066	0.59926090 1.39147595 0.587034023 0.267160406	high Iow Iow
TCGA-50-5931	0	0	2.326002566	0.203805677	0.22657795	0.841334489	0.544152593	0.415554713	low
TCGA-55-6971	0	0.272723401	1.60698724	0.33877991	0.176048087	0.757482373	1.372103485	0.32429998	low
TCGA-64-1679	0.145277945	0.031518512	1.101430227	0.528571119	1.473584323	0.253874935	0.471477583	7.514434228	high
TCGA-95-7948	0	0.077764203	2.227334452	1.994620633	0.052428304	0.726594962	0.067446391	0.23707493	low
TCGA-64-5815	0	0	1.084529537	0.96190428	0.658136234	0.101290634	0.155289209	3.291639594	high
TCGA-05-4426	0.034639374	0.085146248	1.476884534	0.51129112	0.519394659	1.0242984	0.205691657	0.932722689	low
TCGA-97-8172	0.07509404	0.341802824	1.643830798	0.200096133	0.229829685	0.444044698	1.59068393	0.404169021	low
TCGA-L9-A444	0	0.223423662	1.254764544	2.087189212	0.103829977	0.273152529	0.929572646	0.412236486	low
TCGA-86-8055	0.131028385	0.037632871	1.47515785	0.812605842	0.531124712	0.135752474	0.269695728	2.055691789	high
TCGA-78-7633 TCGA-49-6745 TCGA-97-A4LX	0.326205743 0.069147125 0	0.030205753 0.113547992 0.679380394	2.082412727 0.953109623 1.298696561	0.359053315 0.209438813 0.32311852	0.071625119 0.135531286 0.518101215	0.10968009 0.267600791 0.553651332	0.390312900 0.058164189 0.339559401 1.387456138	1.141820796 1.869300687 0.474115659	high high low
TCGA-55-A493	0	0.305542707	1.038038084	0.419593292	0.667654993	0.197578497	1.847630678	1.084428373	high
TCGA-93-A4JQ	0	0.53611389	1.702800255	1.442248181	0.619868872	0.229380209	1.913596407	0.295779774	Iow
TCGA-55-8506	0	0.066174651	1.099169016	0.393357445	0.035754549	0.609466178	0.057364111	1.197601164	high
TCGA-78-7540	0.195691284	0	1.273576759	0.244789172	0.072877959	0.084478436	0.129910135	2.14151939	high
TCGA-55-8204	0	0	1.344583104	0.168420609	0.230789197	0.216021573	0.232988549	1.931123671	high
TCGA-MP-A4TJ	0	0.248342828	1.395935284	0.083702089	0.243798114	0.303060375	1.797249602	0.568907366	Iow
TCGA-97-7554	0	0.148963251	1.36604519	0.428568542	0.220032097	0.395987254	0.229384762	1.211599222	high
TCGA-05-4434	1.185991468	0.265057329	1.408257517	0.505684772	0.956790307	0.472887823	0.901117436	2.51394159	high
TCGA-MP-A4T7	0.58201977	0.14222246	1.502718086	1.084179267	0.373396201	0.228856485	0.228488964	1.516708706	high
TCGA-93-8067 TCGA-44-6148 TCGA-95-7947	0.076195163 0	0.209231434 0.030965655 0.063816719 0.196365945	0.974790956 2.191861573 1.213540769	0.367113371 0.175608919 0.115647317	0.245591799 0.149005135 0.671221712	0.375168246 0.536314497 0.756606683	0.104333546 0.292476241 0.488744711	2.152167876 0.628746781 1.532451341	high Iow high
TCGA-78-8660	0	0.35645882	1.808757288	0.575516254	0.572382622	0.368109267	0.64632184	0.795473409	low
TCGA-05-4402	0	0.026895363	1.541255617	0.990844159	0.528704631	0.303542183	0.880921822	1.051834161	high
TCGA-86-8669	0.463274452	0.073998774	1.471196306	0.680336421	0.577622762	0.726791466	0.386270069	1.362755937	high
TCGA-69-7764	0.767852483	0.457255759	1.956528054	0.492211404	0.137090001	0.261705071	0.568931891	0.631111121	low
TCGA-73-4668	0.033187471	0	1.172904774	0.199256098	0.402295962	0.445984078	0.104963646	2.333569254	high
TCGA-44-2666	0.885715595	0.365663817	1.722754098	1.815223688	0.603918377	1.753443386	0.184083016	0.270370458	low
TCGA-55-7907	0	0.088370754	1.788078858	1.059867468	0.204099514	0.210663536	0.31690652	0.809002922	low
