Article

Prognosis Prediction Based on Cuproptosis-Related lncRNAs and Immune Responses in Patients with LUAD

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Simple Summary: Lung cancer is becoming the deadliest cancer worldwide with lung adenocarcinoma, the most prominent one. There are two main types: small cell lung cancer and non-small cell lung cancer. These two types grow differently and are treated differently. We identified cuproptosis-associated lncRNAs utilizing Pearson's correlation analysis, screened 16,866 lncRNAs and 19 cuproptosis genes from the TCGA database, and constructed a novel predictive risk model for predicting the overall survival of lung adenocarcinoma patients. Then, we examined the association between immunotherapy responses and

cuproptosis-associated lncRNA, and we developed a nomogram that predicts overall survival in cancer of lung adenocarcinoma patients

Abstract:

Lung cancer is the most common cause of cancer deaths worldwide, and lung adenocarcinoma (LUAD) is the most common histological subtype. However, the prognostic and predictive outcomes differ because of the heterogeneity of programmed cell death. The purpose of this work is to investigate and develop a cuproptosis-associated lncRNA-based LUAD prediction marker. We firstly performed bioinformatic analysis of the Cuprotosis database and The Cancer Genome Atlas (TCGA) database to obtain 19 cuprotosis-related gene datasets and transcriptional data for LUAD. Univariate, least absolute shrinkage and selection operator (LASSO), and multivariate Cox regression analysis were utilized to construct cuproptosis-associated lncRNA modes. LUAD patients were thus classified into high-risk and low-risk categories based on prognostic risk values, with a median of It acted as a boundary. Risk models were evaluated and validated using Kaplan-Meier analysis, principal component analysis (PCA), gene set enrichment analysis (GSEA) and nomograms. Utilizing the TCGA-LUAD dataset, we identified seven predicted cuproptosis-associated lncRNAs in tumor microenvironment to create the risk model. 95.54% (214/224) of high-risk category tumor samples included cuproptosis-associated gene alterations, compared to 85.65% (203/237) of low-risk category tumor samples, with TP53 accounting for the bulk of occurrences. According to these findings, risk value was superior to other clinical variables and tumor mutation burden as a predictor of 1-, 3-, and 5-year overall survival (OS). The predictive validity of the cuproptosis-associated lncRNA-based risk model for LUAD is high, and this may have implications for how lung cancer patients are treated individually.

Keywords: lung adenocarcinoma; tumor mutation load; cuproptosis; long noncoding RNA; immunotherapeutic response

Introduction:

Cancer of the lung, which includes adenocarcinoma, squamous cell carcinoma, small cell cancer of the lungs, and large cell cancer of the lungs[1], is the most prevalent malignancy in China, if not the world[2,3]. Adenocarcinoma of the lung accounts for over 40% of all cases, making it the most prevalent kind[4]. Although the overall survival rate of patients with lung adenocarcinoma has increased as a consequence of surgery,

radiation, chemotherapy, immunotherapy, and targeted therapy, the 5-year survival rate remains low[5,6]. Numerous studies have shown that molecular targeted treatment improves the lung cancer patients' prognosis.

Cuproptosis is a sort of regulated cell death with a process that differs significantly from apoptosis, pyroptosis, necroptosis, and ferroptosis[7]. According to Tsvetkov et al[8], cuproptosis is receptor-controlled and copper-dependent. The abnormal aggregation of tricarboxylic acid cycle fatty acylated proteins and the loss of iron-sulfur clusterin are the mechanisms by which proteotoxic stress induces cell death. Recent research[9]indicates that cuproptosis-associated genes influence the clinical outcomes of clear cell renal cell carcinoma. Long noncoding RNAs have gained interest as a research focus during the last decade[10]. Among these are several tumor-associated studies, such as those on prostate, pancreatic, and colon cancers[11-13]. Multiple studies[14,15] have connected LncRNAs to the prevalence and progression of lung cancer. According to research[15], copper may alter the biological process of non-small cell lung cancer through the lncRNA MALAT1, however the precise regulatory mechanism is unknown. Understanding the mechanism of cuproptosis-associated lncRNA in lung adenocarcinoma is advantageous for lung cancer prognostication and immunotherapy. In addition, the relationship between cuproptosis and lncRNAs remains controversial, and few research have shed light on the function of cuproptosis-associated lncRNAs in lung cancer prognosis.

We identified cuproptosis-associated lncRNAs utilizing Pearson's correlation analysis, screened 16,866 lncRNAs and 19 cuproptosis genes from the TCGA database, and constructed a novel predictive risk model for predicting the overall survival of lung adenocarcinoma patients. Then, we examined the association between immunotherapy responses and cuproptosis-associated lncRNA, and we developed a nomogram that predicts overall survival in cancer of lung adenocarcinoma patients.

Materials and methods

Clinical data and extraction of datasets

Lung adenocarcinoma patients' clinical data and cuproptosis-associated genes were extracted from the TCGA database (https://cancergenome.nih.gov/, accessed on June 13, 2022). We excluded patients with insufficient data from this research. Throughout the data analysis process, R is used (Version 4.1.1).

The selection of lncRNAs and genes relevant to cuproptosis.

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From the lncRNA and cuproptosis gene profiles of lung adenocarcinoma patients, we identified 19 cuproptosis genes, including NFE2L2、NLRP3、ATP7B、ATP7A、SLC31A1、FDX1、LIAS、LIPT1、LIPT2、DLD、DLAT、PDHA1、PDHB、MTF1、GLS、CDKN2A、DBT、GCSH、DLST. Utilizing Pearson correlation analysis, 2244 cnuproptosis-associated lncRNAs were identified (R more than 0.4 and p less than 0.001)[16].

The process of generating and confirming the risk signature

To generate and verify the cuproptosis-associated lncRNA prognostic model, the whole collection of TCGA clinical data was randomly split into training and validation sets. Cuproptosis-associated lncRNAs and clinical data were paired, and univariate cox regression analysis was used to identify cuproptosis-associated lncRNAs having prognostic value[17]. Utilizing LASSO Cox regression analysis, we then selected 13 lncRNAs linked to cuproptosis[18]. The 13 cuproptosis-associated lncRNAs were investigated utilizing multivariate regression analysis, and a risk model for 7 cuproptosis-associated lncRNAs was established[19]. Each lncRNA had a coefficient that contributed differentially to prognosis, and risk values were generated utilizing the formula risk $\sum_{i=0}^{n} expr\ i * coef\ i$value= for each patient. We divided lung adenocarcinoma patients into high- and low-risk categories based on the median risk value[16,20].

