

Identification of a nine ferroptosis-related lncRNA prognostic signature for lung adenocarcinoma

Xiwen Tong

Huangzhou District People' Hospital

Yujiao Zhang

Huanggang Central Hospital

Guodong Yang

Huanggang Central Hospital <https://orcid.org/0000-0002-6437-6897>

Guanghui Yi (✉ 201771458@yangtzeu.edu.cn)

Department of neurosurgery, Huangzhou District People's Hospital <https://orcid.org/0000-0002-7507-0359>

Primary research

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Abstract

Background

Recently, mounting of studies has shown that lncRNA affects tumor progression through the regulation of ferroptosis. The current study aims to construct a robust ferroptosis-related lncRNAs signature to increase the predicted value of lung adenocarcinoma (LUAD) by bioinformatics analysis.

Methods

The transcriptome data were abstracted from The Cancer Genome Atlas (TCGA). Differentially expressed lncRNAs were screened by comparing 535 LAUD tissues with 59 adjacent non-LAUD tissues. Univariate Cox regression, lasso regression, multivariate Cox regression were conducted to design a ferroptosis-related lncRNA signature. This signature's prognosis was verified by the log-rank test of Kaplan-Meier curve and the area under curve (AUC) of receiver operating characteristic (ROC) in train set, test set, and entire set. Furthermore, univariate and multivariate Cox regression were used to analyze its independent prognostic ability. The relationship of the ferroptosis-linked lncRNAs' expression and clinical variables was demonstrated by Wilcoxon rank-sum test and Kruskal-Wallis test. Gene set enrichment analysis (GSEA) was performed to signaling pathways it may involve.

Results

1224 differentially expressed lncRNAs were identified, of which 195 are ferroptosis-related lncRNAs. A nine ferroptosis-related lncRNAs (AC099850.3, NAALADL2-AS2, AL844908.1, AL365181.2, SMIM25, FAM83A-AS1, LINC01116, AL049836.1, C20orf197) prognostic signature was constructed. This model's prognosis in the high-risk group is obviously worse than that of the low-risk group in train set, test set, and entire set. The AUC of ROC predicting the three years survival in the train set, test set, and entire set was 0.754, 0.716, and 0.738, respectively. Moreover, the designed molecular signature was found to be an independent prognostic variable. The expression of these lncRNAs and the lncRNA signature are related to clinical stage, T stage, Lymph-node status, distant metastasis. Finally, GSEA analysis results show that the signature is involved in eight tumor-related and metabolism-related signaling pathways

Conclusion

The current study constructed, validated, and evaluated a nine ferroptosis-related lncRNA signature which can independently be used to predict the prognosis of LAUD patients, and may become a new therapeutic target.

Background

Worldwide, lung cancer has remained the leading cause of cancer incidence as well as mortality among cancers, with 2.1 million new cases along with 1.8 million deaths estimated in 2018, which represented about 1 in 5 (18.4%) cancer deaths [1]. Among the types of lung cancer, non-small-cell lung cancer (NSCLC) comprises the most frequent, which is responsible for an estimated 85% of all the lung cancer cases [2]. Notably, lung adenocarcinoma (LUAD) constitutes the most frequent histological subtype of NSCLC, which accounts for about 40–70% cases [3, 4]. Although the current treatment of LUAD has made significant progress, the prognosis is still very poor, with an average 5-year survival rate of 15% [5]. In clinical practice, individualized treatment has attracted mounting attention. Therefore, investigating promising prognostic signatures along with potential targets is considered as an essential phase to achieving this goal.

Ferroptosis is a type of cell death that is characterized by high production of lipid ROS (L-ROS) as a result of inactivation of cellular glutathione (GSH)-dependent antioxidant defenses. This form of cell death is iron-dependent and differs from apoptosis, classic necrosis, ferroptosis, and other forms of cell death [6, 7]. Extensive studies found that ferroptosis was associated with the initiation of multiple diseases, including kidney injury, blood circulation diseases, conditions of the nervous system, and ischemia-reperfusion injury [8]. Scholars have suggested that ferroptosis may be adaptive strategy used for eliminating cancerous cells and hence prevent cancer development in situations of infections, cellular stress, and nutrient deficiency [9]. Increasing studies have shown that many factors were involved in regulating ferroptosis in lung cancer. For example, some inducers include erianin [10], lncRNA-P53RRA [11], concurrent mutations of STK11 and KEAP1 [12], erastin/sorafenib [13], acetaminophen [14], Zinc [15], dihydroartemisinin [16], MT1DP (lncRNA), ginkgetin [17], inhibitors include LINC00336 [18], FSP1 [19, 20], NFS1 [21], EGLN1 [22]. In addition, a study showed ferroptosis inducers may enhance the sensitivity of radiotherapy [23]. Hence, it is essential to discover ferroptosis-linked biomarkers that can be applied as valuable early diagnostic as well as prognostic indicators for LAUD.

Long non-coding RNAs (lncRNAs) is a class of non-coding RNAs with more than 200 nucleotides long that have apparently little or no protein-coding ability [24]. lncRNAs regulate critical biological functions related to growth of cells and survival, allosteric regulation of enzyme activities, chromatin modifications, and genomic imprinting [25]. Besides, a mounting number of studies have chronicled that lncRNAs affect cancer progression and predict dismal prognosis in diverse cancer types by modulating ferroptosis. For example, p53 related lncRNA (P53RRA) promotes apoptosis and ferroptosis of cancerous cells by activating the p53 pathway [11]. lncRNA GABPB1-AS1 regulates the status of oxidative stress in context of erastin-triggered ferroptosis in HepG2 hepatocellular carcinoma cells [26]. lncRNA-linc00336 suppresses ferroptosis in lung cancer tissues by acting as a competing endogenous RNA [27]. linc00618 accelerates ferroptosis via inhabiting vincristine (VCR) and lymphoid-specific helicase (LSH) /SLC7A11 in leukemia [28]. In non-small cell lung cancer cells, lncRNA-MT1DP enriched on folate-modified liposomes promotes erastin-triggered ferroptosis by modulating the miR-365a-3p/NRF2 axis [29]. Hence, it is critical to explore the pivotal lncRNAs closely linked to ferroptosis along with prognosis in LAUD.

This study is the first to propose a predictive model of lncRNA related to ferroptosis genes in LAUD. Herein, we explored the expression of lncRNAs in LAUD from The Cancer Genome Atlas (TCGA) and identified ferroptosis-associated lncRNAs with prognostic potential. We constructed and verified a nine ferroptosis-correlated lncRNA biosignature with the ability to estimate the survival prognosis of LAUD patients.

