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Clinical Value of lncRNA LUCAT1 Expression in Liver Cancer and its Potential Pathways

Yan Jiao[1], Yanqing Li[2], Bai Ji[1], Hongqiao Cai[1], Yahui Liu[1]

1) Department of Hepatobiliary and Pancreatic Surgery, The First Hospital of Jilin University, Changchun, Jilin
2) Department of Pathophysiology, College of Basic Medical Sciences, Jilin University, Changchun, Jilin, P.R. China

Address for correspondence:
Yahui Liu
Department of Hepatobiliary and Pancreatic Surgery, The First Hospital of Jilin University, Changchun, Jilin Province, 130000, P.R. China
liuyh_2008@yeah.net

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ABSTRACT

Background & Aims: Emerging studies indicate that long noncoding RNAs (lncRNAs) play a role as prognostic markers in many cancers, including liver cancer. Here, we focused on the lncRNA lung cancer-associated transcript 1 (LUCAT1) for liver cancer prognosis.
Methods: RNA-seq and phenotype data were downloaded from the Cancer Genome Atlas (TCGA). Chi-square tests were used to evaluate the correlations between LUCAT1 expression and clinical features. Survival analysis and Cox regression analysis were used to compare different LUCAT1 expression groups (optimal cutoff value determined by ROC). The log-rank test was used to calculate the p-value of the Kaplan-Meier curves. A ROC curve was used to evaluate the diagnostic value. Gene Set Enrichment Analysis (GSEA) was performed, and competing endogenous RNA (ceRNA) networks were constructed to explore the potential mechanism.
Results: Data mining of the TCGA -Liver Hepatocellular Carcinoma (LIHC) RNA-seq data of 371 patients showed the overexpression of LUCAT1 in cancerous tissue. High LUCAT1 expression was associated with age (p=0.007), histologic grade (p=0.009), T classification (p=0.022), and survival status (p=0.002). High LUCAT1 patients had a poorer overall survival and relapse-free survival than low LUCAT1 patients. Multivariate analysis identified LUCAT1 as an independent risk factor for poor survival. The ROC curve indicated modest diagnostic performance. GSEA revealed the related signaling pathways, and the ceRNA network uncovered the underlying mechanism.
Conclusion: High LUCAT1 expression is an independent prognostic factor for liver cancer.

Key words: lncRNA; LUCAT1 – liver cancer – prognosis – The Cancer Genome Atlas.

Abbreviations: ceRNA: competing endogenous RNA; DEG: differentially expressed genes; DEM: differentially expressed microRNA; GEAS: Gene Set Enrichment Analysis; lncRNA: long noncoding RNA; LUCAT1: lncRNA lung cancer-associated transcript 1; OS: overall survival; RFS: relapse-free survival; TCGA-LIHC: The Cancer Genome Atlas Liver Hepatocellular Carcinoma.

INTRODUCTION

Liver cancer is one of the most frequent malignant cancers with a poor prognosis despite some advances in surgical treatment and neoadjuvant therapy. The lack of useful markers makes it difficult for clinicians to predict clinical outcomes for liver cancer patients. Hence, novel markers need to be explored to identify liver cancer patients with poor prognosis and facilitate precision medicine.

Long noncoding RNAs (lncRNAs), a type of noncoding RNA with a length of more than 200 nucleotides, have recently attracted increasing attention in the field of cancer [1]. Lung cancer-associated transcript 1 (LUCAT1), a novel lncRNA, is involved in smoking-related lung cancer [2]. A previous study demonstrated that LUCAT1 can be induced by cigarette smoke and is related to unfavorable prognosis in non-small cell lung cancer [2].

Recent studies on LUCAT1 have focused on different cancer types, including renal cancer [3], bladder cancer [4], glioma [5], osteosarcoma [6], colorectal cancer, and head and neck cancer [7]. However, the role of LUCAT1 in the prognosis of liver cancer remains unclear.

In the present study, we aimed to conduct data mining of The Cancer Genome Atlas Liver Hepatocellular Carcinoma (TCGA-LIHC) cohort data, evaluate potential clinical correlations, and evaluate the independent prognostic value of LUCAT1 for overall survival and relapse-free survival

in liver cancer. In addition, we preliminarily explored the potential mechanism by conducting GSEA and constructing a competing endogenous RNA (ceRNA) network.

METHODS

TCGA analysis

RNA-seq data and phenotype data, including 321 tumors and 50 matched normal samples, were downloaded from The Cancer Genome Atlas (TCGA) (https://cancergenome.nih.gov/).

GSEA

Gene Set Enrichment Analysis (GSEA) is a computational method that determines whether a priori defined set of genes shows statistically significant, concordant differences between two biological states [8, 9]. It was performed by using GSEA software 3.0 from the Broad Institute.

The expression data were RNA-seq data from TCGA-LIHC. The gene set of "h.all.v6.2.symbols.gmt" was downloaded from the Molecular Signatures Database (http://software.broadinstitute.org/gsea/msigdb/index.jsp). The normalized enrichment score (NES) was obtained with 1,000 permutations.

Conduction of a ceRNA network

Differentially expressed microRNAs and encoding genes were analyzed using the limma package [10]. The predicted miRNA-mRNA interactions were obtained from starBase v2.0 (http://starbase.sysu.edu.cn/starbase2/index.php) by default options [11, 12]. The competing endogenous RNAs (ceRNA) network was constructed by merging differentially expressed genes (DEGs), differentially expressed microRNA (DEMs) and miRNA-mRNA interactions.