Analysis of Gene Networks and Enrichment

We identified differentially expressed genes and regulatory pathways utilizing GO and KEGG analysis utilizing the R software clusterProfiler. The p value was used to define these analytic criteria, with p less than 0.05 being a highly enriched functional comment[20].

The model evaluation in immunotherapeutic therapy

The mutation data were analyzed and summarized utilizing the R package maftools. The TMB was computed utilizing altered tumor-specific genes[16,21]. We evaluated the probability of an immunotherapeutic response utilizing the TIDE algorithm[17].

PCA and Kaplan-Meier analysis of survival

PCA, an efficient method for dimensionality reduction, model identification, and categorying, was utilized to visualize high-dimensional data from the gene expression profiles, 19 cuproptosis genes, 7 cuproptosis-associated lncRNAs, and a risk model based on the expression patterns of the 7 cuproptosis-associated

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lncRNAs[22].utilizing kaplan-meier survival analysis, the R packages survMiner and survival tools were used to determine survival differences between high- and low-risk categories[16,23].

Self-contained model of the cuproptosis-associated lncRNA

The connection between risk value and clinical variables (gender, age, tumor stage, T stage, N stage, and history of tobacco use) and OS in patients with LUAD was studied utilizing univariate and multivariate Cox regression[24].

Analysis of gene networks and enrichment of cuproptosis-associated genes

We used the GENEMANIA website to do a gene network analysis in order to research the possible connections between these genes[25]. Additionally, we did pathway enrichment analysis on cuproptosis-related genes utilizing the website Metascape[26]. As references, Gene Ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes (KEGG) were used. The enrichment research was conducted utilizing the clusterProfiler R program[27]. Multiple correction was performed utilizing the Benjamini-Hochberg technique, and a false discovery rate (FDR) less than 0.05 or below was deemed significant.

Developing and exhibiting a projected nomogram

The R package "regplot" was used to construct better regression nomograms of the cuproptosis-associated lncRNAs risk values and other clinical data (age, gender, risk value, tumor stage, T stage, N stage, and smoking history) for the 1-, 3-, and 5-year OS of LUAD patients.

RESULTS

Extraction of lncRNAs linked to cuproptosis

Figure 1 depicts the whole flowchart for the building of the prognostic risk model and subsequent analysis. We began by searching the TCGA database for 16866 lncRNAs and 19 cuproptosis genes. utilizing Pearson correlation analysis, 2244 lncRNAs associated with cuproptosis were identified (R more than 0.40 and p less than 0.001). Figure 2A depicts the coexpression network between cuproptosis and lncRNA utilizing a Sankey diagram. Figure 2B demonstrates the relationship between cuproptosis genes and cuproptosis-associated lncRNAs in the TCGA dataset.

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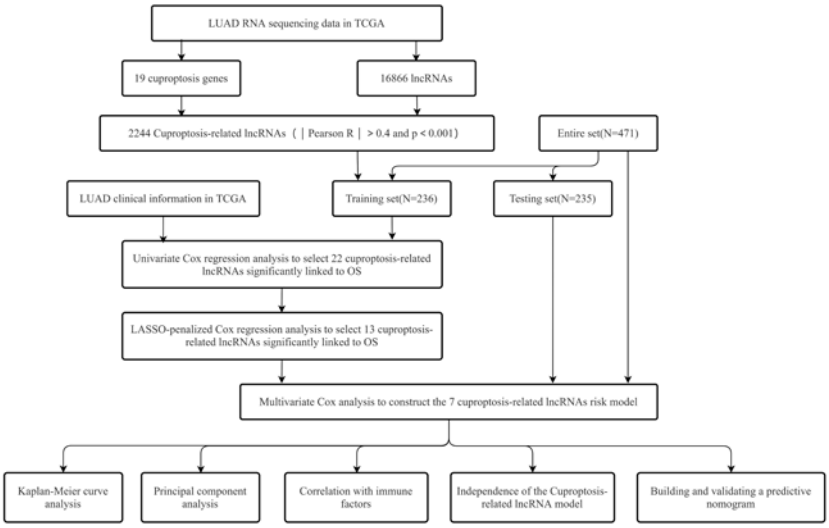

Figure 1 Flow chart of this study

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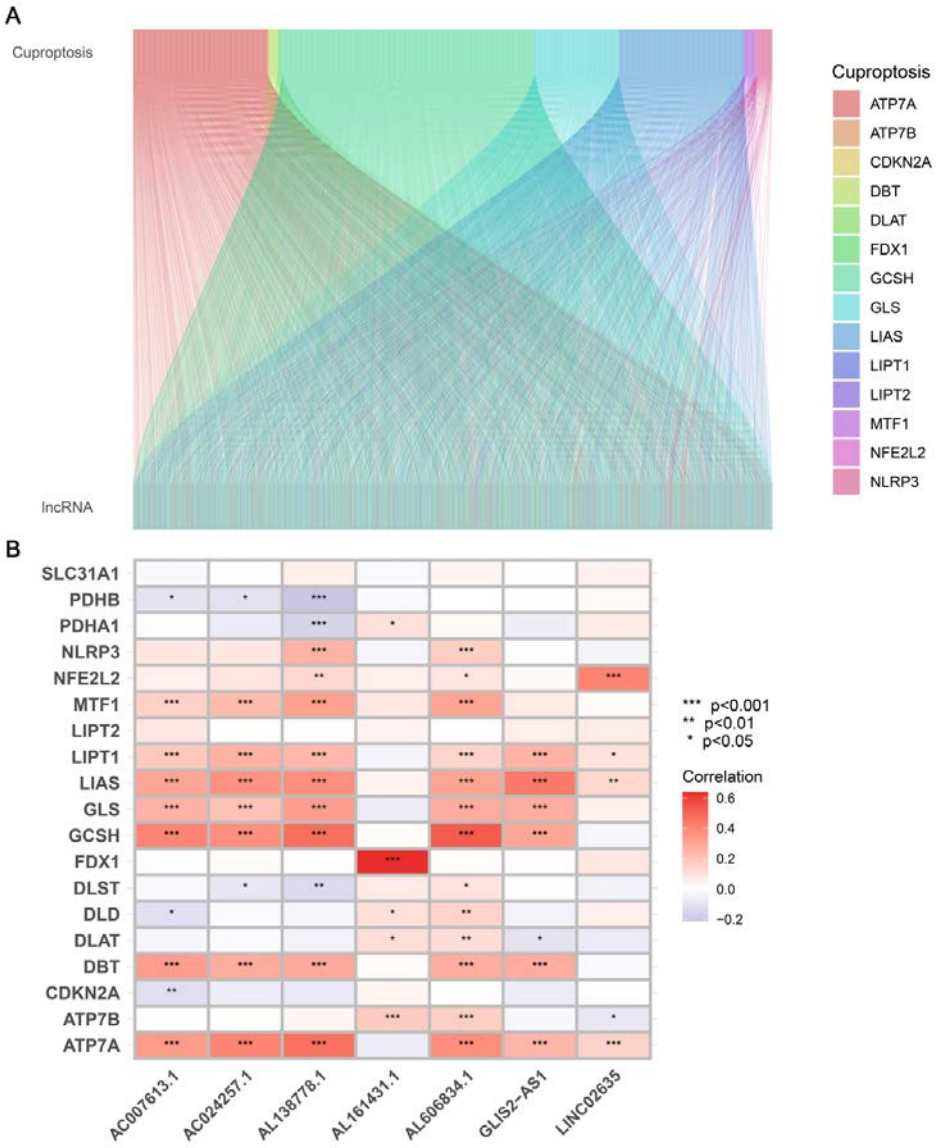