Methods

Data download and processing

The transcriptome data (Cases (594): Primary Site (lung and bronchus), Program (TCGA), Project (TCGA-LUAD); Files (594 including 535 LUAD tissues and 59 non-LUAD tissues): Data Category (Transcriptome Profiling), Workflow Type (HTSeq - FPKM)), Data Type (Gene Expression Quantification), clinical information (Files (522), Data Category (clinical), and Data Format (bcr xml)) were abstracted from The Cancer Genome Atlas (TCGA) web data resource (<https://cancergenome.nih.gov/>) on November 15, 2020 (**Table 1**). Patients with no follow-up time and follow-up time shorter than 30 days were excluded from this study.

Screening of ferroptosis-related lncRNAs (AlncRNAs)

The ferroptosis genes (259) were downloaded from the world's first database (ferroptosis regulators and markers and ferroptosis-disease associations (FerrDb)) (<http://www.zhounan.org/ferrdb/>). We employed the "limma" R package [30] to screen differentially expressed lncRNAs by comparing 535 LAUD tissues with 59 adjacent non-LAUD tissues. The included criteria are False Discovery Rate (FDR) < 0.05 and $|\log_{2}FC| > 2$. Furthermore, we identified ferroptosis-related lncRNAs by the correlation analysis between the lncRNAs expression levels and the ferroptosis genes based on the criteria of $P < 0.001$ and $|\text{Correlation Coefficient}| > 0.3$.

Development, verification, and assessment of prognostic biosignature

We utilized the R language 4.0.1 version "caret" package to randomly classify the entire data set (**Additional file 1**) with FRlncRNAs expression profiles into two sets (train set (**Additional file 2**) and test set (**Additional file 3**)), and conducted univariate Cox regression for FRlncRNAs in the train group ($P < 0.05$). Lasso regression analysis was utilized to minimize overfitting using the "glmnet" package [31] ($P < 0.05$). Afterward, multivariate Cox regression was employed to develop the optimal prognostic risk model and leveraged "coxph" and "direction = both" functions of the R language "survival" package [32] ($P < 0.05$). Then, the prognostic lncRNA signature's risk score constituting multiple lncRNAs was developed by summing up the product of each lncRNA with its corresponding coefficient. Additionally, the Proportional Hazards Assumption was tested in the Cox model. Similarly, on the basis of the previous training set's risk score formula, we applied it to the testing set as well as the entire set as validation.

This model was employed to explore each patient's survival prognosis by the Kaplan-Meier curve along with the log-rank test on the basis of the median of risk score, namely low-risk group and high-risk group in the train set, test set, entire set. The lncRNA signature's predictive power was explored by computing the AUC of 3 years using the ROC curve by the "survival ROC" package [33].

To further enhance the prognostic signature's credibility, we conducted a stratified survival prognostic analysis on gender, age, clinical stage, postoperative tumor status, KRAS status, EGFR status, ALK status, ECOG score.

Independent and prognostic ability of the lncRNA signature

Multivariate Cox regression and univariate Cox regression analyses were conducted to analyze the independent and prognostic ability of the lncRNA signature (**Additional file 4**). The clinical parameters include age, gender, clinical stage, T stage, lymph nodes as well as distant metastasis. Besides, compared with clinical variables, The ROC curve was employed to explore whether the lncRNA biosignature has better predictive power. The "rms" package was employed to construct the nomogram according to the multivariate Cox regression result ($P < 0.05$). To further investigate whether the ferroptosis-associated lncRNAs are involved in LAUD development, we explored the relationship of the ferroptosis-linked lncRNAs' expression with clinical variables using the Wilcoxon rank-sum test and Kruskal-Wallis test.

GSEA analysis of the lncRNA signature.

Gene set enrichment analysis (GSEA4.1.0) downloaded from <https://www.gsea-msigdb.org/gsea/index.jsp> website was employed to identify the biological function of the prediction model [34]. Based on the median expression of lncRNA signature riskScore in 568 tumor samples, we divided them into low and high-risk groups for Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis of GSEA. The abundant signaling cascades in each phenotype were based on the normalized enrichment score (NES), the nominal (NOM) P-value as well as the false discovery rate (FDR). $FDR < 25\%$ and $NOM\ P\text{-value} < 5\%$ serve as a standard for inclusion.

2.6 | Statistical Analysis

R software 4.0.3 version and attached packages were employed to conduct data analyses. All the statistical analyses were two-sided. $P < 0.05$ signified of statistical significance.

Results

Screening of ferroptosis-related lncRNAs in LAUD.

Comparing LAUD tissues with adjacent non-LAUD tissues, 1224 differentially expressed lncRNAs were found, of which 1044 are up-regulated and 180 are down-regulated (**Additional file 5**). The correlation results between 259 ferroptosis-related genes and differentially expressed lncRNAs shown that there are 195 ferroptosis-related lncRNAs (FRlncRNAs) (**Additional file 6**).

Construction, validation, and evaluation of a nine ferroptosis-related lncRNAs prognostic signature

The entire set (N = 477) with 195 FRlncRNAs expression data was randomized into the test set (N = 237) and train set (N = 240). In the univariate Cox regression assessment, 22 FRlncRNAs modulated the overall survival of the patients in the train set (Fig. 1a). Lasso regression was used for further analysis to eliminate overfitting lncRNAs, and the 14 lncRNAs we obtained were used for the subsequent multivariate Cox regression analysis (Fig. 1b-c) (concordance index [C-index], 0.75). The ferroptosis-associated lncRNA prognostic biosignature was developed based by summing up the product of each lncRNA expression with its corresponding coefficient in multivariate Cox regression as indicated below: lncRNA biosignature risk score = (0.049 × expression of AC099850.3) + (0.060 × expression of NAALADL2-AS2) + (0.051 × expression of AL844908.1) + (0.056 × expression of AL365181.2) + (-0.078 × expression of SMIM25) + (0.090 × expression of FAM83A-AS1) + (0.090 × expression of LINC01116) + (0.089 × expression of AL049836.1) + (-0.232 × expression of C20orf197). Analysis using the Proportional Hazards Assumption in the Cox model revealed that all the P values > 0.05, implying they conformed to the PH test (**Additional file 7**).