Statistical analysis

All statistical analyses and visualizations were carried out using R (version 3.5.1) [13]. The ggplot2 package was used to draw all boxplots and survival curves [14]. The ROC package was used to determine the optimal cutoff value of LUCAT1 expression [15]. The clinical correlation was tested by the Chi-square test using R. The survival package was used to perform survival analysis and Cox analysis [16, 17]. The p value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

The records of 371 patients with liver cancer were retrospectively reviewed from the TCGA database. The clinical records of patients included values for age, sex, histologic grade, stage, TNM classification, residual tumor, vital status, relapse, and LUCAT1 expression. Detailed information is provided in Table I.

LUCAT1 expression in liver cancer

As shown in the boxplot, LUCAT1 was overexpressed in cancerous tissues compared with normal tissues (Fig. 1). Interestingly, LUCAT1 was significantly differentially expressed in the different groups of stage, histologic grade, sex, and age (Fig. 1).

Table I. Baseline characteristics of patients with liver cancer

Characteristics		Number of patients (%)
Age	< 55	117 (31.62)
	≥ 55	253 (68.38)
Gender	Female	121 (32.61)
	Male	250 (67.39)
Histological type	Fibrolamellar Carcinoma	3 (0.81)
	Hepatocellular Carcinoma	361 (97.3)
	Hepatocholangiocarcinoma	7 (1.89)
Histologic grade	G1	55 (14.82)
	G2	177 (47.71)
	G3	122 (32.88)
	G4	12 (3.23)
	NA	5 (1.35)
Stage	I	171 (46.09)
	II	86 (23.18)
	III	85 (22.91)
	IV	5 (1.35)
	NA	24 (6.47)
T classification	T1	181 (48.79)
	T2	94 (25.34)
	T3	80 (21.56)
	T4	13 (3.5)
	Tx	1 (0.27)
	NA	2 (0.54)
N classification	N0	252 (67.92)
	N1	4 (1.08)
	Nx	114 (30.73)
	NA	1 (0.27)
M classification	M0	266 (71.7)
	M1	4 (1.08)
	Mx	101 (27.22)
Radiation therapy	No	338 (91.11)
	Yes	8 (2.16)
	NA	25 (6.74)
Residual tumor	R0	324 (87.33)
	R1	17 (4.58)
	R2	1 (0.27)
	Rx	22 (5.93)
	NA	7 (1.89)
Vital status	Deceased	130 (35.04)
	Living	241 (64.96)
Relapse	No	179 (56.29)
	Yes	139 (43.71)
LUCAT1	High	58 (15.63)
	Low	313 (84.37)

LUCAT1: lncRNA lung cancer-associated transcript 1; NA: not available.

The clinical correlation of LUCAT1

To explore the clinical correlation of LUCAT1, we used the Chi-square test and concluded that LUCAT1 expression