Figure 2 Identification of cuproptosis-associated lncRNAs in LUAD patients.(A) Sankey relational diagram for 19 cuproptosis genes and cuproptosis-associated lncRNAs. (B) Heatmap for the correlations between 19 cuproptosis genes and the 7 prognostic cuproptosis-associated lncRNAs

Development and validation of a risk model utilizing lncRNAs associated with cuproptosis

Utilizing univariate regression analysis, we determined that 22 cuproptosis-associated genes out of 2244 cuproptosis-associated lncRNAs in the TCGA database were significantly associated with OS (Figure 3A). LASSO-penalized the advantage of Cox analysis over conventional stepwise regression analysis is that it may assess all independent samples simultaneously, hence enhancing the stability of the model. Principal benefit of the lasso approach is that its ability to remove unimportant independent variables and reduce overfitting. To minimize data overfitting, we ran Lasso regression on the major screen variables for further screening analysis and provided the spectrum of Lasso regression coefficients. The subsequent multivariate analysis will

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concentrate on 13 cuproptosis-associated genes (Figures 3B and 3C). They were used to develop a risk model for LUAD patient prognosis risk assessment. In the training queue, 7 cuproptosis-associated lncRNAs separately associated with OS were predictive proteins. The median value was used to split patients in the training category into high-risk and low-risk categories based on LUAD patients prognostic risk values. The survival status, survival time, and risk value distributions for all lung adenocarcinomas are shown in Figures 4A and 4B. Clearly, death rates increase in proportion to risk values as patient risk rises. Figure 4C illustrates the relative expression criteria for each patient's 7 cuproptosis-associated lncRNAs. According to the Kaplan-Meier survival curve, the OS of high-risk lung adenocarcinoma patients was considerably lower than that of low-risk patients (p less than 0.001). (See Figure 4D.)

To evaluate the model's ability to predict outcomes, we computed the risk value for each patient in the testing set and the entire set, and then created separate plots for each category. Figure 5 illustrates the expression of cuproptosis-associated lncRNAs in the testing and entire sets (Figures 5A-5C), together with the distribution of risk grades, survival status, and survival time. According to Kaplan-Meier analyses conducted on the testing set and the whole set, the OS of LUAD patients with greater risk ratings was inferior than that of patients with lower risk ratings (Figures 5D and 5H).

To more thoroughly evaluate the clinical effectiveness of the prognostic model, a Kaplan-Meier survival analysis was conducted on the clinical characteristics of the low-risk and high-risk categories in the TCGA full set. The OS of the low-risk category remained superior to that of the high-risk category across subcategories defined by age, gender, tumor stage, T stage, and N stage (Figures 6).

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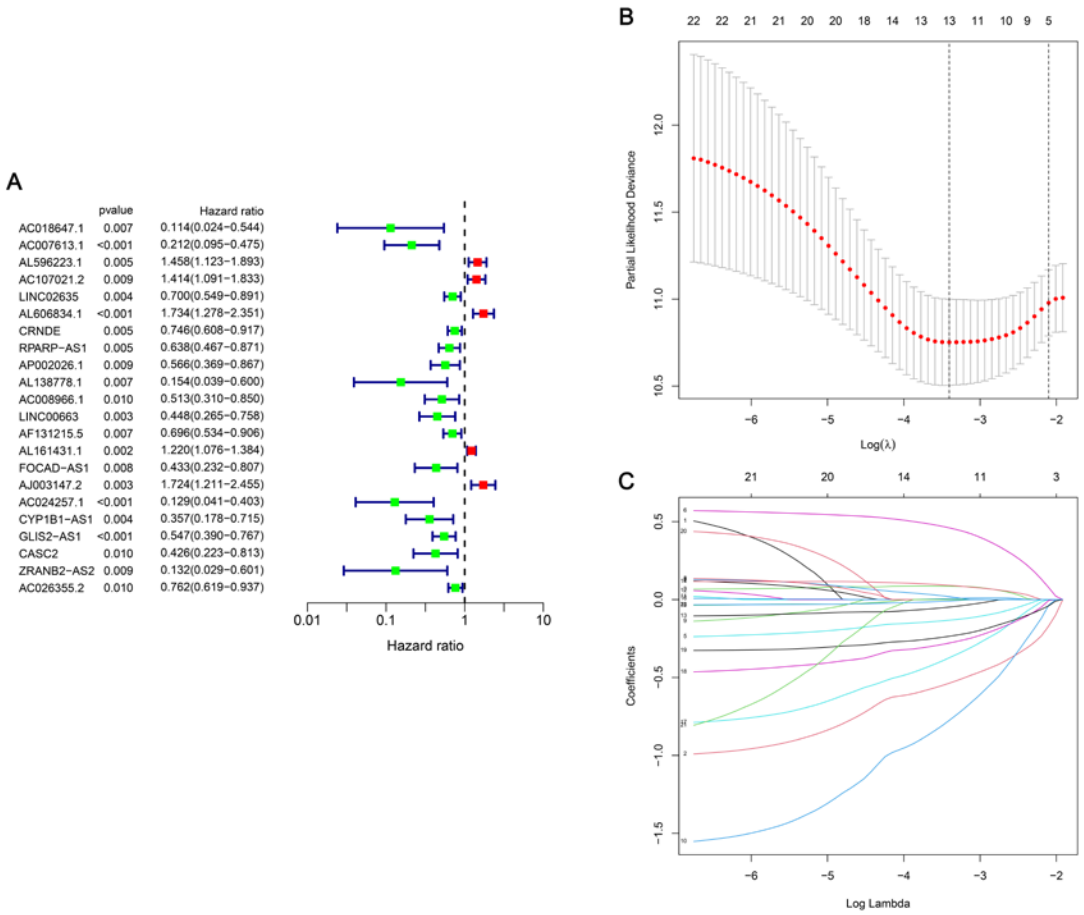

Figure 3 Risk model for LUAD patients based on cuproptosis-associated lncRANs.(A) Univariate Cox regression analysis revealed that the selected lncRNAs significantly correlated with clinical prognosis. (B) The tuning parameters (log l) of OS-related proteins were selected to cross-verify the error curve. According to the minimal criterion and 1-se criterion, perpendicular imaginary lines were drawn at the optimal value. (C) The LASSO coefficient profile of 13 OS-related lncRNAs and perpendicular imaginary line were drawn at the value chosen by 10-fold cross-validation.