According to the median value of the risk score, results of the Kaplan-Meier curves demonstrate that the high-risk group has a remarkably dismal overall survival (OS) in contrast with the low-risk group in the train set (P = 8.66E-06), test set (P = 2.766E-04), and entire set (P = 7.533E-09) (Fig. 2a-c). The train set shows three years' OS for patients with high and low-risk group were 38.3% and 73.3%, respectively. The test set is 41.3% and 79.3%, respectively. The entire set is 40.9% and 78.4%, respectively. The AUC of three years dependent ROC for the seven-lncRNA biosignature achieves 0.754, 0.716, and 0.738 respectively in the train set, test set, and entire set (Fig. 2d-f), which demonstrate the good performance of the model in estimating the LAUD patients' OS. The mortality rate was higher in patients with high-risk scores relative to those with low-risk scores in the three sets (Fig. 2g-i). The seven lncRNAs' (AC099850.3, NAALADL2-AS2, AL844908.1, AL365181.2, FAM83A-AS1, LINC01116, AL049836.1) expression of signature were lower in low-risk group compared to the high-risk group in cluster heat map, SMIM25 and C20orf197 oppositely (Fig. 2j-l).

It is worth noting that AC099850.3, FAM83A-AS1 and LINC01116's high expression of this lncRNA signature also has a worse OS than low, C20orf197 oppositely (Fig. 3). The association of the seven lncRNAs with ferroptosis genes is shown by network diagram in Fig. 4. In addition, we stratified according to various clinical factors (gender, age, clinical stage, postoperative tumor status, KRAS status, EGFR status, ALK status, ECOG score) and applied the prognostic model to OS detection, which is shown in Fig. 5, the results shown that the signature has good predictive significance for LAUD patients in most stratification factors, and part of results are not satisfactory (P > 0.05), which might be due to there are not enough samples in these stratifications.

Independent prognostic analysis of the nine ferroptosis-associated lncRNAs signature and its correlation with clinical variables.

The Univariate Cox regression assessment demonstrated that the lncRNA biosignature risk score was evidently correlated with the patients' OS (hazard ratio HR = 1.003, confidence interval 95%CI = 1.001–1.006, P = 0.009) (**Table 2**). Moreover, the multivariate Cox regression analysis demonstrated that the lncRNA biosignature risk score remained independent with OS considering other conventional clinical factors including Lymph-node status, the clinical stage, distant metastasis, and T stage (HR = 1.004, 95% CI = 1.002–1.007, P = 0.001). Meanwhile, clinical stage was demonstrated as an independent prognostic index. Compared to clinical variables, this signature risk score's ROC curves of three years demonstrate the largest AUC value (0.737) (Fig. 6).

Based on the stratification of clinical variables, the correlation between the lncRNAs and clinical variables shows that clinical stage is related to AC099850.3, AL365181.2, FAM83A-AS1, LINC01116, C20orf197' expression and signature' risk score. T stage is associated with AC099850.3, FAM83A-AS1, AL049836.1 and C20orf197' expression and signature' risk score. Lymph-node status is correlated to AC099850.3, FAM83A-AS1' expression and signature' risk score. Distant metastasis is concerning to AL365181.2 (Fig. 7).

Functional enrichment analysis of the nine ferroptosis-related lncRNAs signature.

GSEA analysis is used to discover potential biological functions of the nine ferroptosis-associated lncRNAs signature of LAUD (Fig. 8 and **Table 3**). The results showed that eight tumor-related and metabolism-related signaling pathways (KEGG_CELL_CYCLE, KEGG_MISMATCH_REPAIR, KEGG_P53_SIGNALING_PATHWAY, KEGG_SMALL_CELL_LUNG_CANCER, KEGG_UBIQUITIN_MEDIATED_PROTEOLYSIS) are obviously enriched in the high-risk group, and three signaling cascades (KEGG_ALPHA_LINOLENIC_ACID_METABOLISM

KEGG_ARACHIDONIC_ACID_METABOLISM, KEGG_FATTY_ACID_METABOLISM) were abundant in the low-risk group by c2.cp.kegg.v7.2.symbols.gmt. These results suggest that this signature model function as LAUD' prognostic factor through signaling pathways.

Discussion

Lung cancer is one of the leading causes of cancer-related death globally, while LAUD ranks first in the proportion of lung cancer subtypes [35]. Although the current treatment methods have made great advancements, the prognosis is still very poor. Ferroptosis is differs from other types of cell death in terms of biochemically and morphologically and has been shown to regulate cancer development [6]. More and more reports have documented that lncRNA plays a very important role in regulating gene expression and regulation in tumor [25, 36]. In addition, many lncRNAs influence the progression of LAUD by regulating ferroptosis. However, there are no reports on that prognostic model of lncRNA related to ferroptosis was constructed. Although two previous genetic prognostic models of ferroptosis have been reported in hepatocellular carcinoma [37] and glioma [38], our study is the first to report the study of ferroptosis-related lncRNA prognostic models in LAUD

In the present study, we downloaded ferroptosis genes from FerrDb, and used the R language and its attached packages to find differentially expressed lncRNAs related to ferroptosis (FRlncRNAs). We randomly grouped all the patients into train set as well as the test set, then a nine ferroptosis-related lncRNAs signature model (AC099850.3, NAALADL2-AS2, AL844908.1, AL365181.2, FAM83A-AS1, LINC01116, AL049836.1, SMIM25 and C20orf197) was established through univariate Cox regression, Lasso regression, as well as multivariate Cox regression in the train set. At the same time, the biosignature was verified in the test set as well as the entire set. On the basis of the median risk score, the Kaplan-Meier curves revealed that the high-risk group had an evidently dismal overall survival relative to the low-risk group in the three data sets and various clinical stratification factors. Assessment of the biosignature for OS in the three sets by ROC curve exhibited well predictive value. The Univariate Cox regression as well as the multivariate Cox regression analyses demonstrated that the biosignature had independent prognostic ability considering other conventional clinical variables for LAUD patients. On the basis of the multivariate Cox regression results, we developed the nomogram of the clinical prediction model. Furthermore, the nine lncRNAs and the signature model are linked to the T stage, Lymph-node status, distant metastasis, clinical stage to varying degrees. Finally, GSEA analysis results show that the signature model is involved in eight KEGG signal pathways based on high and low-risk group, such as KEGG_CELL_CYCLE, KEGG_MISMATCH_REPAIR, KEGG_P53_SIGNALING_PATHWAY, KEGG_SMALL_CELL_LUNG_CANCER, KEGG_UBIQUITIN_MEDIATED_PROTEOLYSIS, KEGG_ALPHA_LINOLENIC_ACID_METABOLISM

KEGG_ARACHIDONIC_ACID_METABOLISM, KEGG_FATTY_ACID_METABOLISM. These results suggest that this signature model function as LAUD' prognostic factor through signaling pathways.