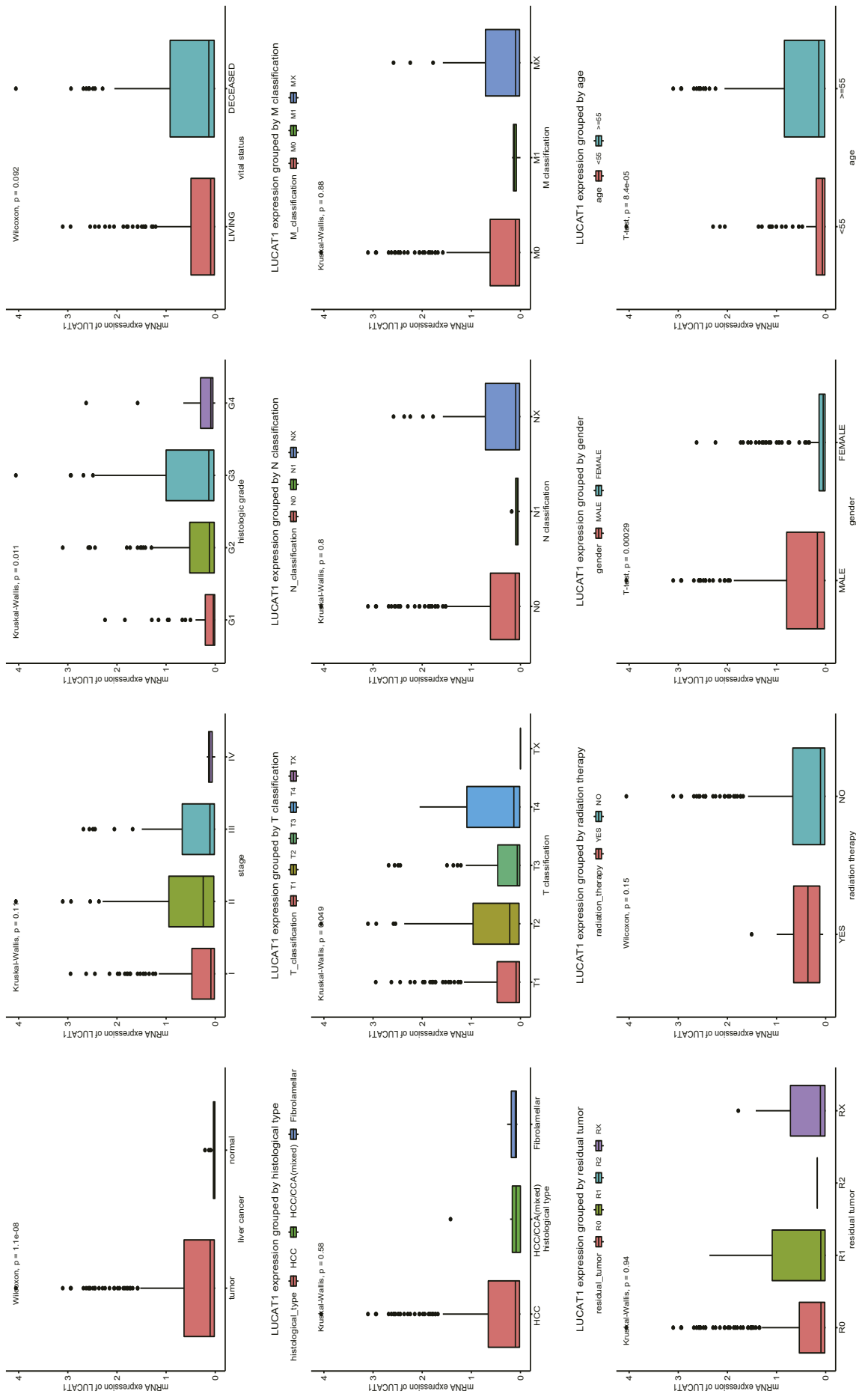

Fig. 1. LUCAT1 expression in liver cancer tissue vs. normal tissue, also grouped by stage, histologic grade, vital status, histological type, TNM classification, residual tumor, radiation therapy, sex, and age.

was correlated with age, histologic grade, T classification, and vital status (Table II).

Impact of LUCAT1 expression on overall survival and relapse-free survival in patients

To explore the impact of LUCAT1 expression on the prognosis of patients, we performed survival analysis and found that patients with high LUCAT1 expression had a poor overall survival and relapse-free survival (Figs. 2 and 3).

Subgroup analysis indicated that patients with high LUCAT1 expression in the stage G3/G4, stage I/II and male groups had shorter overall survival (Fig. 2). In addition, high LUCAT1 expression showed a poor relapse-free survival in all groups except in the female group (Fig. 3).

High LUCAT1 expression is an independent prognostic factor

We used the univariate Cox analysis to select the related variables for multivariate Cox analysis. Following multivariate Cox analysis, high LUCAT1 expression was an independent prognostic factor for overall survival (hazard ratio: 2.35, confidence interval (CI): 1.56-3.54, p<0.001) and relapse-free survival (hazard ratio: 2.04, CI: 1.32-3.16, p=0.001) in liver cancer (Tables III and IV).