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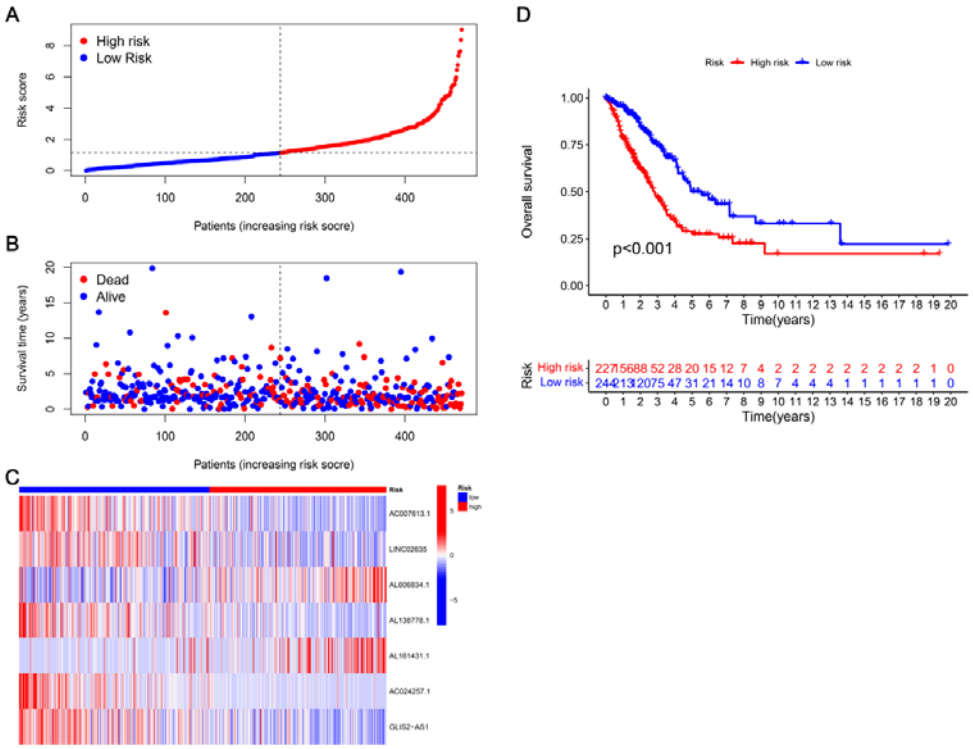

Figure 4 Prognostic value of the risk patterns of the 7 cuproptosis-associated lncRNAs in the TCGA training set. (A) Distribution of cuproptosis-associated lncRNA model-based risk score. (B) Different patterns of survival status and survival time between the high- and low-risk groups. (C) Clustering analysis heatmap shows the expression standards of the 7 prognostic lncRNAs for each patient. (D) Kaplan-Meier survival curves of the OS of patients in the high- and low risk groups

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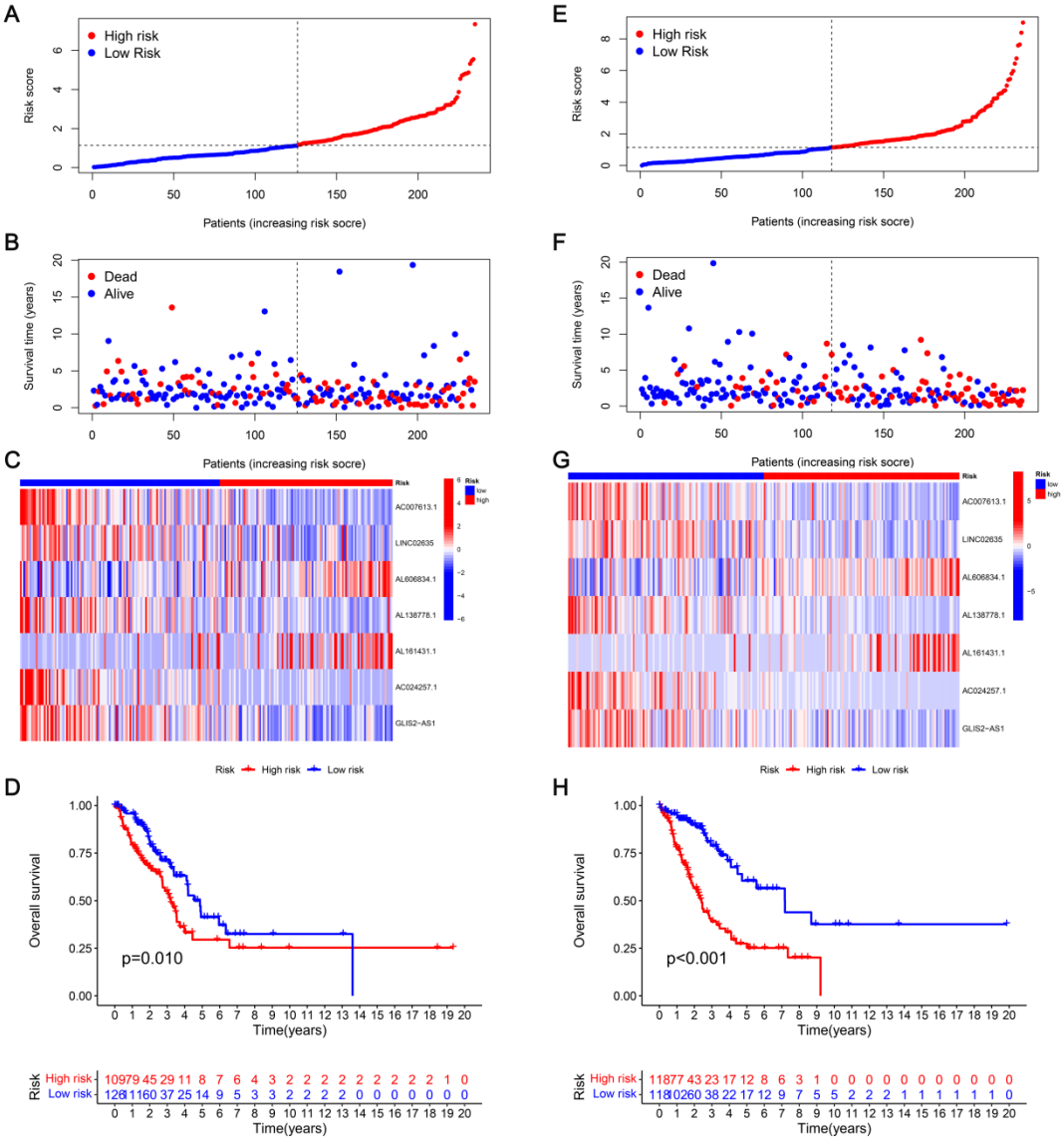