Before this study, many prognostic models of lung adenocarcinoma have been constructed from different research perspectives, such as Zhang et al. identified a novel glycolysis-associated gene biosignature for the prediction of metastasis along with survival for individuals with lung adenocarcinoma [39], Li B et al. developed and validated of an individualized immune prognostic biosignature in early-Stage non-squamous NSCLC [40], Li Y et al. showed prognostic alternative mRNA splicing signature in NSCLC [41]. Yerukala et al. identified the miRNA biosignature related to the survival time in individuals with lung adenocarcinoma using miRNA expression profiles [42]. Xu Z et al. demonstrated an oxidative phosphorylation-related gene signature in lung adenocarcinoma [43]. Mo Z et al. constructed a Hypoxia-related biosignature for Lung Adenocarcinoma [44]. Zhao S et al. present a circular RNA Signature in Lung Adenocarcinoma by MiOncoCirc Database [45]. The examples we have cited are only the tip of the iceberg, and the relationship between lncRNA, ferroptosis, and LAUD has also been well demonstrated in this study from a new perspective.

Among these lncRNAs of the signature, some studies have shown that AC099850.3 is also used as an autophagy-related lncRNA signature model in hepatocellular carcinoma as well as oral and oropharyngeal squamous cell carcinoma [46, 47]. Benoist GE et al revealed that patients with NAALADL2-AS2 high-expression showed a longer time to progression [48].

Xiao G et al. discovered FAM83A-AS1 promoted LAUD cell migration as well as invasion via targeting miR-150-5p as well as modifying MMP14 [49], Shi R et al. found FAM83A-AS1 facilitated LUAD proliferation and invasion by increasing FAM83A expression [50]. He J et al. revealed long noncoding RNA FAM83A-AS1 promotes the progression of hepatocellular carcinoma by binding with NOP58 to promote the mRNA stability of FAM83A [51]. Huang GM et al. reflected lncRNA FAM83A-AS1 aggravates the malignant development of esophageal cancer by binding to miR-495-3p [52]. LINC01116 has been studied as an oncogene in many tumors, such as LAUD, its overexpression promotes LAUD proliferation and metastasis [53], contributes to gefitinib resistance in NSCLC through regulating IFI44 [54], results in resistance of LAUD to cisplatin via the EMT process [55]. Leng X et al. indicated that SMIM25 (Aliases LINC01272) promoted gastric cancer metastasis through regulating EMT process [56]. The remaining lncRNAs have not seen relevant reports in previous studies, which are worthy of further research.

Our current study also has some limitations. First, we use the data in the TCGA database as the starting point for research; although the model has been internally verified, it is still needed for further verification in external data; second, TCGA's race is mainly white (75%), and whether the model fits other race needs further verification. Third, the analysis of the lncRNA expression of the model and the KEGG function enrichment analysis by the GSEA model requires further cell function experimental analysis.

Conclusion

Herein, we established a novel ferroptosis-related lncRNA prognostic signature model comprising nine lncRNAs (AC099850.3, NAALADL2-AS2, AL844908.1, AL365181.2, FAM83A-AS1, LINC01116, AL049836.1, SMIM25 and C20orf197) in LAUD. In the future, the ferroptosis-related lncRNA prognostic biosignature could enhance predictive accuracy as well as guide individualized therapy for LAUD patients with prospective validation.

Abbreviations

LAUD: Lung adenocarcinoma; GSEA: Gene set enrichment analysis; MsigDB:

Molecular signatures database; FDR: False discovery rate; OS: Overall survival;

HRs: Hazard ratios; CI: Confidence interval; TCGA: The Cancer Genome Atlas; AUC: Area under curve; ROC: Receiver operating characteristic; KEGG: Kyoto Encyclopedia of Genes and Genomes.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

Xiwen Tong downloaded the lncRNA and mRNA expression information, Xiwen Tong and Guodong Yang constructed lncRNA signature model and performed the statistical analysis using R language software, and wrote the first draft of the manuscript. Guanghui Yi and Yujiao Zhang revised the manuscript. Guanghui Yi contributed conception and design of the study and checked the manuscript.

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Availability of data and materials

The transcriptome data (HTSeq - FPKM)) and clinical information were downloaded from The Cancer Genome Atlas (TCGA) (<https://cancergenome.nih.gov/>). The ferroptosis genes were downloaded from Human Ferroptosis Database (HADb) (<http://www.ferroptosis.lu>).

Ethics approval and consent to participate

lncRNA and mRNA sequencing profiles were obtained from the TCGA data portal, which is a publicly available dataset. Therefore, no ethics approval is needed.

Consent for publication

All listed authors have actively participated in the study and approved the submitted manuscript.

Competing interests

The authors declare that they have no competing interests.

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Tables

Due to technical limitations, table 1, 2, 3 is only available as a download in the Supplemental Files section.

Figures

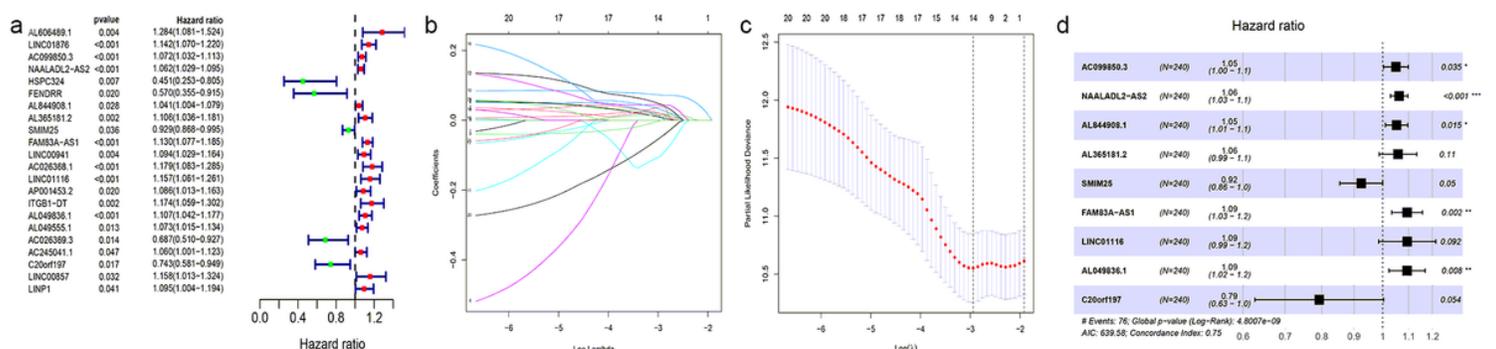


Figure 1

Construction of the ferroptosis-related lncRNAs prognostic signature. a Univariate Cox regression. b-c Lasso regression. d Multivariate Cox regression.