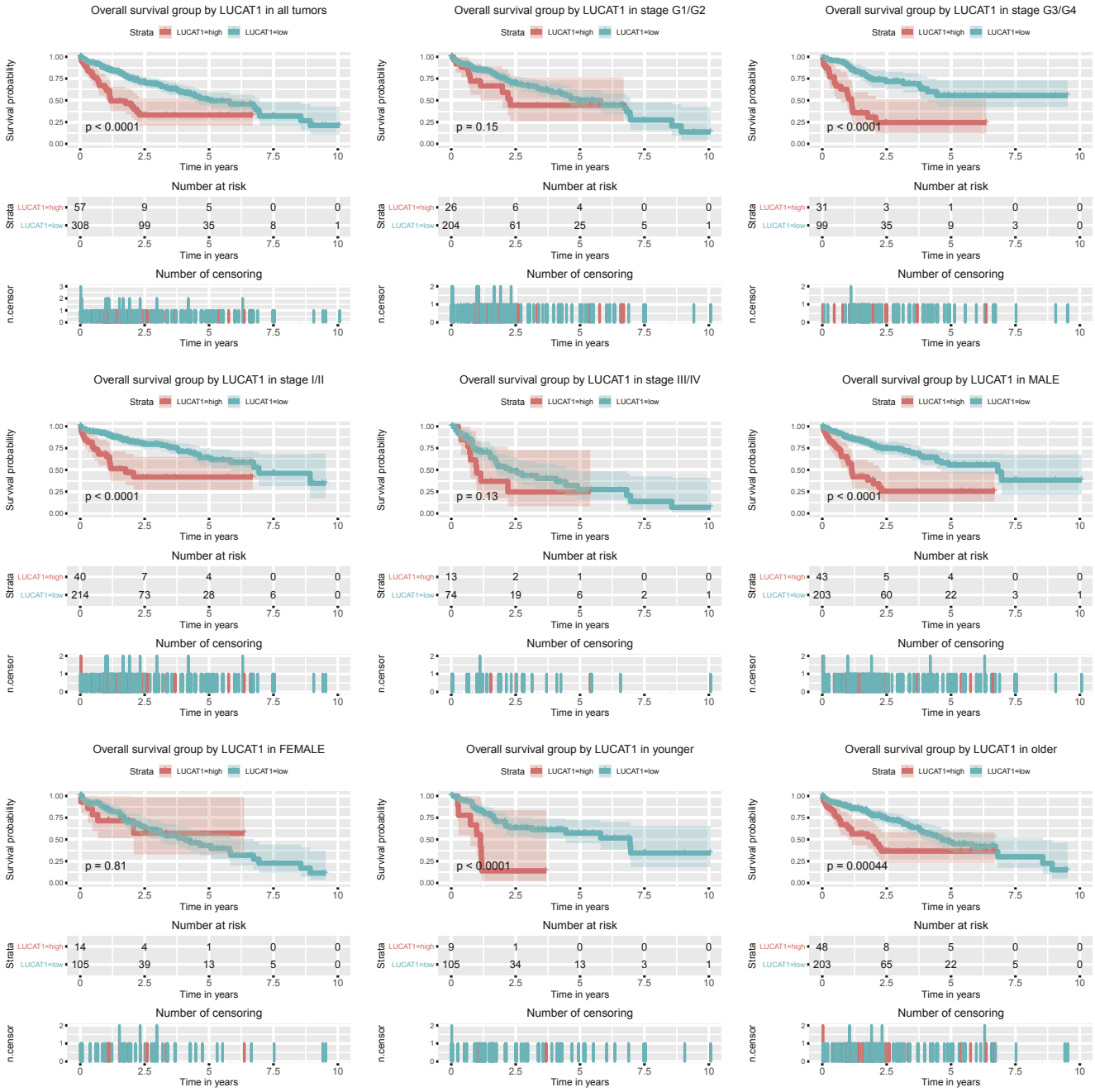

Fig. 2. High LUCAT1 expression is correlated with a shorter overall survival (OS) in patients with liver cancer, and the OS of the G1/G2, G3/G4, stage I/II, stage III/IV, male, female, younger, and older subgroups.

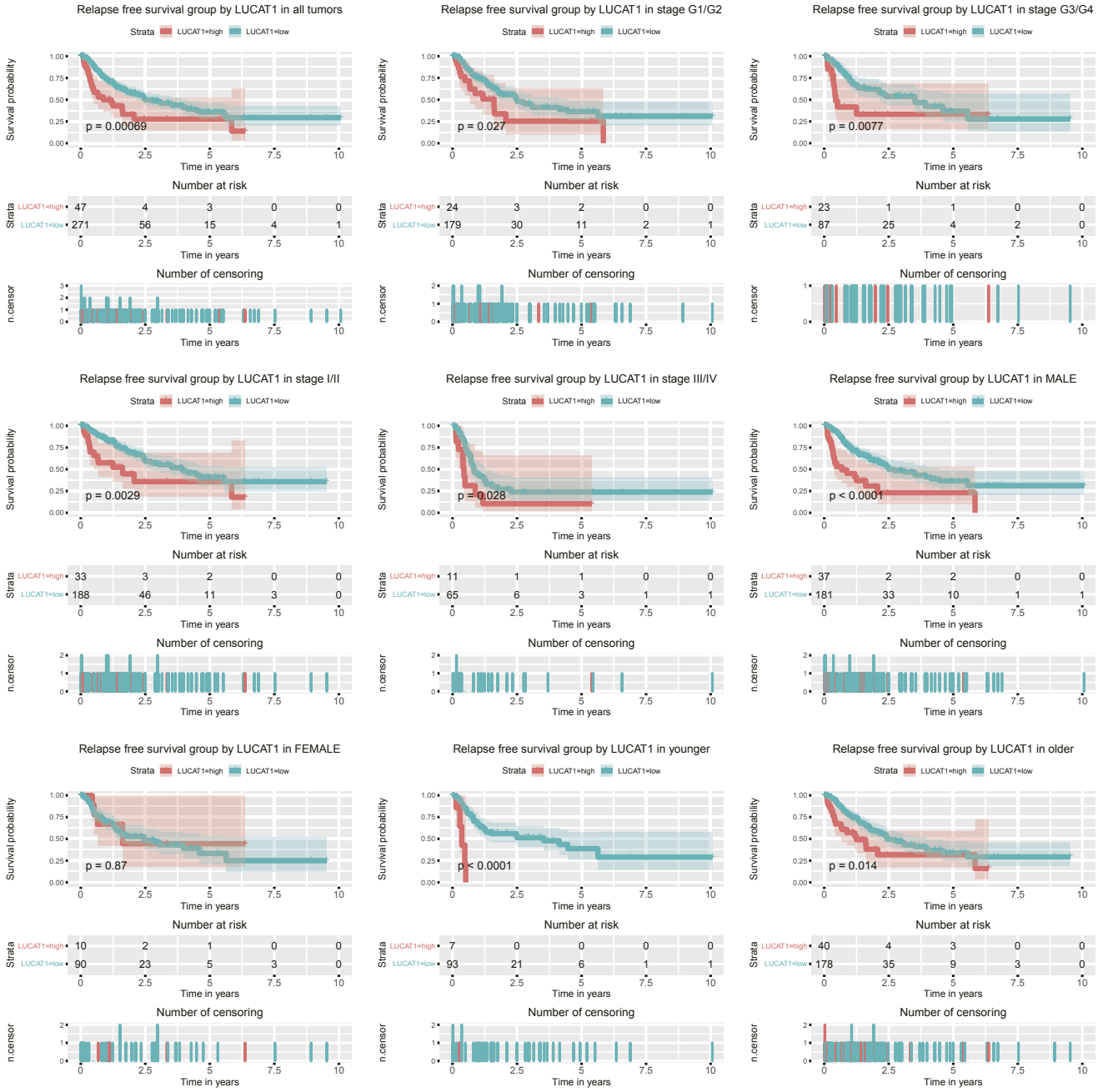

Fig. 3. High LUCAT1 expression is correlated with a shorter relapse-free survival (RFS) in patients with liver cancer, and the RFS of the G1/G2, G3/G4, stage I/II, stage III/IV, male, female, younger, and older subgroups.