Figure 5 Prognostic value of the risk model of the 7 cuproptosis-related lncRNAs in the TCGA testing and entire sets. (A) Distribution of cuproptosis -related lncRNA model-based risk score for the testing set. (B) Patterns of the survival time and survival status between the high- and low-risk groups for the testing set. (C) Clustering analysis heatmap shows the display levels of the 7 prognostic lncRNAs for each patient in the testing set. (D) Kaplan-Meier survival curves of the OS of patients in the high- and low-risk groups for the testing set. (E) Distribution of the cuproptosis-associated lncRNA model-based risk score for the entire set. (F) Patterns of the survival time and survival status between the high- and low-risk groups for the entire set. (G) Clustering analysis heatmap shows the expression levels of the 7 prognostic lncRNAs for each patient for the entire set. (H) Kaplan-Meier survival curves of OS of patients in the low- and high-risk groups for the entire set

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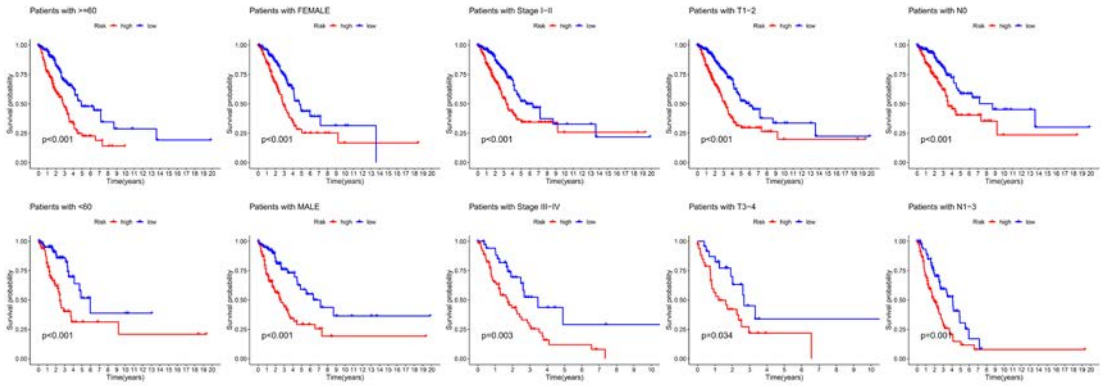

Figure 6 Kaplan-Meier curves of OS differences stratified by gender, age, tumor grade, or TNM stage between the high- and low-risk groups in the TCGA entire set

Principal-component analysis verifies the cuproptosis-associated lncRNA model's potential to further cluster.

Utilizing data dimensionality reduction techniques like PCA, which transform high-dimensional data into low-dimensional data by extracting feature vectors, these attributes are shown on two- or three-dimensional graphs. PCA is often used to evaluate sample-to-sample variations in expression pattern datasets. utilizing PCA, we compared the expression profiles of the entire gene, 19 cuproptosis genes, 2244 cuproptosis-associated lncRNAs, and a risk model based on the expression profiles of 7 cuproptosis-associated lncRNAs (Figures 7A-7D). These four graphs illustrate the patterns of distribution between the high-risk and low-risk categories. The test findings indicate that the prognostic risk model can discriminate between categories with low and high risk.

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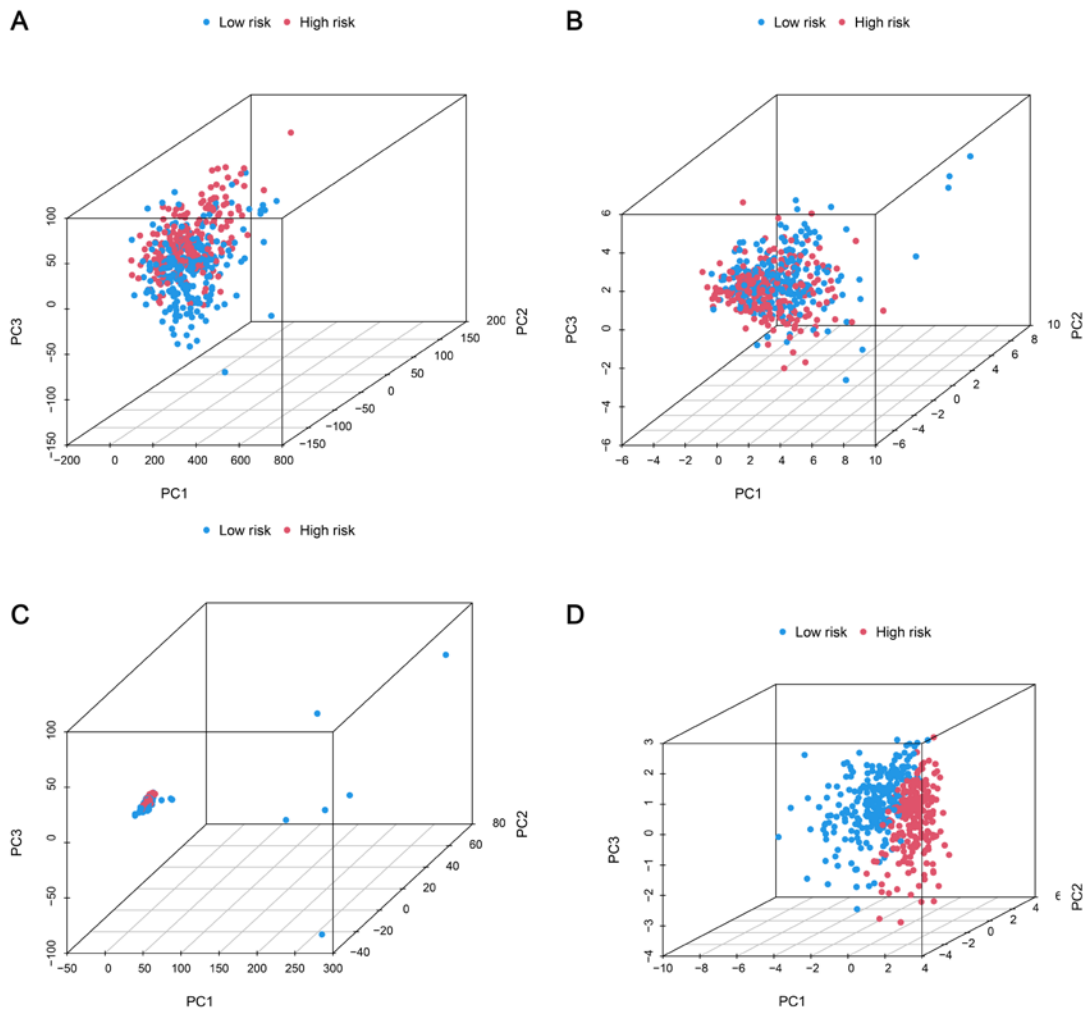