TCGA-44-6774	0	0.097136652	1.411859763	0.845861527	0.476082905	0.333447428	0.275799613	1.46166379	high
TCGA-50-5933	0	0	0.959408361	0.4638117	0.636752117	0.150450106	0.054035978	4.363413741	high
TCGA-05-4422 TCGA-L4-A4E6 TCGA-55-7570	0 0.311823123 0 0.063215142	0.095332372 0.342867826 0.163629986 0.153233171	1.662796132 1.434939349 1.391686896 2.312323964	0.605357027 0.922787063 0.653415853 0.192243916	0.208153762 0.162877725 0.305009065 0.188760274	0.553413885 0.474561474 0.320889211 0.065549816	1.105124894 1.116946243 0.544399821 0.079279911	0.496214882 0.458566215 1.061582126 0.945001586	low low high low
TCGA-78-7166	0.829255153	0	1.325474494	0.239083071	0.882924167	0.264870389	0.188970673	5.707469931	high
TCGA-50-6593	0	0	1.254329299	0.262010793	0.170629315	0.176181468	0.306585886	1.850197957	high
TCGA-44-2659	0.346667272	0.105012622	1.269417415	1.0401581	0.164907763	0.12956037	0.476642153	1.301943843	high
TCGA-44-6778	0	0.58343308	1.630649659	0.144912301	0.786885266	0.271124592	1.233887307	0.856763282	low
TCGA-62-A470	0	0	1.219711259	0.357630147	0.366272634	0.315732806	0.594237333	1.716339666	high
TCGA-86-8076	0.592714397	0.125378207	1.530940194	1.048432903	0.386714616	0.500075935	0.594561639	0.987034849	high
TCGA-44-3398 TCGA-MP-A4TI TCGA-55-8302 TCGA-97-7547	0 0 0	0.081029019 0.271239573 0.123509458 0	1.373307993 1.252826403 1.343740954 1.42263184	1.961079854 1.100651429 0.596097707 0.201131214	0.734686732 0.634966102 0.178116599 0.035834795	0.443046119 0.647354816 0.47436512 0.209285286	0.432410438 1.243346587 0.366993791 0.435461648	1.094036528 0.640853186 0.969726696 1.282816161	high Iow Iow bigh
TCGA-91-6830	0.107320809	0.174792066	1.741179605	0.744871674	1.023520088	0.486165092	0.27346397	1.87386688	high
TCGA-35-4123	0	0.093969387	1.585897545	0.470138035	0.271291202	0.370879144	0.455005468	1.025173014	high
TCGA-86-8668	0	0.085391029	1.814854364	0.232061257	0.407056371	0.875531348	0.559983239	0.656343354	low
TCGA-50-5941	0.088058196	0.073801394	1.211680909	0.32234392	0.54891142	0.258155495	0.931433343	1.816111777	high
TCGA-55-6968	0	0.217070618	1.938853485	0.072632915	0.382740184	0.182320829	0.27558035	1.207124778	high
TCGA-50-6597	0	0	1.749213299	0.087258405	0.097447655	0	0.939454005	1.032869239	high
TCGA-44-A47B	0	0.050163463	1.294291961	0.959869175	0.306197483	0.234041277	0.136684916	1.564836647	high
TCGA-50-5935	0.251876001	0	1.759341646	0.85549527	0.311450452	0.411355411	0.311011748	1.037718005	high
TCGA-NJ-A55A	0	0.478657913	1.77316186	0.378821947	0.275411303	0.258035316	1.643901621	0.34623951	Iow
TCGA-55-6972	0.450013986	0	2.190463788	2.344004676	0.029133956	0.130892055	0.240457706	0.433274949	low
TCGA-69-8253	0.406105375	0	1.559816781	0.922428433	0.243621437	0.142493037	0.390548942	1.430893269	high
TCGA-05-4249	0	0	1.499051689	0.578538524	0.111067175	0.139613358	0.290952285	1.314475471	high
TCGA-MP-A4TK TCGA-MP-A4TA TCGA-97-8179	0 2.60642038 0.904669213	0.109178659 0.321562759 0.046921618	1.348262025 2.380975366 2.031447073	1.70041335 1.109003528 1.829668146	0.983415085 0.204830911 0.074532098	0.476457387 0.657225029 0.365103694	0.783952325 0.263471119 0.050621622	0.209180834 1.27993658 0.798685239 0.652542767	high Iow Iow
TCGA-75-6206	0	0	1.727117548	0.596844238	0.156858542	0.341827981	0.173314876	1.020167316	high