Diagnostic value of LUCAT

We performed receiver operating characteristic (ROC) analysis to determine the diagnostic value of LUCAT1 expression (Supplementary Fig. 1). LUCAT1 expression had potential diagnostic value overall (AUC = 0.749) and was also able to distinguish noncancerous tissue from stage I cancer (AUC = 0.725), stage II cancer (AUC = 0.799), stage III cancer (AUC = 0.745), and stage IV cancer (AUC = 0.784).

LUCAT1-related signaling pathways and ceRNA network

To identify the LUCAT1-related signaling pathways activated in liver cancer, we conducted GSEA between low and high LUCAT1 expression data sets. Significant differences (FDR<0.25, NOM p-value<0.05) were found in the enrichment of the MSigDB collection (h.all.v6.2.symbols.gmt), and the details are shown in Supplementary Fig. 2 and Supplementary Table I. Myc targets, reactive oxygen species pathway, DNA repair, mTORC1 signaling, and G2M checkpoint are differentially enriched in the LUCAT1 high-expression phenotype.

To explore the underlying mechanism of LUCAT1, we selected 17 downregulated DEMs and 465 upregulated DEGs between the low and high LUCAT1 expression groups. Next, we merged the DEMs, DEGs, and predicted miRNA-mRNA targets and constructed a LUCAT1-related ceRNA network (Supplementary Fig. 3).

Table II. The correlation between LUCAT1 expression and clinical parameters

Clinical characteristics	Variable	No. of patients	LUCAT1 expression		χ^2	p value
			High (%)	Low %		
Age	< 55	117	9 (15.52)	108 (34.62)	7.3905	0.007
	≥ 55	253	49 (84.48)	204 (65.38)		
Gender	Female	121	14 (24.14)	107 (34.19)	1.8137	0.178
	Male	250	44 (75.86)	206 (65.81)		
Histologic type	Fibrolamellar	3	0 (0)	3 (0.96)	0.5722	1.000
	Hepatocellular	361	57 (98.28)	304 (97.12)		
	Hepatocholangiocarcinoma	7	1 (1.72)	6 (1.92)		
Histologic grade	G1	55	4 (6.9)	51 (16.56)	11.5817	0.009
	G2	177	22 (37.93)	155 (50.32)		
	G3	122	30 (51.72)	92 (29.87)		
	G4	12	2(3.45)	10 (3.25)		
Stage	I	171	20 (37.04)	151 (51.54)	8.0049	0.063
	II	86	21 (38.89)	65 (22.18)		
	III	85	13 (24.07)	72 (24.57)		
	IV	5	0 (0)	5 (1.71)		
T classification	T1	181	21 (36.21)	160 (51.45)	10.7821	0.022
	T2	94	23 (39.66)	71 (22.83)		
	T3	80	10 (17.24)	70 (22.51)		
	T4	13	4 (6.9)	9 (2.89)		
	Tx	1	0 (0)	1 (0.32)		
N classification	N0	252	40 (68.97)	212 (67.95)	0.7521	1.000
	N1	4	0 (0)	4 (1.28)		
	Nx	114	18 (31.03)	96 (30.77)		
M classification	M0	266	42 (72.41)	224 (71.57)	0.7494	1.000
	M1	4	0 (0)	4 (1.28)		
	Mx	101	16 (27.59)	85 (27.16)		
Radiation therapy	No	338	54 (98.18)	284 (97.59)	0	1.000
	Yes	8	1 (1.82)	7 (2.41)		
Residual tumor	R0	324	49 (87.5)	275 (89.29)	3.4377	0.334
	R1	17	5 (8.93)	12 (3.9)		
	R2	1	0 (0)	1 (0.32)		
	Rx	22	2 (3.57)	20 (6.49)		
Vital status	Deceased	130	31 (53.45)	99 (31.63)	9.298	0.002
	Living	241	27 (46.55)	214 (68.37)		

For abbreviations see Table I.

DISCUSSION

Liver cancer is one of the most frequent malignancies with a poor prognosis. Most liver cancer patients are diagnosed at an advanced stage with no effective treatment options. Therefore, exploring novel biomarkers and understanding the underlying mechanisms may lead to promising improvements in the outcomes of liver cancer.

Recently, increasing research has revealed the critical roles of lncRNAs in physiological processes and their dysregulation in human diseases, especially cancer. Accumulating evidence illustrates that aberrant lncRNA expression is involved in various cancers. The use of lncRNAs, such as ATB, PVT1, MALAT1, HOTAIR, and UCA1, as novel prognostic biomarkers has gained more attention.

Our team has focused on novel biomarkers in many types of cancer [18-30]. In this study, we focused on LUCAT1, a novel lncRNA, and found that LUCAT1 was significantly up-regulated in liver cancer. Additionally, LUCAT1 expression correlated with age, histologic grade, T classification, and survival status. Moreover, patients whose cancerous tissues showed high LUCAT1 expression had shorter overall survival (OS) and relapse-free survival (RFS). Subgroup analysis revealed the specific groups in which LUCAT1 had the most prognostic value. Importantly, the Cox multivariate model showed that LUCAT1 expression plays a vital role in OS/

Table III. Univariate and multivariate cox analysis of overall survival.