Figure 7 Principal component analysis between the high- and low-risk groups based on cuproptosis-associated lncRNAs model.(A) entire gene expression profiles, (B) 19 cuproptosis genes, (C) 7 cuproptosis - associated lncRNAs, and (D) risk model based on the representation profiles of the 7 cuproptosis- associated lncRNAs in the TCGA entire set

Functional Enrichment Analysis of cuproptosis-related lncRNA

Enhancing Gene set variation analysis was utilized to examine the biological processes and pathways of the cuproptosis-based model, as well as the KEGG pathway analysis, in order to comprehend the molecular mechanism behind the cuproptosis-based risk model (Figure8A-D). Axoneme assembly, collage-containing extracellular matrix, motile cilium, axoneme, ciliary plasm, lamellar body, glycosaminoglycan binding, endopeptidase inhibitor activity, peptidase inhibitor activity, heparin binding, and secine-type endopeptidase inhibitor activity were the seven cuproptosis-associated lncRNAs that were most heavily involved in the GO analysis (Figure 8A). In the KEGG pathway enrichment analysis, the seven lncRNAs associated with cuproptosis were also significantly associated with endopeptidase activity regulation, proteolysis regulation, humoral immune response, cilium movement, endopeptidase activity regulation, peptidase activity regulation,

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hormone metabolic process, protein processing, cell killing, microtubule bundle formation, and leukocyte-mediated cytotoxicity (Figure 8B).

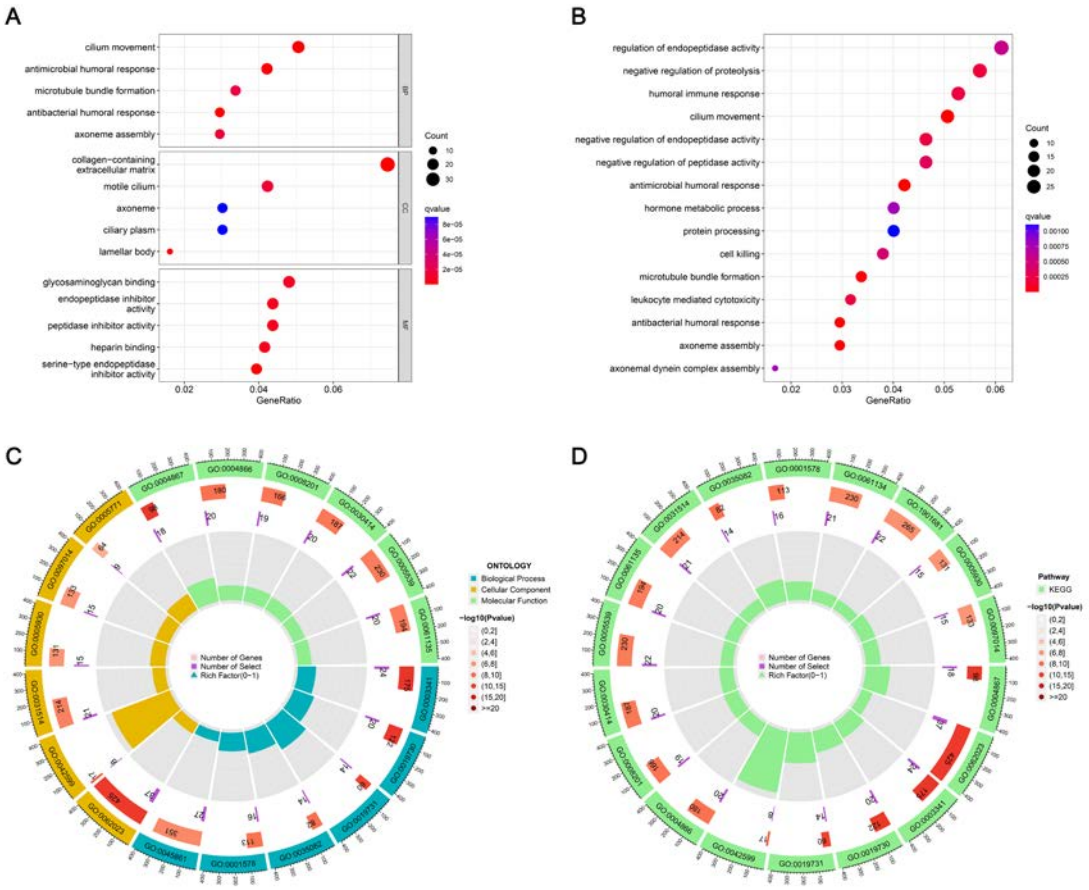

Figure 8 Pathway enrichment analysis of cuproptosis- associated lncRNAs in LUAD patients of TCGA. (A and C) the enriched item in the gene ontology analysis; (B and D) the enriched item in the Kyoto Encyclopedia of Genes and Genomes analysis

Estimation of the tumor immune microenvironment and cancer immunotherapy response using the cuproptosis-related lncRNA model

Utilizing the cuproptosis-associated lncRNA model, estimate the tumor immune milieu and therapeutic response.We analyzed immunological markers in 471 cancer of the lungs patients. The immune-associated processes of patients in the low- and high-risk categories vary significantly, according to studies (Figure 9A). 95.54% (214/224) of high-risk category tumor samples included cuproptosis-associated gene alterations, compared to 85.65% (203/237) of low-risk category tumor samples, with TP53 accounting for the bulk of occurrences (Figures 9B and 9C). This research examined the connection between the cuproptosis-associated lncRNA model and immunotherapy biomarkers. As anticipated, the cuproptosis-based classifier index indicated that the low-risk category responded less favorably to immunotherapy than the high-risk category,

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showing that it might be used to predict tumor immune dysfunction and exclusion (Figure 9D). We discriminated these categories further by generating TMB values in tumor patients utilizing TCGA somatic mutation data. TMB was strongly associated with the cuproptosis-based classifier index, as shown by the fact that TMB values were greater in the low risk category than in the high risk category (Figure 9E). Additionally, the research found that H-TMB patients had longer life spans (Figure 9F). Therefore, we compared the TMB and OS of patients in both categories to see if cuproptosis-associated lncRNAs might more correctly predict OS than TMB. The high-risk category had both high TMB values (H-TMB+high risk) and low TMB values (L-TMB+high risk), while the low-risk category had both high TMB values (H-TMB+low risk) and low TMB sores (H-TMB+low risk). (Please check Figure 9G.) Contrary to expectations, those with H-TMB+high risk fared better in terms of survival than those with L-TMB+high risk. The survival curves of patients with H-TMB and L-TMB in the low-risk category (H-TMB+low risk) were comparable, demonstrating that TMB mutation status failed to differentiate the survival rate in the low-risk category. These results suggest that the cuproptosis-associated lncRNA model may be more prognostic than the TMB model.