TCGA-49-AARN	0	0.258131235	1.911294079	0.32102994	0.188602875	0.982063717	0.733939041	0.308514575	Iow
TCGA-55-6985	0	0.15814688	1.048238432	0.221303132	0.319320534	0.194304605	0.459902941	1.987596263	high
TCGA-L9-A443	0	0.293970276	2.162869992	0.828802323	0.195336762	0.224971056	0.233624646	0.54335186	low
TCGA-97-A4M2	0.183593389	0.53872378	1.536599762	1.675957223	0.203208374	0.460021649	0.62097575	0.335248135	low
TCGA-55-7576	0	0.085799124	1.420644085	0.256837484	0.11356125	0.297205036	0.353897883	1.206180906	high
TCGA-78-7160	1.292607438	0.133189929	1.299949712	0.872163844	0.158771451	0.163959291	0.645403314	1.725573054	high
TCGA-55-8510	0	0.19532778	1.469985624	1.136673232	0.054855067	0.310999065	0.673693435	0.556034087	Iow
TCGA-55-8615	0.903036727	0.060292891	1.127980541	0.315318592	0.199501488	0.399070553	0.052251331	2.649734324	high
. CGA-49-4488 TCGA-49-AAR3 TCGA-38-4631 TCGA-95-7562	U O 0.523998863 O	0.004405041 0.442068088 0 0.111185139	0.000031419 1.419379242 1.248902749 1.238134442	1.324843431 0.550452227 0.236752204	0.342960418 0.19715003 0.789195971	0.292705078 0.236925316 0.381822026 0.449495346	0.814880965 0.05582225 0.08877352	0.567316533 2.021125301 3.021434471	nign Iow high hiah
TCGA-55-7903	0	0.15644024	1.529289737	0.285143073	1.205548286	0.361837517	0.318981181	3.511392035	high
TCGA-95-7043	0	0.172089471	1.336884909	1.256956893	0.07148341	0.109465887	0.019610191	1.070817754	high
TCGA-MP-A4TH	0	0.409274593	1.707870625	1.609485968	0.081957849	0.397790807	1.841066169	0.149601715	Iow
TCGA-50-5930	0.564026913	0	1.817768682	0.465288148	0.512535279	0	0.51698037	2.207096028	high
TCGA-50-6592	0.170987447	0.274845415	1.553192908	0.222610248	0.952301474	0.762509597	0.493718806	1.539449311	high
TCGA-NJ-A55R	0.092272547	0.026247375	1.737003104	1.591804343	0.467587605	0.496983395	0.777360628	0.607613454	Iow
TCGA-91-8499	0	0.075909237	2.362796404	0.072503923	0.489902742	0.182008921	0.725642662	0.898617244	low
TCGA-55-6986	0	0.153359685	1.347096402	0.806516184	0.361552332	0.097322472	0.327030587	1.557094639	high
TCGA-67-6215	0.037976075	0.062793086	1.370563269	1.476365614	0.382087735	0.187008454	0.200344896	1.324777586	high
тода-78-7536 TCGA-78-7143 TCGA-73-7499 TCGA-49-4497	0.18530039 0 0.57642899	0.032606735 0.154255432 0.163005298 0.423656055	1.633025199 1.132820622 1.788832515 1.448102147	0.586467216 0.552388605 1.295703382 0.541892225	0.609258726 0.391436358 0.142629723 0.429497472	0.191854824 0.553956762 0.200198872	0.103099868 0.98793857 0.403856394	2.34319652 0.943897638 0.605966898 0.811689947	high Iow Iow
TCGA-MP-A4SW TCGA-75-5146 TCGA-49-4490	0 0 0 0	0.239036227 0.41438345 0.091785435	1.419280294 1.939432716 1.91124212	1.184072402 1.077917011 0.460481309	0.43983716 0.180668818 0.167243201	0.853847042 0.427662271 0.494391851	0.642132793 0.89734174 0.635507568	0.517832451 0.285841319 0.572259643	low low low
TCGA-55-7913	0.566195088	0.066471741	1.559430629	0.210941397	0.113602201	0.269483125	0.126557506	1.674425327	high
TCGA-55-8505	0.487040744	0.067418092	1.35847339	0.586915631	0.343171243	0.375923026	0.086803443	1.963273941	high
TCGA-50-6595	0.461615936	0	1.067044584	0.137502002	0.667568907	0.091153412	0.125102707	5.877765807	high
TCGA-62-A471	1.637130736	0.1634968	1.307404626	1.074936947	1.250516573	0.483588384	0.072930615	6.50451676	high