	Univariate analysis			Multivariate analysis		
Parameters	Hazard Ratio	95% CI (lower~upper)	p-value	Hazard Ratio	95% CI (lower-upper)	p-value
Age	1.02	0.7-1.48	0.926			
Gender	0.82	0.57-1.16	0.263			
Histologic type	0.98	0.27-3.63	0.982			
Histologic grade	1.05	0.85-1.31	0.651			
Stage	1.38	1.15-1.65	0.001	0.88	0.7-1.1	0.265
T classification	1.65	1.38-1.98	<0.001	1.78	1.4-2.25	<0.001
N classification	0.71	0.5-1.03	0.071			
M classification	0.70	0.48-1.02	0.061			
Radiation therapy	0.52	0.26-1.03	0.061			
Residual tumor	1.42	1.12-1.79	0.004	1.44	1.12-1.85	0.004
LUCAT1	2.58	1.71-3.88	<0.001	2.35	1.56-3.54	<0.001

Table IV. Univariable and multivariable cox analysis of relapse free survival

	Univariate analysis			Multivariate analysis		
Parameters	Hazard Ratio	95% CI (lower~upper)	p-value	Hazard Ratio	95% CI (lower-upper)	p-value
Age	0.89	0.63-1.27	0.521			
Gender	0.98	0.69-1.4	0.919			
Histologic type	2.03	0.66-6.29	0.218			
Histologic grade	0.98	0.8-1.21	0.873			
Stage	1.66	1.38-1.99	<0.001	1.14	0.88-1.47	0.334
T classification	1.78	1.49-2.12	<0.001	1.64	1.25-2.14	<0.001
N classification	0.98	0.68-1.42	0.926			
M classification	1.19	0.8-1.78	0.394			
Radiation therapy	0.75	0.26-2.17	0.592			
Residual tumor	1.27	1.01-1.61	0.042	1.36	1.07-1.73	0.012
LUCAT1	2.09	1.35-3.22	0.001	2.04	1.32-3.16	0.001

RFS. Moreover, ROC curves showed the diagnostic value of LUCAT1. Therefore, LUCAT1 may be a potential clinical biomarker for liver cancer.

The lncRNA LUCAT1 has been reported to be overexpressed in lung cancer [2], ovarian cancer [31], clear cell renal cell carcinoma [3], colorectal cancer [32], HPV-negative head and neck squamous cell carcinoma [7], osteosarcoma [6], esophageal squamous cell carcinoma [33], and glioma [5]. Consistent with these findings in cancer research, we found LUCAT1 overexpression in liver cancer.

Many studies have reported that LUCAT1 has an effect on the proliferation [2], migration and invasion of tumor cells [5], being involved in cell cycle [34] of many cancer cells. LUCAT1 contributes to the malignant biological behavior of cancer. Accordingly, our study found that LUCAT1 expression was associated with histologic grade, T classification, and vital status in liver cancer.

Importantly, LUCAT1 promotes cell proliferation by regulating p21 and p57 expression and predicts unfavorable survival in non-small cell lung cancer [2]. In addition, the Akt/GSK-3β signaling pathway is also involved in the proliferation and invasion regulated by LUCAT1 [34]. Moreover, the function of LUCAT1 involves DNA methylation. LUCAT1 activates DNMT1, a DNA methylation protein, to repress the expression of tumor suppressor genes, resulting in the development of cancer [33, 35]. Our study found that LUCAT1 overexpression was correlated with shorter OS and RFS in liver cancer. GSEA revealed that the potential mechanism might be involved in myc targets, reactive oxygen species pathways, DNA repair, mTORC1 signaling, and the G2M checkpoint.

The ceRNA theory has recently attracted much attention in the field of regulatory mechanisms of lncRNAs. The interplay between lncRNAs and miRNAs plays a crucial role in cancer biology. However, few studies have reported the LUCAT1-related ceRNA regulatory mechanism. For example, Han et al. [6] found that LUCAT1 sponges microRNA-200 and unregulated ABCB1 to modulate methotrexate resistance in osteosarcoma [6]. Yu et al. found that LUCAT1 acted as a ceRNA of HOXA13 to promote the malignancy of ovarian cancer by sponging microRNA-612 [31]. Additionally, miR-495-3p and miR-375 have been found in the regulatory mechanism of LUCAT1 [5, 36]. In this study, we constructed

the LUCAT1-related ceRNA network, parts of which have been indicated by some published research while other parts still need to be verified in the future.

To the best of our knowledge, this is the first study to identify a correlation between lncRNA LUCAT1 expression and clinical features in liver cancer based on data mining. Of note, LUCAT1 may serve as an independent prognostic factor for poor OS/RFS in liver cancer.

However, we did not utilize the LUCAT1 expression and clinical data to construct a predictive model because it is not enough to use some clinical parameters and a single gene to predict patients' prognosis. The related molecular mechanisms and multiomics of LUCAT1 still need to be elucidated in future studies.

CONCLUSION

Our study revealed the critical role of LUCAT1 overexpression in liver cancer, indicating that LUCAT1 expression is an independent predictor of poor prognosis and could be a useful biomarker for liver cancer patients.

Conflicts of interest: The authors declare that no competing interests exist.

Authors' contributions: Y.J. and Y.L. analyzed the data, designed the study and drafted the manuscript. H.C. Y.L and B.J. interpreted the results and reviewed the manuscript. All authors critically revised the manuscript and approved the final version.