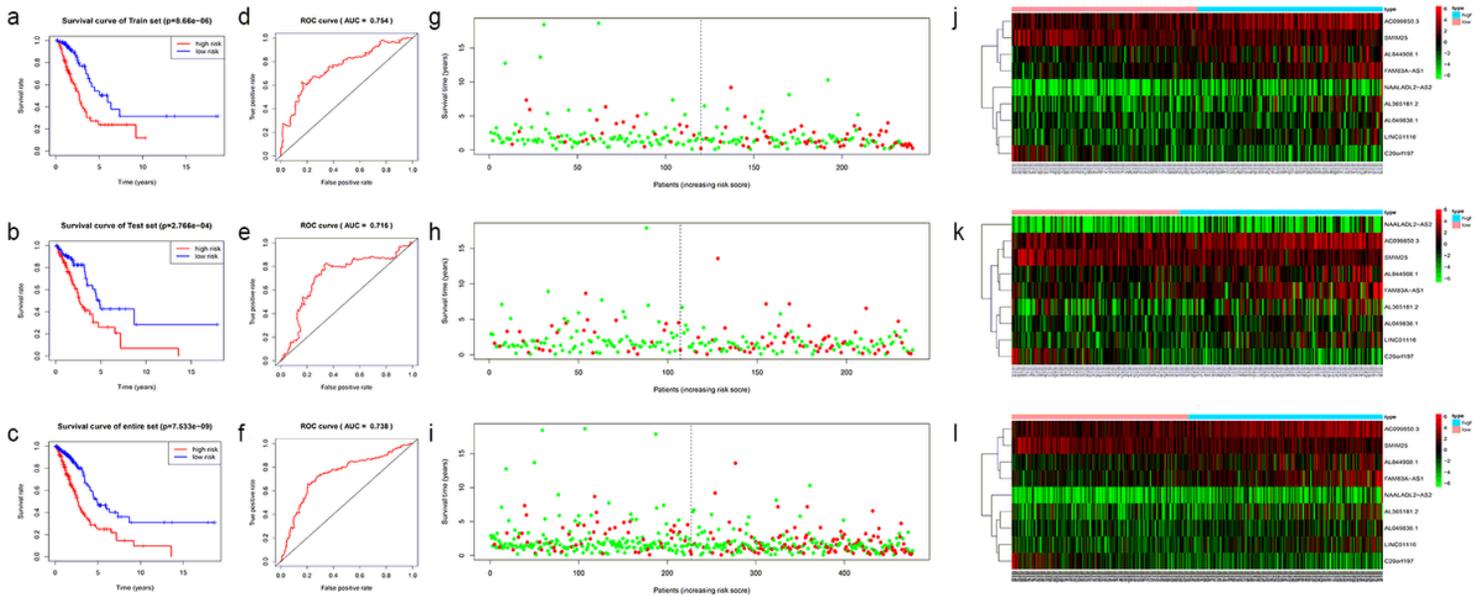


Figure 2

Validation and evaluation of the ferroptosis-related lncRNAs prognostic signature. Kaplan-Meier curves in the train set (a), test set (b), entire set (c); The AUC of three years dependent curve in the train set (d), test set (e), entire set (f); Survival status in high and low-risk patients for train set (g), test set (h), entire set (i), red dots represent death, and green dots represent alive; The cluster heat map of seven lncRNAs' expression in high and low risk groups for the train set (j), test set (k), entire set (l)

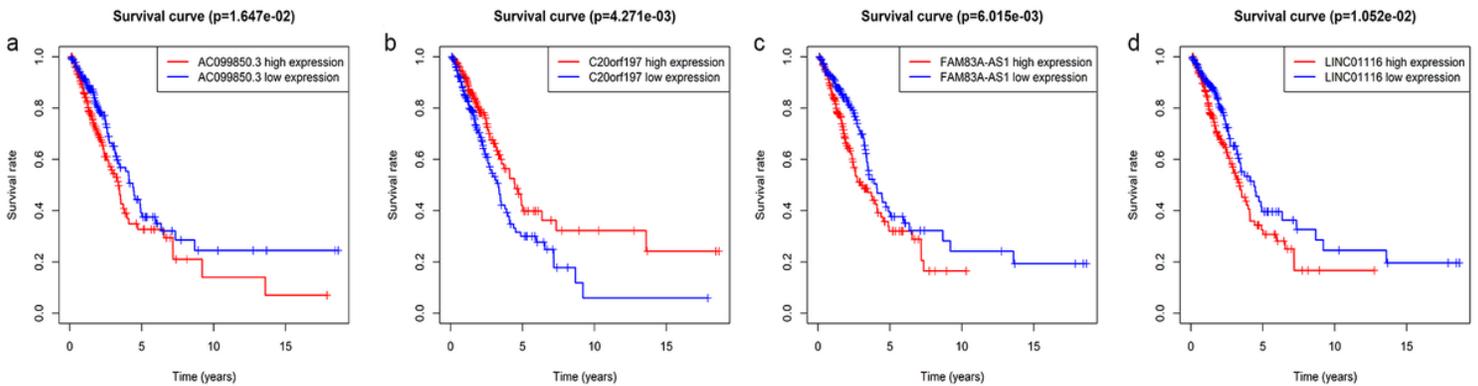


Figure 3

Four lncRNAs associated with overall survival in LAUD patients using Kaplan-Meier curves and log-rank tests. a AC099850.3. b C20orf197. c FAM83A-AS1. d LINC01116.