TCGA-80-5608	0	0.037321519	1.605136342	0.070393161	0.153263948	0.134666233	0.19099304	1.59364233	high
TCGA-62-A46O	3.067561988	0.127754542	1.877553372	0.122119946	0.603835686	0.488812013	0.028575387	5.630624576	high
TCGA-44-A47A TCGA-95-A4VN TCGA-44-2657	0 0 0.089485134	0.169820098 0 0.214237107	1.621968858 0.989361546 2.28389274	2.739966667 1.20077059 0.384550849	0.542350974 0.084940211 0.174250315	0.697609172 0.410759626 0.55075757	0.462407215 0.56753362 2.087875563	0.36945469 0.972056635 0.170570038	low low
TCGA-MP-A5C7 TCGA-55-A492 TCGA-NJ-A550 TCGA-05-4000	0.281120285 0.233719736 0.144107732	0.162991768 0 0.336631992	1.804008113 1.798515089 1.467737522	3.008269228 2.626840465 0.876348617	0.121573507 0.134884217 0.1597338	0.639846903 0.064367789 0.522117836	0.26335549 0.04500277 0.349853605	0.235881332 0.640484473 0.625287332	low low low
TCGA-78-8655 TCGA-49-4494 TCGA-86-6851	U 0 0 0	U 0.577184131 0 0.2000 <u>99147</u>	1.526652644 0.986403508 1.366684784	0.200521348 1.625648978 0.52065105 0.033730528	0.159480621 0.195305136 0.204699779	0.26790931 0.216579898 0.318299717	0.249683204 0.129264445 1.212801521	2.007403953 0.428465959 2.240177628 0.817719889	nign Iow high Iow
TCGA-67-6216 TCGA-69-8453 TCGA-73-7498	- 0 0 0.113288272	0.123813104 0.101742661 0.095079627	1.187567451 1.367762178 1.943729329	1.243563311 0.097216959 1.812695363	0.323669227 0.108525974 0.141680238	0.416350699 0.585073842 0.794714294	0.795513309 0.670834079 0.452021405	0.829748564 0.834851225 0.274058749	low low
TCGA-55-8096 TCGA-93-A4.IN	0.229025377	0.252531075 0.199774908	1.868328812	0.241835791 0	0.831707755	0.40852438	0.428820207	1.584701346	high

* The testing cohort patients were divided into high-risk and low-risk groups using the median risk score in the training cohort as the cut-off.



Figure S2 Survival analysis of the CLPS in the entire LUAD cohort. Kaplan-Meier curves of (A) OS and (B) PFS in the entire cohort. (C) ROC curves for the risk signature at 1, 3, and 5 years in the entire cohort. (D) The C-index of the CLPS risk score and other clinical characteristics in the entire cohort. (E) Survival state (the middle section) of the patients sorted according to the risk scores (the top section) and the differences in the CLPS lncRNAs between the high and low-risk groups (the bottom section) in the entire cohort. (F-K) Kaplan-Meier curves of OS in distinct subgroups with different clinical characteristics: (F) age ≤ 65 , (G) age >65, (H) female, (I) male, (J) Stage I-II, and (K) Stage III-IV. CLPS, cuproptosis-related lncRNAs prognostic signature; LUAD, lung adenocarcinoma; OS, overall survival; PFS, progression-free survival; ROC, receiver operating characteristic; lncRNAs, long non-coding RNAs; AUC, area under the curve.

Table S6 Identification of DEGs between low- and high-risk groups

DEGs SNTN	lowMean 1.575024382	highMean 0.751718132	logFC -1.067110455	P-Value 2.77E-08	FDR* 2.83E-07
CD40LG	1.509770222	0.718730555	-1.070806072	2.43E-18	1.71E-15
SNORA28 LYPD3	1.558088649 5.194157605	0.702483671 11.21319845	-1.149240723 1.110236156	0.01111661 0.011532043	0.021841023 0.022522053
PI3	8.144978174	48.3185615	2.568594767	1.14E-05	5.25E-05
CFAP157 SCGB3A1	1.770221411 733.0557381	0.848344995 338.0194345	-1.06120683 -1.116816701	4.50E-07 4.60E-13	3.17E-06 2.34E-11
IGFBP1	0.44921233	5.045141978	3.489425437	7.97E-06	3.85E-05