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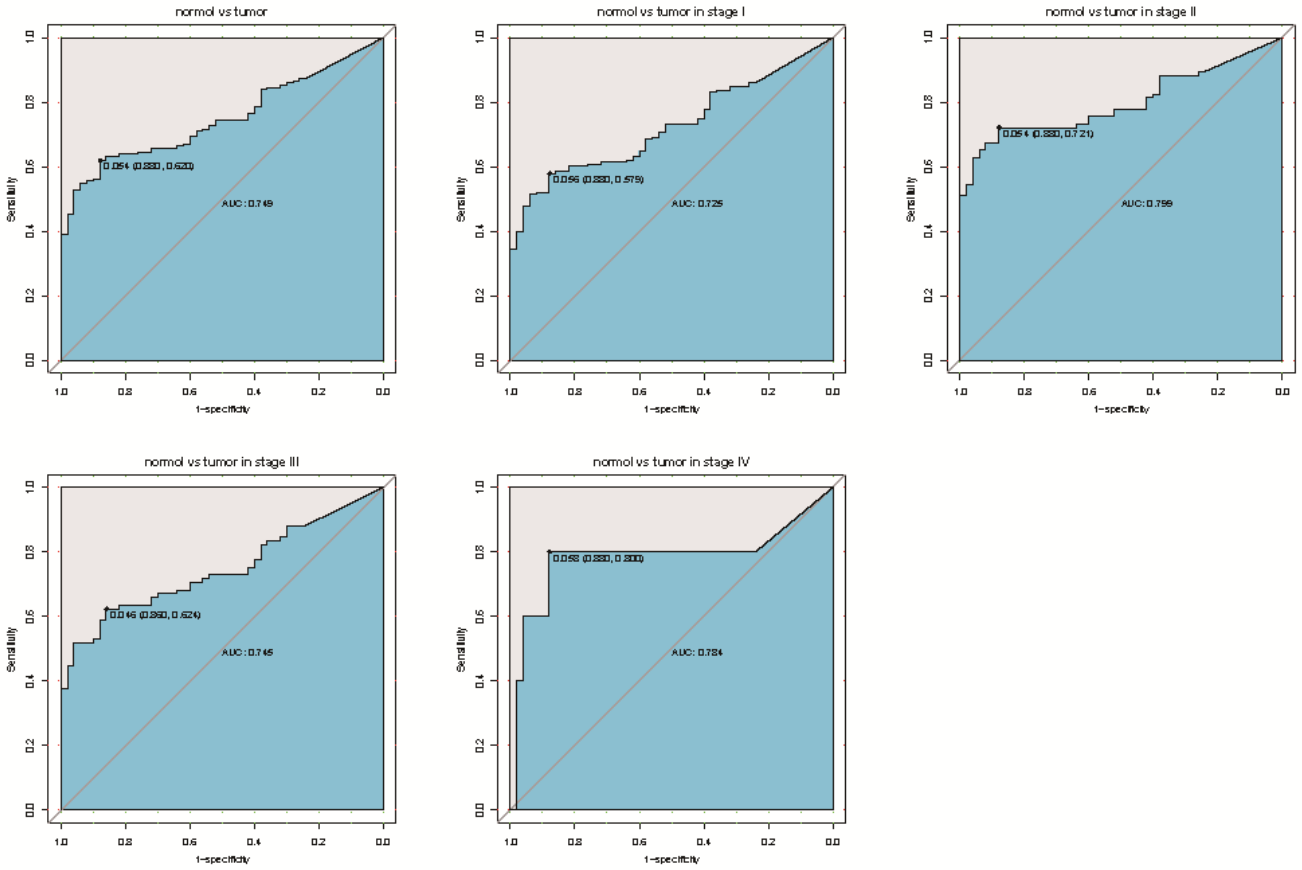
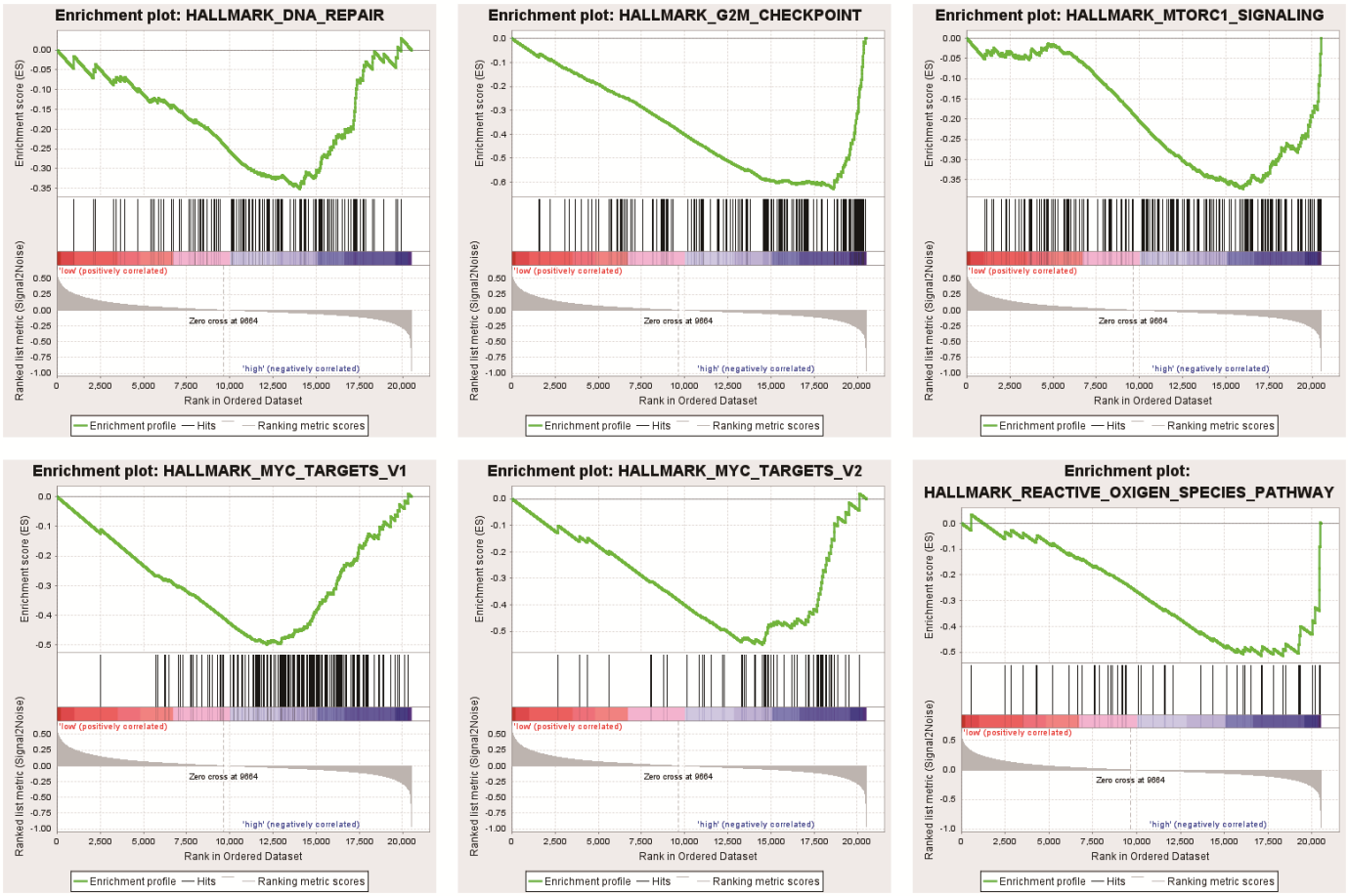
Supplementary Table I. Gene sets enriched in phenotype high