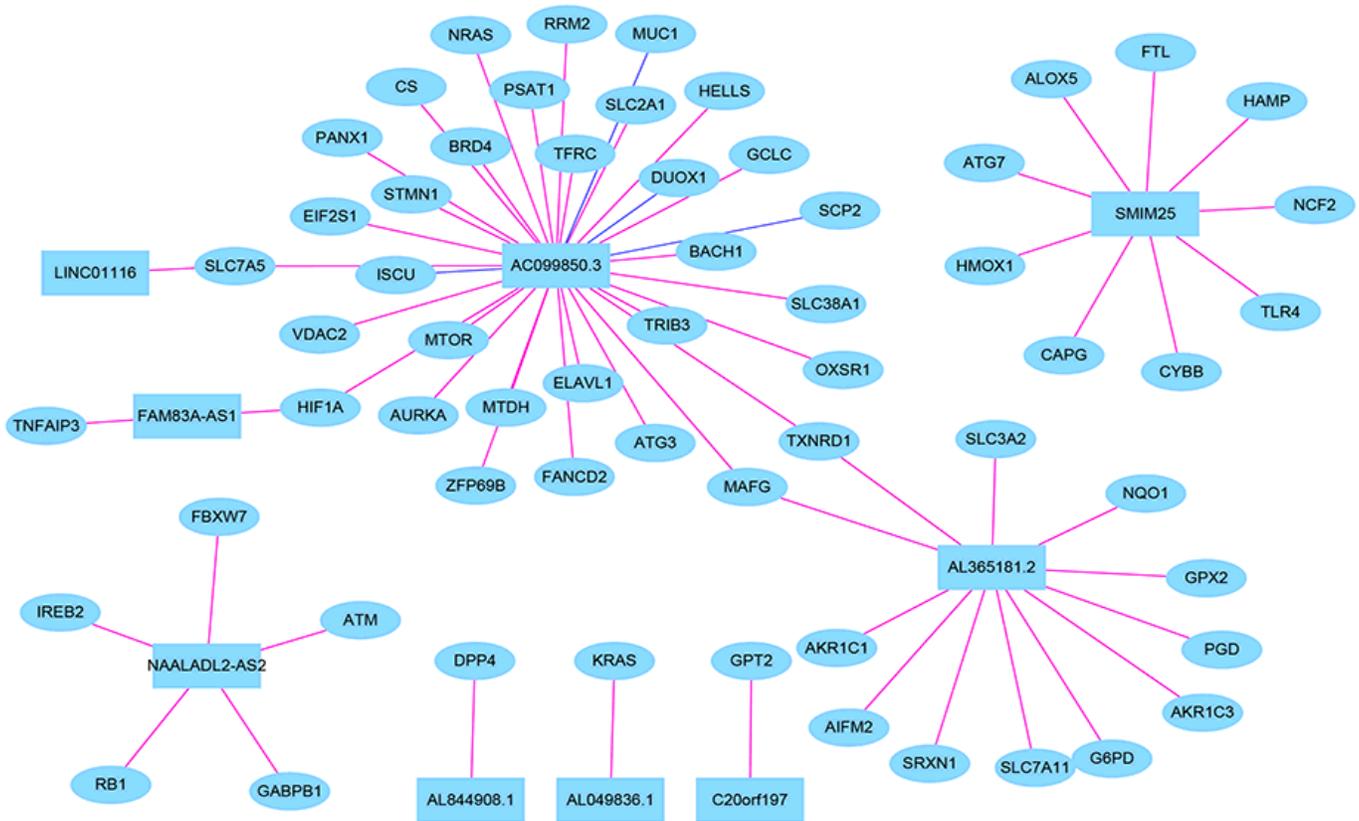


Figure 4

The network relationship between these nine lncRNAs and ferroptosis genes. Rectangle represent lncRNA, and circles represent ferroptosis genes. The red line represents positive correlation, and the blue line represents negative correlation.

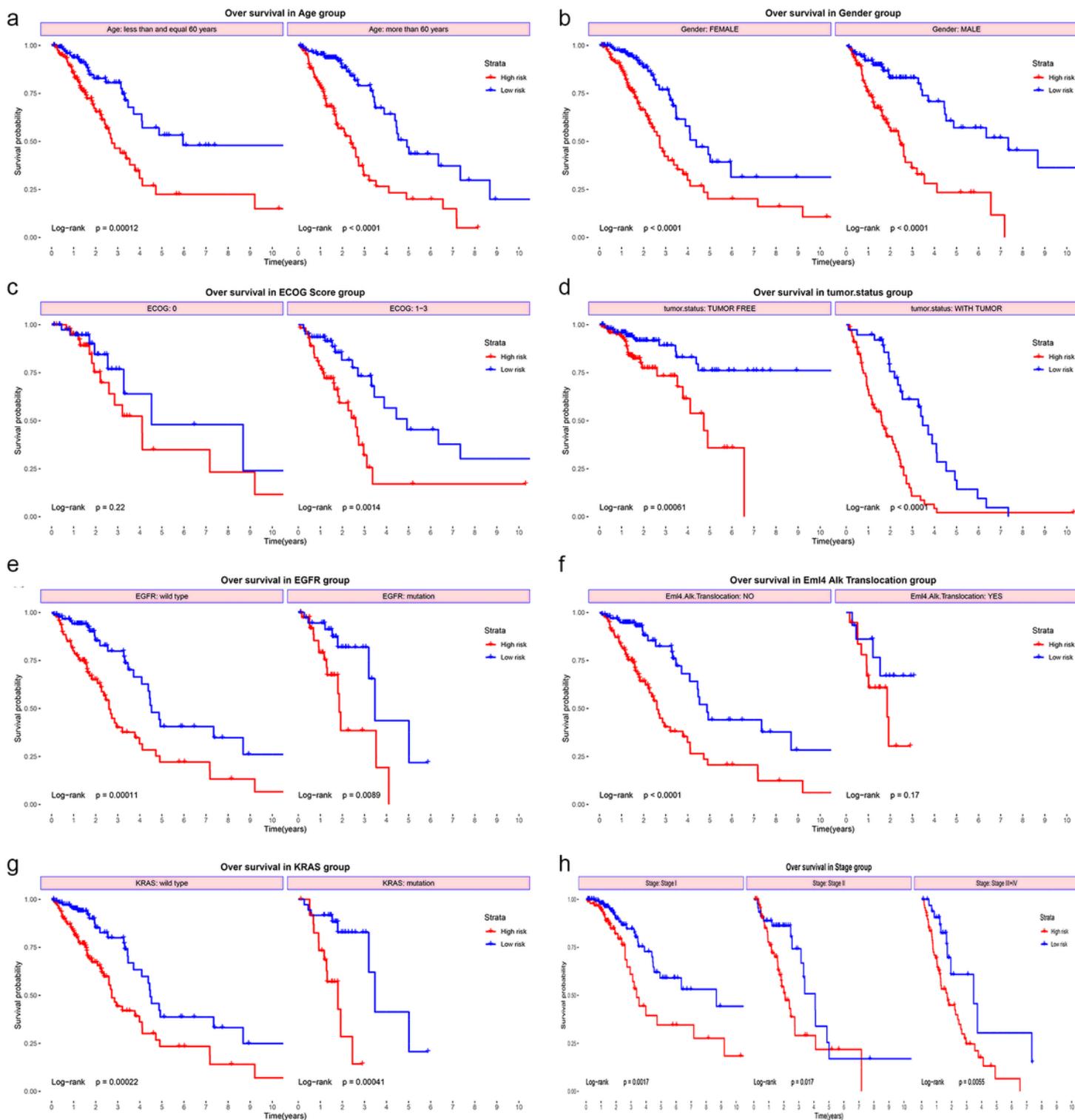


Figure 5

The overall survival of the ferroptosis-related lncRNAs prognostic signature in the stratification of clinical variables. a Age group. b Gender group. c ECOG group. d Tumor status group. e EGFR group. f ALK group. g KRAS group. h clinical stage group.