AC083809.1	2.099841734	9.161792285	2.125349259	0.007398223	0.015212433
SLC2A1 AKAP12	25.5801515 3.90455062	52.42149069 11.60194342	1.035133571 1.571138067	5.31E-14 2.09E-06	4.08E-12 1.19E-05
RN7SL8P	2.23517716	0.873030364	-1.356285447	3.02E-07	2.23E-06
AC026347.1	2.16201659	1.042840762	-1.051858713	2.53E-06	1.40E-05
SCGB3A2 TFF1	515.6111989 46.66714472	211.2804455 157.5547506	-1.28712435 1.75537415	2.44E-09 2.32E-06	3.53E-08 1.30E-05
GNG4	1.522552158	3.205815668	1.074199823	0.000116022	0.000401323
LRMP LINC00926	2.659279438 1.595386228	1.266852448 0.582131075	-1.069786882 -1.454489792	8.52E-13 1.49E-19	3.92E-11 1.81E-16
AC089999.1	2.264697154	1.032042907	-1.133815188	5.06E-06	2.58E-05
SPINK13 AC084375.1	2.917467118 3.082267239	0.71690618 1.389612427	-2.024860161 -1.149309391	0.000543799 2.63E-08	0.001568857 2.70E-07
ACE2	3.840786035	1.899008411	-1.0161553	0.000219378	0.000705046
SLC46A2	3.419820177	1.691114637	-1.015946006	1.65E-06	9.67E-06
AC092071.1 COL11A1	3.547262979 5.666886342	1.398778823 12.7752343	-1.34253843 1.172721579	2.75E-11 1.13E-06	7.78E-10 6.98E-06
ITGB2-AS1	3.636276287	1.500084043	-1.27741849	8.05E-20	1.56E-16
GJB3 RHOV	3.218857953 13.0209154	7.782395492 27.09117224	1.273665385 1.056991944	9.13E-05 0.000270163	0.000324052 0.000847558
IGHD2-2	2.675350688	1.304761001	-1.035942448	0.000578974	0.001656543
DEFB1	9.271790551	23.91435186	1.36695681	0.003654087	0.008312119
ADAMTS8 SRGAP3-AS2	1.655923994 2.400857217	0.735125154 1.108268333	-1.171574664 -1.115242379	4.76E-14 5.54E-06	3.70E-12 2.79E-05
SCNN1D	1.638543643	0.781592669	-1.06792526	2.12E-14	2.01E-12
TNFRSF13C	4.745552553 2.30517114	0.908414197	-1.343451705	2.18E-14	2.04E-12
MIR3189 SFTPD	8.501705126 239.2860937	3.599402987 94.04679918	-1.239994587 -1.347285808	7.40E-10 6.99E-15	1.23E-08 7.89E-13
H19	17.61234305	73.58439571	2.062813011	0.000248292	0.000786853
MALAT1 DUSP4	114.9921504 10.61657859	51.44463754 21.25054206	-1.160442776 1.001180739	3.07E-05 7.19E-06	0.000124738 3.51E-05
CHAD VPBEB3	4.278662922	1.654104787 2 184403142	-1.371109395	2.51E-10 1.36E-07	4.82E-09
FCMR	7.8262466	3.83993285	-1.027239487	1.93E-16	3.84E-14
PI15 CR2	0.802938259 4.175032661	2.714826473 1.578793031	1.757499024 -1.402965428	0.003019998 6.02E-10	0.007053844 1.02E-08
SCGB2A1	9.508064165	3.768416304	-1.335193288	1.82E-06	1.06E-05
PEBP4	24.59743915	11.69430882	-1.072701528	3.92E-11	1.04E-09
SUSD2 WIF1	55.34045104 26.08232092	20.1330201 7.818953171	-1.458770799 -1.73802488	6.92E-13 7.92E-09	3.33E-11 9.66E-08
FGB	37.91906586	162.0721706	2.095641058	0.001710547	0.004263978
SNORA73B DMBT1	159.2883839 37.60735922	53.57928054 16.85715732	-1.571893948 -1.157653734	0.002562681 0.000114418	0.006111184 0.000396388
CTSG	1.464764951	0.677653365	-1.11204978	1.04E-08	1.22E-07
RNU5F-1	1.554879747	0.707418811	-1.136166521	2.63E-06	4.69E-07 1.45E-05
RN7SL381P COL12A1	2.700689593 8.222479607	1.27015006 17.2968233	-1.088328879 1.072861669	2.74E-05 8.99E-08	0.00011318 7.89E-07
CYCSP6	0.672224255	1.494910277	1.153044395	0.000301013	0.00092978
SERPINB3 PTCSC3	2.754651639 3.752759741	б.391750011 1.74024457	1.214341101 -1.108661856	0.003402457 5.01E-11	0.007817903 1.27E-09
PCSK1	6.738620651	15.14594665	1.168406535	3.25E-05	0.000131509
LINC01116	0.736110055	1.854737185	1.333221389	4.91E-06	2.51E-05