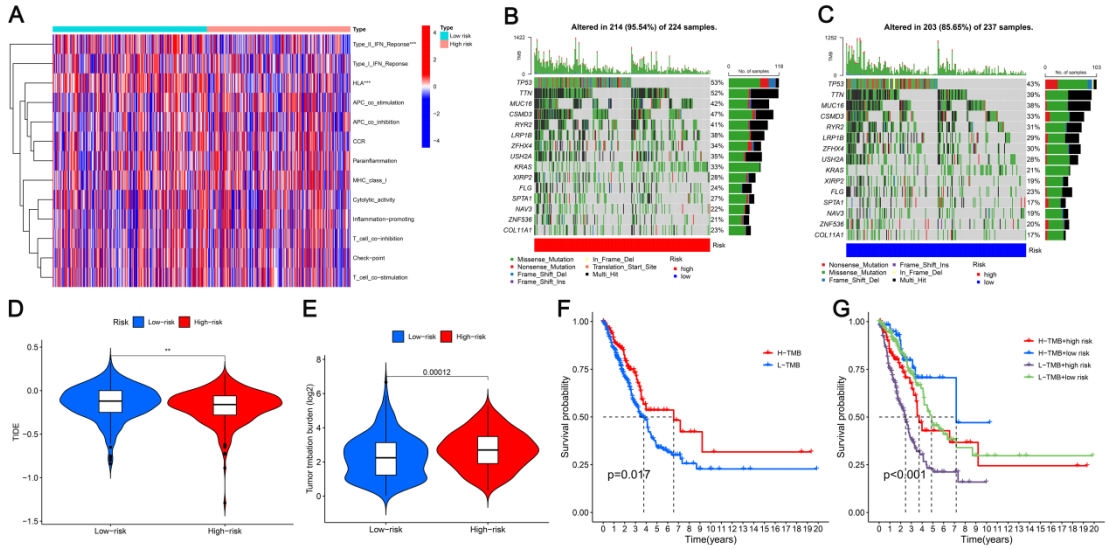

Figure 9 Estimation of the tumor immune microenvironment and cancer immunotherapy response using the cuproptosis-associated lncRNA model in the TCGA entire set. (A) The indicated standards of the immunity index for each patient. (B and C) Waterfall plot displays mutation information of the genes with high mutation frequencies in the high-risk group (B) and low-risk group (C). (D) TIDE prediction difference in the high- and low-risk patients. (E) TMB difference in the high- and low-risk patients. (F) Kaplan-Meier curve analysis of OS is shown for patients of the entire set. (G) Kaplan-Meier curve analysis of OS is shown for patients classified according to the TMB and cuproptosis- associated lncRNA model.

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Evaluation of LUAD clinical characteristics and cuproptosis-associated lncRNAs predictive risk model

Using univariate and multivariate Cox regression analyses, it was determined whether the risk model of 7cuproptosis-associated lncRNAs exhibited independent LUAD prediction value. In a univariate Cox regression analysis, the risk value's hazard ratio was 1.317 (95% confidence interval: 1.209-1.434) (P less than 0.001) , but it was 1.253 in a multivariate Cox regression research (95% CI 1.144-1.372). (Fig. 10B) The findings indicate that clinicopathological variables such as gender, age, tumor stage, N stage, and M stage had no influence on the risk model of the seven cuproptosis-associated lncRNAs. The area under the ROC curve and risk value conformance index were generated to evaluate the independence and dependability of this risk model. Throughout time, the risk grade seemed to be able to predict the prognosis of LUAD more accurately than other clinical indicators, as shown by the fact that its c-index remained the highest. (Fig. 10C) With AUCs of 0.744, 0.684, and 0.644 in 1, 3, and 5 years, respectively, the risk value demonstrated excellent predictive capacity (Figure 10D). The AUC of the risk grade was greater than the AUCs of the other clinicopathological parameters, suggesting that the predictive risk model of the 7 cuproptosis-associated lncRNAs for LUAD is rather accurate (Figure 10E).

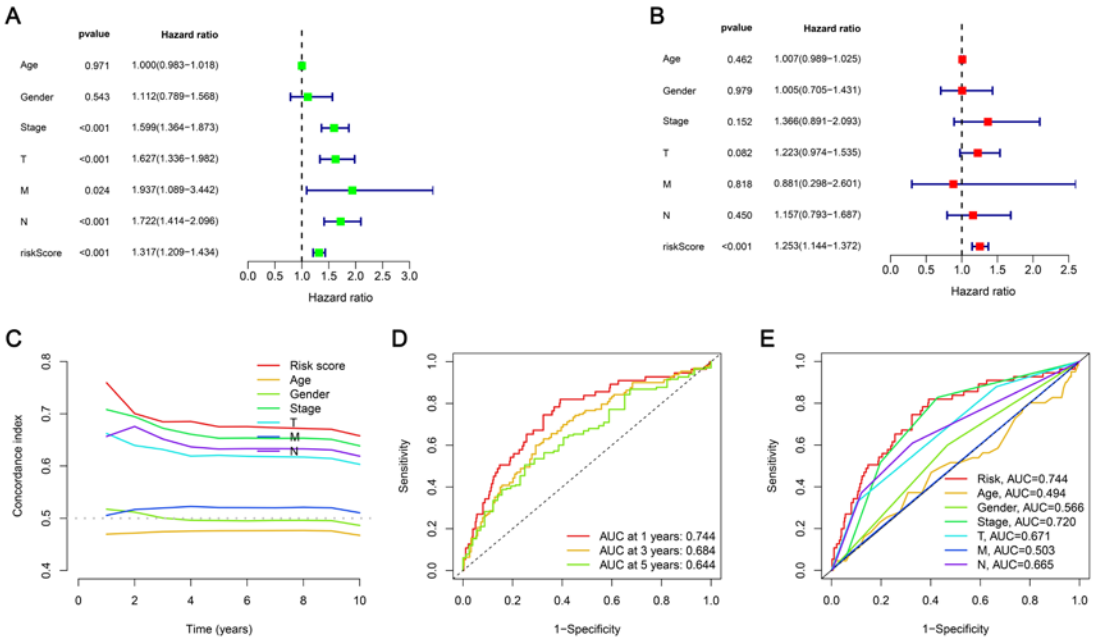

Figure 10 *Assessment of the prognostic risk model of the cuproptosis- associated lncRNAs and clinical features in LUAD in the TCGA entire set. (A and B) Univariate(A) and multivariate analyses(B) of the clinical characteristics and risk score with the OS. (C) Concordance indexes of the risk score and clinical characteristics. (D) ROC curves of nomogram in predicting 1-, 3-, and 5-years OS. (E) ROC curves of the clinical characteristics and risk score.*