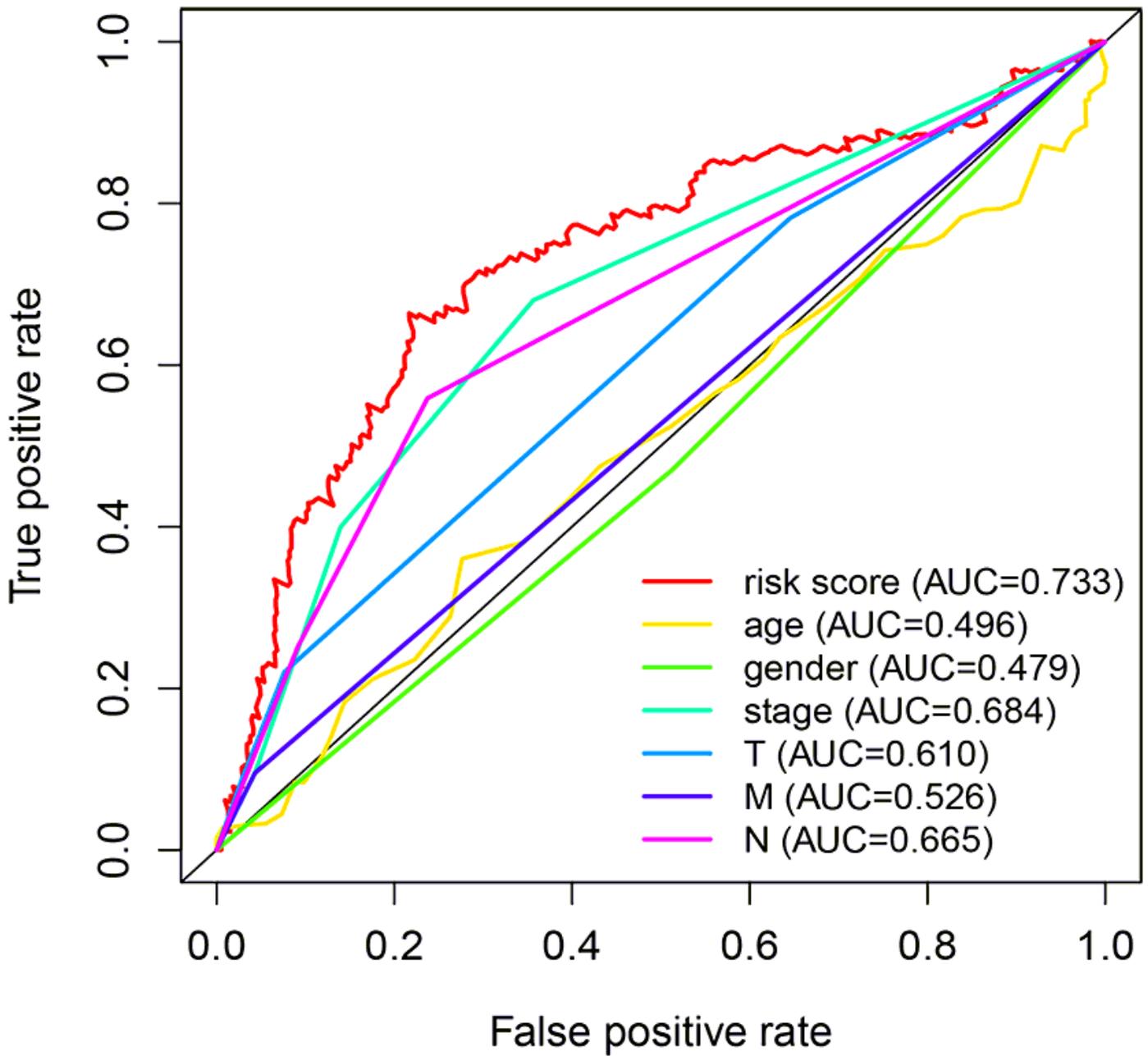


Figure 6

The ROC curve of the ferroptosis-related lncRNAs prognostic signature and clinical variables.