FGA CHRDL1	33.24931463 7.323516877	178.7107359 3.649135384	2.426229798 -1.004981945	0.015574373 6.19E-16	0.029270923 1.01E-13
PITX2	0.910394971	2.088378678	1.197818841	0.001340085	0.003444797
GLB1L3 CCDC78	3.871593464 2.453963096	ı.741285494 1.19626276	-1.15277471 -1.03657924	1.38E-10 2.89E-11	2.97E-09 8.10E-10
TUBA4B CFMIP	1.626312881	0.765576355	-1.086986662	1.15E-06	7.07E-06
ATP13A4	0.27031829 9.539770152	4.212704535	۰. ، ، م499188 -1.179207773	∠.uoE-U8 1.50E-13	≥.19E-07 9.54E-12
RN7SKP80 PAEP	1.830035034 34.40301787	0.877098137 92.74259347	-1.06106109 1.430696946	2.09E-09	3.09E-08 7.92F-06
WDR38	3.281333836	1.57802485	-1.056162454	4.87E-05	0.000187014
FOSL1 CCL17	4.691059585 8.207867489	9.903429515 3.9526097	1.078014385 -1.054201936	1.28E-06 1.43E-08	7.75E-06 1.59E-07
PRRT2	1.529315452	0.742913185	-1.041620486	1.51E-11	4.58E-10
FAM216B PTHLH	2.871924723 1.503826356	1.32268777 3.033671345	-1.118545392 1.012426808	2.00E-07 3.74E-08	1.58E-06 3.70E-07
CALB1	4.12937733	0.607574472	-2.764791094	0.010083587	0.020037286
CA3	1.851251013	0.837665524	າ. ເອສຣບ1762 -1.144054322	1.60E-09 1.29E-21	∠.ruE-08 5.79E-18
CABCOCO1 COLCA2	2.013408197 3.594390226	0.944555513 1.770109722	-1.091932199 -1.021908254	7.47E-09 3.60E-08	9.15E-08 3.57E-07
C1QL2	2.321651552	0.771594783	-1.589236166	7.35E-06	3.58E-05
CYP4B1 RPL39P40	44.26085821 1.933952404	18.68284041 0.881636526	-1.244317616 -1.133296389	3.39E-16 4.61E-09	5.91E-14 6.10E-08
MSTN	2.405742043	0.053244344	-5.497709874	1.23E-11	3.89E-10
HHLA2 FLNC	13.7701317 2.090144644	5.71755494 4.810678852	-1.268072129 1.202637707	3.92E-06 0.00011384	2.05E-05 0.000394691
PRSS3 CHIA	1.266304578 4.876869395	3.695395555 2.043428708	1.545104348 -1.254963426	0.001012586 1.60E-08	0.002695968 1.75E-07
PARP15	2.259859951	1.077958956	-1.06793112	1.25E-15	1.84E-13
RNU4ATAC RASGRF1	2.124661629 2.689879298	0.896719575 1.242786049	-1.244504301 -1.113963486	1.72E-05 1.01E-11	7.51E-05 3.26E-10
STC2 FAM92B	2.256440718 2.873034238	4.637348873	1.03925139	8.01E-10 2.52E-06	1.32E-08 1.40E-05
BARX1	6.328640609	13.44666556	1.087280918	0.000254626	0.000805404
AC068587.2 SERPINB5	1.94048612 2.382471132	0.787733462 6.383598233	-1.300638648 1.421911122	1.81E-13 4.01E-06	1.10E-11 2.10E-05
CYP24A1	13.16618868	39.04786044	1.568405723	8.63E-08	7.61E-07
CCL19	47.1832142	19.95265509	-1.241692963	1.76E-13	1.09E-11
SCTR C7	9.376525878 25.40805419	4.224852399 11.39334502	-1.150152545 -1.157094518	1.16E-12 1.69E-11	5.12E-11 5.08E-10
TLR10	1.567543032	0.71595927	-1.130555627	2.34E-16	4.43E-14
AC105118.1 SCARNA12	1.532690874 3.246023785	0.605204067 1.242668614	-1.340573164 -1.385231951	0.000622146 0.00075387	0.001760081 0.002085261
DYNLRB2 FFAR2	1.393187575 0.974715173	0.667064802 2.012993786	-1.062490687 1.046290112	1.19E-07 0.018141728	1.00E-06 0.03340836
ECRG4	1.969948882	0.961178902	-1.035281308	9.81E-11	2.27E-09
SCARNA21 DKK1	11.67804601 4.911374992	4.41730275 12.14215386	-1.402561281 1.305825475	0.001831886 0.001062706	0.004539464 0.002813687
TMEM190	5.096970528	2.234461615	-1.18971275	0.000277211	0.000866229
AC012511.1	1.620805865	0.76802411	-1.077487794	1.26E-13	8.15E-12
MS4A1 MYBPHL	5.249549989 3.430810412	1.331650111 1.62222465	-1.978978688 -1.080575782	1.13E-16 1.71E-10	2.86E-14 3.56E-09
MORN5	2.304129605	1.098037179	-1.069294966	1.16E-06	7.10E-06
RSPH4A TNS4	2.354614583 5.099833625	1.131418774 11.28352449	-1.057357915 1.145695688	3.67E-07 0.001352224	2.64E-06 0.003472011