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Discussion

The most prevalent histological subtype of lung cancer is adenocarcinoma[1,4]. Several studies on the prevalence, progression, and therapy of lung adenocarcinoma are now being conducted[28,29]. Numerous investigations have shown that the clinical symptoms and prognosis of diverse subcategories of lung cancer vary. In recent years, there has been an increase in research on the predictive value of lncRNAs in cancer of the lungs patients' survival and immunotherapy response.

LncRNAs are transcription factors that are longer than 200 nucleotides but lack the ability to encode proteins[30]. LncRNAs have a role in the beginning and progression of several diseases[31,32] and have the ability to specifically inhibit or stimulate gene expression. LncRNAs are likely to be employed as biomarkers for illness diagnosis and prognosis, since several studies in recent years have shown their role in the development and survival of cancer patients.Copper is a vital trace element and cofactor for enzymes.

Throughout the whole animal kingdom[33]. Genetic variations in copper homeostasis cause illnesses with a high death rate. Copper concentrations in cells are a good indicator of cell viability. Cuproptosis is a new kind of programmed cell death in which excessive copper in the cellular matrix disrupts certain mitochondrial enzymes, induces protein lipoylation, and results in a unique mode of cell death[8]. Despite the fact that copper may influence the expression of a large number of genes in the body, no research has been undertaken to explain the molecular mechanism of copper-associated lncRNA in cancer of the lungs. We evaluated the functions of cuproptosis and lncRNA in cancer of the lungs and created a risk prediction model for cuproptosis-associated genes. Since the connection of cuproptosis and lncRNAs in LUAD piqued our interest, we wanted to construct an independent model based on cuproptosis-associated lncRNAs in this investigation.

Using the TCGA database, 2244 genes associated with cuproptosis were identified, and their predictive roles were investigated in this work. 13 cuproptosis-associated genes in LUAD patients were evaluated by univariate regression, and 7 of these genes were leveraged to create a cuproptosis-associated lncRNA model to predict patients' overall survival. According to one research[34], AL606834.1 accelerates the progression of prostate cancer. AL606834.1, one of the predictive risk models of ferroptosis-associated lncRNA in LUAD, was verified in a second research[22]. Several additional studies[11,14,35] have demonstrated that immune-associated disorders are prevalent. Breast cancer, prostate cancer, non-small cell cancer of the lungs, endometrial cancer, and lung adenocarcinoma are affected by AL161431.1. Additionally, other cuproptosis-

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associated lncRNAs are the first reporter genes. On the basis of their median risk value, LUAD patients were then divided into high- and low-risk categories, with the high-risk category exhibiting markedly worse clinical outcomes. The cuproptosis-associated lncRNA model was identified as an autocephalous risk factor for OS by multivariable Cox regression analysis. According to ROC analysis, the system outperformed conventional clinical indications in LUAD survival prediction. Also, for the 1-year, 3-year, and 5-year OS, we produced a nomogram that demonstrates perfect agreement between observed and anticipated rates. The observed and anticipated 1-, 3-, and 5-year OS rates exhibited a high degree of concordance. The risk model was quite accurate, and this prediction model might aid in the identification of new biomarkers for further investigation. It was based on seven cuproptosis-associated lncRNAs that were separately linked to OS.

Mutational load refers to the number of somatic mutations remaining in the tumor genome after germline mutations have been eliminated[36]. Greater tumor immunogenicity is associated with a larger mutational load, indicating that PD-1/PD-L1 immune checkpoint inhibitor treatment will be more effective[37,38]. According to our results, the category at low risk had a greater TMB than the category at high risk. In addition, recent research has used the TIDE algorithm, which has been shown to accurately forecast the infiltration of immune cells into tumor tissue[39,40]. We found that the TIDE algorithm accurately predicted improved immunotherapy outcomes in high-risk patients. This work demonstrates that, when combined with previously disclosed data, this prediction model offers a viable immunological biomarker for tumor treatment.

Our findings provide novel insights into the molecular biological processes involving lncRNAs that are associated with cuproptosis in LUAD.In actual clinical practice, the prognosis of lung cancer patients is closely associated to tumor stage. Due to the variability of the human body, people with the same stage have different survival lengths. This suggests that the exact treatment of malignancies remains difficult. Consequently, more research on novel biological targets for diagnosis and treatment is essential. The discovery of cuproptosis-associated lncRNA expands the potential cuproptosis gene regulation of lncRNA and offers a novel way for predicting the prognosis of LUAD patients. In this work, we applied a range of methods to verify the model's prediction abilities.

According to the findings of this research, the prognostic risk model based on cuproptosis-associated lncRNA may predict the OS of lung adenocarcinoma consistently and is an independent prognostic signal for the disease. For more precise treatment, the number of digits may be used to classify LUAD patients into high-

risk and low-risk categories. This research also shown that these 7 cuproptosis-associated lncRNAs have the potential to serve as therapeutic targets as well as prognostic and diagnostic biomarkers for LUAD. Nonetheless, there are limitations to this research. Since the TCGA database lacks detailed information, such as smoking history and treatment, this is the retrospective research in which original data and clinical data were extracted from the database. The model's ability to predict outcomes was further hindered by the lack of clinical information for 471 participants in the TCGA database. Therefore, more field research is required to determine the precise role of cuproptosis-associated lncRNAs in cancer of the lung development.

Data Availability:

Datasets produced and/or studied during present research are usable in [https://portal.gdc.cancer.gov/].

Conflicts of interest:

Authors assert they have no conflict of interest competing interests.

Author contributions:

Q.Z, Y.L, H.D, N.I and L.Q have conceptualized the manuscript: Y.G and Z.A, and S.Q were responsible for the experimentation: J.L, L.W, J.B.N, A.A and M.S.K were responsible for gathering the data amd writing: A.H.M and Before rewriting the paper, each author analyzed the material and discussed the findings. All authors have read and agreed to the published version of the manuscript.

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