Gene set name	NES	NOM p-val	FDR q-val
HALLMARK_MYC_TARGETS_V2	-1.9075	0.02549	0.06957
HALLMARK_MYC_TARGETS_V1	-1.8553	0.02519	0.04965
HALLMARK_REACTIVE_OXIGEN_SPECIES_PATHWAY	-1.7538	0.0332	0.06838
HALLMARK_DNA_REPAIR	-1.6681	0.03953	0.09399
HALLMARK_MTORC1_SIGNALING	-1.6427	0.04921	0.09195
HALLMARK_G2M_CHECKPOINT	-1.6052	0.04717	0.0981

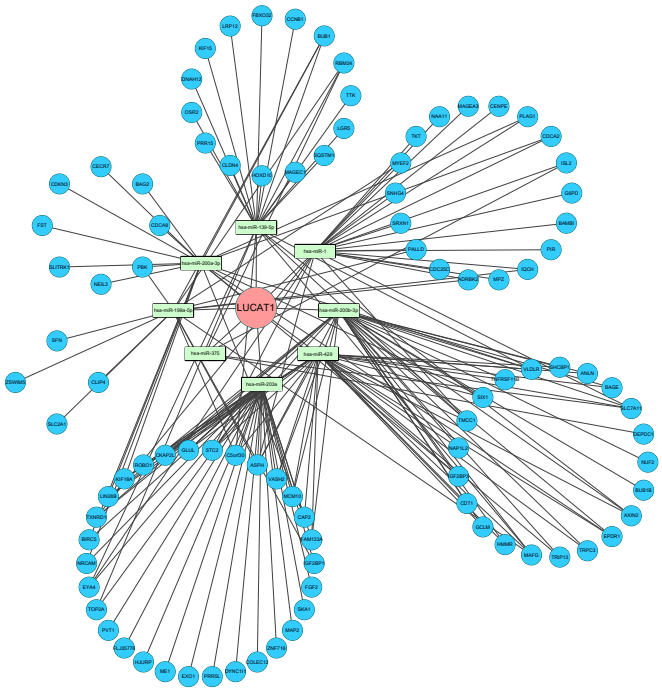
NES: normalized enrichment score; NOM: nominal; FDR: false discovery rate. Gene sets with NOM p-val <0.05 and FDR q-val <0.25 are considered as significant.



Supplementary Fig. 1. ROC analysis of the performance of LUCAT1 expression in the identification of cancerous vs. normal tissues in all patients and subgroup analysis of patients with different stages of liver cancer.



Supplementary Fig. 2. Enrichment plots from GSEA. Myc targets, the reactive oxygen species pathway, DNA repair, mTORC1 signaling, and the G2M checkpoint are differentially enriched in LUCAT1-related liver cancer.



Supplementary Fig. 3. LUCAT1-related ceRNA network. The red circle represents the lncRNA LUCAT1, the green rectangles represent the microRNAs, and the blue circles represent the mRNAs