IGF2BP1 SNOBD94	0.660287312	1.542431357 2 997077593	1.224040458	0.000313034	0.000961379
CD22	2.51451869	1.009632916	-1.316451426	1.22E-17	5.46E-15
C16orf89 ATP12A	170.8931606 2.059153241	71.60206159 0.652999113	-1.255021628 -1.656898261	2.51E-12 0.01490578	9.85E-11 0.028166735
GGTLC1	19.94723605	8.668283118	-1.202370676	1.80E-12	7.40E-11
VEGFD TCN1	3.256855785 10.71195994	1.555800392 27.49514893	-1.065822862 1.35995463	3.85E-15 0.000165331	4.64E-13 0.00054772
KRT6A	17.51931089	51.92339147	1.56743859	7.41E-05	0.000270021
LOXL2 MIR4538	7.102834251 2.411368544	15.00124755 1.021851419	-1.238666725	1.42E-14 6.15E-08	1.45E-12 5.65E-07
IL1R2 MST1L	1.257578161 2.727284745	2.67171636 1.300737856	1.087118785 -1.068135096	1.98E-06 2.58E-08	1.13E-05 2.66E-07
MYEOV	2.676251663	8.753660828	1.709672699	5.59E-08	5.22E-07
SLC16A14 AGTR2	5.302758067 3.796033439	10.99702514 1.675982027	1.052298473 -1.179486023	1.49E-05 0.000302799	6.62E-05 0.000934436
LINC00973 CXCL5	0.926229761 4.671508187	2.507664518 12.84362338	1.436902335 1.459091965	0.00700235 3.85E-08	0.014527521 3.79E-07
INSL4	1.608156927	3.947784178	1.295634927	0.00055826	0.0016054
AL590560.3 IGHJ3P	3.073702539 23.3470931	1.41805613 11.60593558	-1.116062914 -1.008380108	5.60E-12 9.23E-07	1.95E-10 5.85E-06
SLC16A11	2.094799901	0.863722958	-1.2781719	5.42E-13	2.68E-11
AC018629.1	0.615872653	1.477986871	1.26292948	0.026412931	0.046187354
SCARNA13 SPIB	14.99481955 2.127885857	6.068264518 0.773307357	-1.305108281 -1.46030692	7.39E-09 2.25E-13	9.07E-08 1.32E-11
MFAP5	1.252698147	3.627945177	1.534113833	0.000313399	0.000961842
MIR8071-2	∠∠rэ∪8538 8.526620933	3.583966544	-1.25041695	1.77E-11	5.25E-10
C9orf24 AC026355.2	4.257394129 1.959305024	1.884601837 0.705750869	-1.175710899 -1.473111109	2.96E-07 3.24E-17	2.20E-06 1.01E-14
C1orf189 ZMAT1	2.197691693	1.069720296	-1.038755391	0.000115241	0.000398826
COL4A3	2.0025/6801 3.956646212	1.914193796	- 1.047541173	∠.08⊏-19 4.24E-15	∠.45E-16 5.03E-13
ZMYND10 SBSN	3.391763566 0.568531716	1.675113006 1.586298087	-1.01777718 1.48035116	1.10E-08 0.001279957	1.28E-07 0.003306064
AC110285.2	2.579150386	1.22803776	-1.070540975	1.68E-12	7.02E-11
OEO3 ANKRD44-AS1	∠.404982551 2.76475327	1.197695732	-1.137968302 -1.206889292	∠.∪4E-08 9.29E-11	2.18E-07 2.18E-09
MIR27B AC004687.1	1.408499051 2.186143028	0.693136528 0.887301119	-1.022947137 -1.3008921	5.09E-07 1.84E-17	3.53E-06 6.51E-15
DNER	1.322123774	2.866050294	1.116206681	0.021915554	0.039395748
MIR5195 CD79B	1.659800389 5.966757466	0.653573894 2.665791445	-1.344587486 -1.162383219	4.54E-12 1.64E-11	1.62E-10 4.97E-10
STC1	5.534637344 2.064750070	12.52637858 0.801925047	1.178408694	1.04E-13	6.99E-12
SPOCK1	∠.004750873 1.613701523	3.904479573	1.274756508	3.46E-08	∠.∠əE-06 3.45E-07
FAM83A-AS1 SNORA54	1.961607671 9.963724902	4.107953985 3.031525294	1.066383496 -1.716641329	4.87E-11 8.14E-05	1.24E-09 0.000293693
MIR4537	2.360173616	1.077506799	-1.131196017	7.94E-06	3.83E-05
IGKV2-26 AL162511.1	5.459805889	1.670000144	-1.709001433	4.03E-13	2.10E-11
CNMD INHA	18.15734222 2.441870409	3.499135904 11.16332195	-2.37548244 2.192707862	0.005644995 0.02746372	0.012071619 0.047765304
SCGB1A1	454.0884375	172.3270297	-1.397824294	1.13E-06	6.98E-06
AC 104031.1 AC 120498.2	2.43061037 1.52342461	ı.125897699 0.583219154	-1.110242899 -1.3852081	1.68E-05 2.24E-09	7.38E-05 3.27E-08