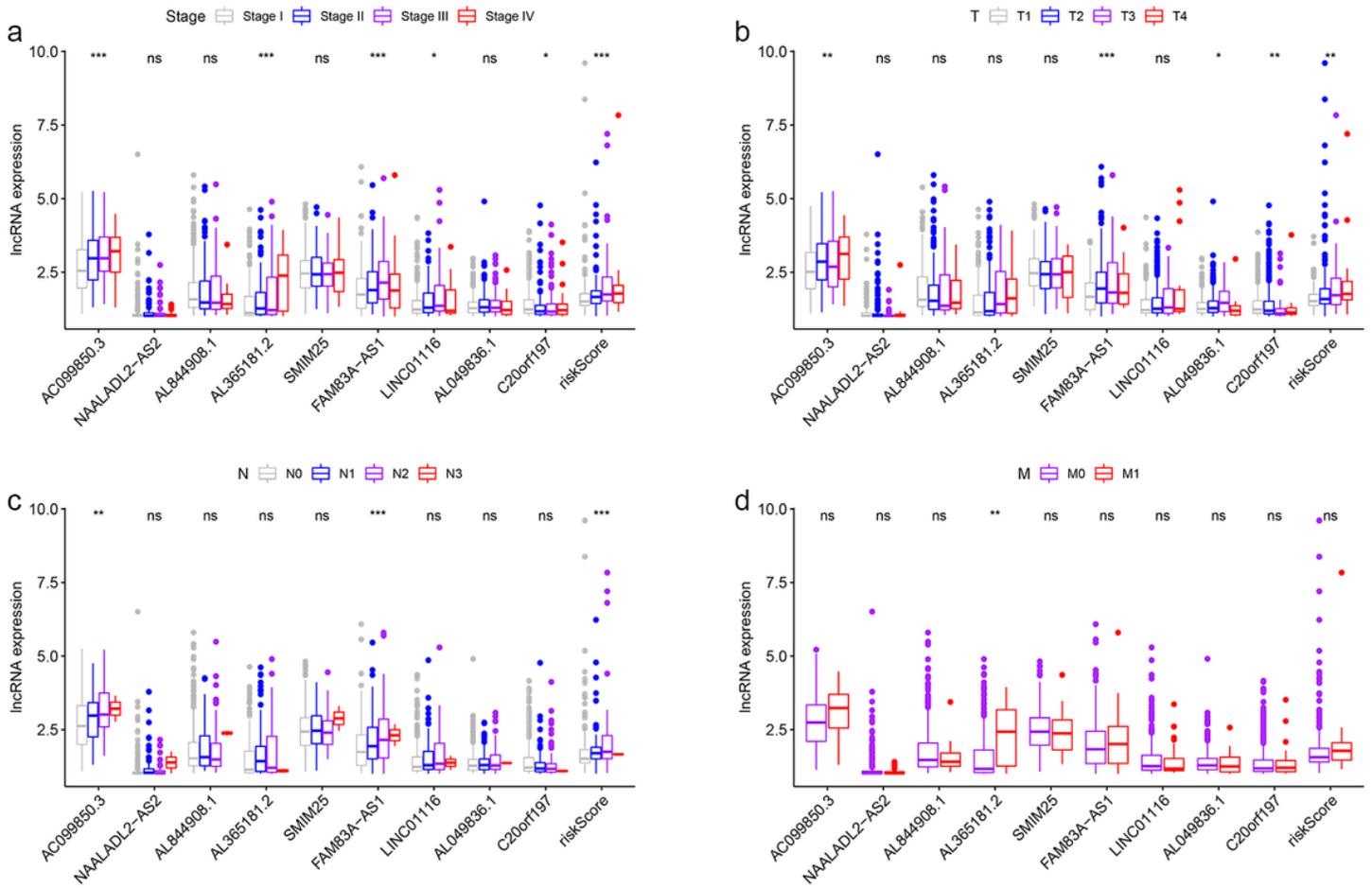


Figure 7

The correlation between the lncRNAs constituting the signature and clinical variables. a Clinical stage. b T stage. c Lymph-node status. d Distant metastasis. * represents $P < 0.05$, ** represents $P < 0.01$, *** represents $P < 0.001$, "ns" represents no statistical significance.

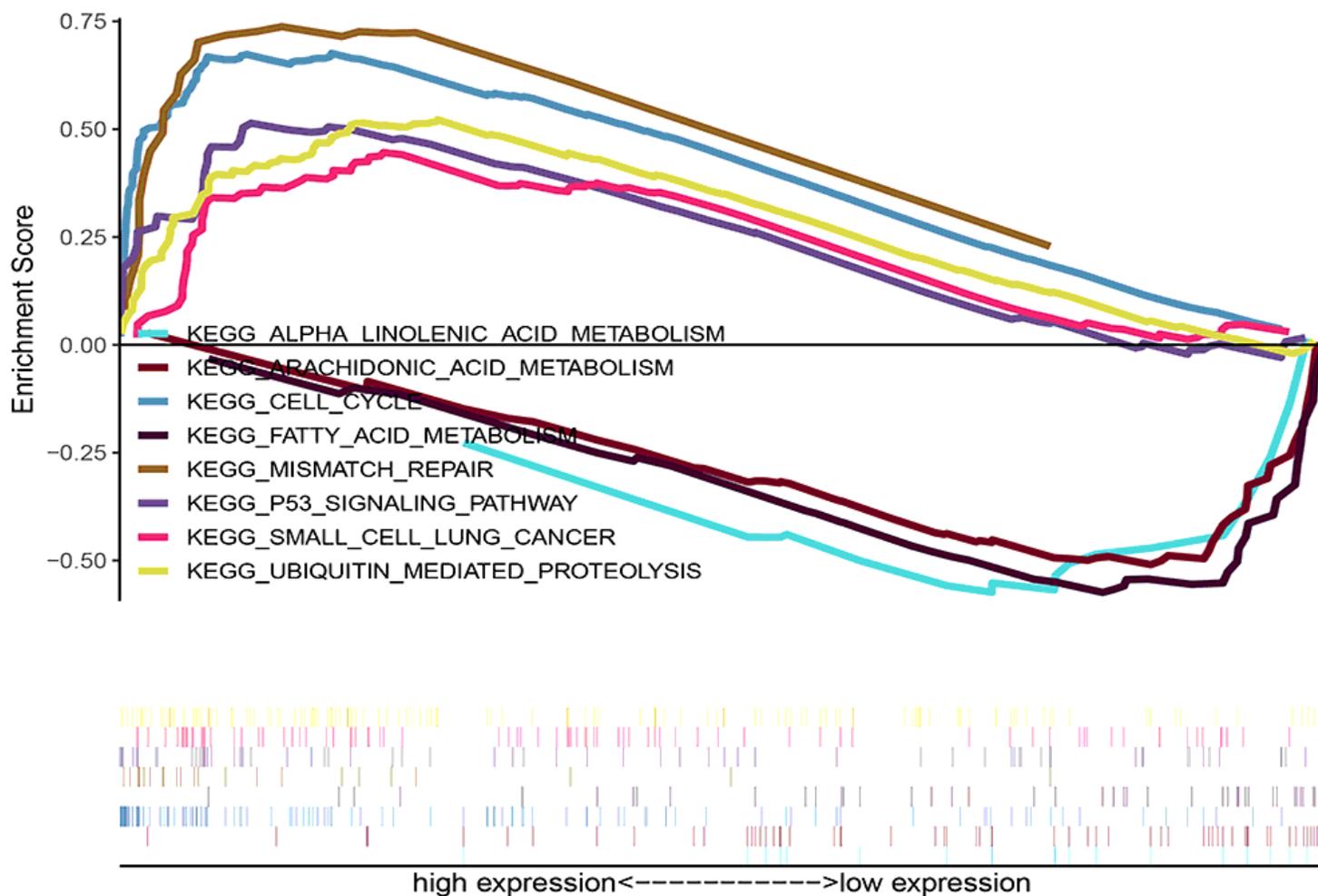


Figure 8

The representative eight KEGG pathways of GSEA analysis enriched in the high-risk group and low-risk group of the ferroptosis-related lncRNAs prognostic signature.

Supplementary Files

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