CXCL13 RASGRP2	36.89852621 1.885011849	16.05424777 0.804871119	-1.200608126 -1.227743898	4.38E-08 4.00E-21	4.22E-07 1.34E-17
CCR7	4.902370393	2.284082861	-1.1018645	5.51E-16	9.13E-14
SERPIND1 ZNF385B	9.760629336 4.214472091	3.972922553 2.080376486	-1.296773501 -1.018507293	3.14E-07 1.36E-07	2.30E-06 1.13E-06
FAM177B FAM834	1.06652961	2.739240469	1.360851901	0.010536016	0.020849878 3.60E 10
SERPINB4	າ3.8397812 0.700559419	34.6/50673 1.601901968	1.19325077548 1.193206536	4.57E-14 0.00014533	з.60E-12 0.000490564
CYP2A6 CH25H	3.837408232 10.67975872	0.632195629 5.227320395	-2.601689284	1.68E-05 2.69F-12	7.39E-05
C20orf85	15.31874285	7.087872674	-1.111873313	6.49E-06	3.21E-05
gal PopdC3	1.178560874 0.794164057	4.583260072 1.743372848	1.959347874 1.134372173	2.53E-08 0.003821438	2.61E-07 0.008625549
CA12	4.688196377	11.81509206	1.333525964	7.57E-08	6.77E-07
SY 113 CCDC17	2.097579568 2.951067554	ວ.223598857 1.196447045	1.316318573 -1.302480401	u.002616382 1.33E-11	0.006224865 4.12E-10
AL359881.1 AC007906.2	1.596558865 9.603991216	0.708254721 4.57 <u>9604924</u>	-1.172625527	5.64E-11 3.74F-07	1.42E-09 2.68F-06
LRRC36	1.478562979	0.601355569	-1.297905512	9.76E-14	6.72E-12
CFAP73 MIR4539	2.228517327 2.617693338	0.934674554 1.107082167	-1.253548156 -1.241533794	8.46E-09 3.05E-07	1.03E-07 2.25E-06
RNU6-418P FST	4.149729771	2.044423013	-1.021323656	4.77E-09	6.29E-08
CPS1	2.04328421 11.99368071	ാത്ത∠18836 38.88070112	1.696779763	0.000206894 2.61E-07	0.000009252 1.98E-06
SCARNA6 ADH1B	12.15096346 10.3295449	3.8717363 4.895681762	-1.65001811 -1.077195008	0.015478067 9.85E-14	0.029118465 6.74E-12
TNFRSF14-AS1	1.540817001	0.757430479	-1.024510146	1.49E-15	2.13E-13
LKRK2-DT TEKT1	4.690659773 1.918452523	2.308062225 0.869719391	-1.023108742 -1.141321157	2.57E-14 7.90E-06	2.31E-12 3.82E-05
AC116407.1 CCDC114	1.907971171	0.938031871	-1.024330526	7.11E-13	3.40E-11
CFAP43	1.456547604	0.698277661	-1.06068013	2.60E-05	0.000108076
LILRP1 STAP1	0.468843686	2.009108651 0.726524148	2.099376676 -1.093536243	0.011530973 1.13E-14	0.022522053 1.23E-12
KLK6					
	3.144205673	6.976065402	1.149717974	0.002227336	0.005390996
MUC5AC CD19	3.144205673 10.23818748 2.877339351	6.976065402 28.38694582 1.109101145	1.149717974 1.471267306 -1.375344442	0.002227336 0.000935292 2.71E-12	0.005390996 0.002517213 1.04E-10
MUC5AC CD19 PDCL3P4 FDCSP	3.144205673 10.23818748 2.877339351 4.328979497 14.45858602	6.976065402 28.38694582 1.109101145 2.13369051 3.868285502	1.149/1/9/4 1.471267306 -1.375344442 -1.020676038 -1.90216025	0.0002227338 0.000935292 2.71E-12 3.22E-13 1.51E-11	0.005390996 0.002517213 1.04E-10 1.75E-11 4.58E-10

FDR <0.05. * The false discovery rate (FDR) was generated by the Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995) with statistical significance of FDR <0.05.



Figure S3 Functional annotation for DEGS between the high-risk and low-risk groups using KEGG pathway analysis. (A) Bar plot and (B) bubble plot showing the significantly enriched KEGG pathways. Bubble color representing the P value, and the bubble size representing the number of genes in the relevant pathway.



Figure S4 Correlation between the risk score and immune-checkpoint related gene expression: (A) HAVCR2, (B) CD80, (C) IDO1, (D) CD86, (E) PDCD1, (F) LAG3, (G) PDCD1LG2, (H) TIGIT, (I) TNFRSF9.