Genes & Diseases (2022) 9, 151–164

Available online at www.sciencedirect.com

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FULL LENGTH ARTICLE

# LPCAT1 functions as a novel prognostic molecular marker in hepatocellular carcinoma

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Received 3 May 2020; received in revised form 11 July 2020; accepted 14 July 2020
Available online 21 July 2020

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Peer review under responsibility of Chongqing Medical University.

https://doi.org/10.1016/j.gendis.2020.07.007

**KEYWORDS**
CDK1;
HCC;
LPCAT1;
Overall survival;
Prognostic marker

**Abstract** This study aimed to investigate the relationships between LPCAT1 expression and clinicopathologic parameters of hepatocellular carcinoma (HCC), further, to explore the effect of LPCAT1 on overall survival (OS) in patients with HCC, and its possible mechanism. Bioinformatics analysis using high throughput RNA-sequencing data from TCGA was utilized to explore the differential expression of LPCAT1 between normal and tumor tissues, and the associations between LPCAT1 expression and clinicopathological parameters. Survival analyses and subgroup survival analyses were utilized to elucidate the effect of LPCAT1 on OS in patients with HCC. Univariate analysis and multivariate analysis were used to investigate the prognostic factors. Potential LPCAT1 related tumor genes were identified by the methodology of differentially expressed genes (DEGs) screening. GO term enrichment analysis, KEGG pathway analysis and the PPI network were used to explore the potential mechanism. LPCAT1 was significantly overexpressed in HCC tumor tissues compared with normal tissues. The LPCAT1 expression was related to tumor grade, ECOG score, AFP and TNM stage, with *P* values of 0.000, 0.000, 0.007 and 0.000, respectively. Multivariate analysis demonstrated that LPCAT1 expression was independently associated with OS, with an HR of 1.04 (CI: 1.01−1.06, $P = 0.003$). The KEGG pathway enrichment analyses showed that overlapped DEGs mainly participate in the cell cycle. Finally, we identified a hub gene, CDK1, which has been reported to act on the cell cycle, consistent with the result of KEGG enrichment analysis. Collectively, these data confirmed LPCAT1 was upregulated in HCC, and was an independent predictor of the prognosis.


## Background

Hepatocellular carcinoma (HCC) is the sixth most common malignant tumor and the third leading cause of cancer death worldwide, according to 2018 global cancer statistics.[1] The 5-year survival rate of patients with HCC is lower than 20%−40%, making it a malignant tumor with a poor prognosis.[2,3] Improvement of the prognosis was expected in HCC when immunotherapies revolutionized cancer therapy. However, the anti-PD-1 monoclonal antibody (mAb) nivolumab did not lead to better overall survival (OS) than sorafenib in first-line treatment of unresectable HCC.[4] The median OS of patients given another anti-PD-1 mAb, Pembrolizumab monotherapy, in the treatment of advanced HCC was only 13 months.[5] At present, the prognosis of HCC has not improved significantly. The evaluation of HCC prognosis in clinical practice still depends on TNM staging or BCLC staging.[6,7] However, patients with same stage frequently show significantly different prognoses. More accurate methods of prognosis evaluation are required to develop precise individual treatment plans for patients with HCC. In recent years, molecular marker detection, a convenient and noninvasive method of examination, has attracted wide attention. A large number of molecular markers such as AFP, Ki-67, AFP-L3, PIVKA-II, β-catenin, etc. have been shown to be associated with the diagnosis and prognosis of HCC.[8−17] Unfortunately, most of these molecular markers lack sensitivity and specificity. Therefore, it is necessary to explore more effective prognostic molecular markers for HCC.

Lysophosphatidylcholine acyltransferase 1 (LPCAT1) is an enzyme involved in phosphatidylcholine metabolism.[18−20] It is critical for the regulation of phosphatidylcholine composition, especially for the accumulation of polyunsaturated fatty acids.[21] Its function *in vivo* is still controversial. In recent years, the expression of LPCAT1 has been found to be elevated in prostate cancer, breast cancer, colorectal cancer and HCC, and it is positively correlated with tumor stage and grade. Overexpression of LPCAT1 in tumor tissues is positively correlated with early recurrence of prostate cancer and breast cancer. LPCAT1 promotes proliferation, migration and invasion of colorectal cancer and HCC cells.[22−26] However, the relationships between LPCAT1 expression and clinicopathological parameters, and especially the effect of LPCAT1 on OS among HCC patients, and its potential mechanism has not been reported. We therefore utilized bioinformatics analyses using high throughput RNA-sequencing data from TCGA to demonstrate that LPCAT1 is a novel and effective prognostic marker for hepatocellular carcinoma.

## Materials and methods

### Acquisition of LPCAT1 mRNA expression data and clinical information

The RNA-Seq gene expression data (424 tissues including 50 normal tissues and 374 tumor tissues, workflow type: HTSeqFPKM) and corresponding clinical information (377 cases) of HCC projects were downloaded from TCGA official website (https://portal.gdc.cancer.gov/). The clinical information (377 cases) was obtained and further

**Table 1** The clinical characteristics of 377 HCC patients.

| Clinical characteristic | Total ($n$ = 377) | % |
|---|---|---|
| Age at diagnosis (year) | 61 (16–90) | |
| Gender | | |
| Female | 122 | 32.36 |
| Male | 255 | 67.64 |
| Race | | |
| Asian | 161 | 42.71 |
| White | 187 | 49.60 |
| American Indian or Alaska native | 2 | 0.53 |
| Black or African American | 17 | 4.51 |
| Unknown | 10 | 2.65 |
| Grade | | |
| G1 | 55 | 14.59 |
| G2 | 180 | 47.75 |
| G3 | 124 | 32.89 |
| G4 | 13 | 3.45 |
| Unknown | 5 | 1.33 |
| Stage | | |
| I | 175 | 46.42 |
| II | 87 | 23.08 |
| III | 86 | 22.81 |
| IV | 5 | 1.3 |
| Unknown | 24 | 6.37 |
| T-stage | | |
| T1 | 185 | 49.07 |
| T2 | 95 | 25.20 |
| T3 | 81 | 21.49 |
| T4 | 13 | 3.45 |
| Unknown | 3 | 0.80 |
| N-status | | |
| N0 | 257 | 68.17 |
| N1 | 4 | 1.06 |
| Unknown | 116 | 30.77 |
| M-status | | |
| M0 | 272 | 72.15 |
| M1 | 4 | 1.06 |
| Mx | 101 | 26.80 |
| Child-Pugh Classification | | |
| A | 223 | 59.15 |
| B | 21 | 5.57 |
| C | 1 | 0.27 |
| Unknown | 132 | 35.01 |
| ECOG score | | |
| 0 | 166 | 44.03 |
| 1 | 86 | 22.81 |
| 2 | 26 | 6.90 |
| 3 | 12 | 3.18 |
| 4 | 3 | 0.80 |
| Unknown | 84 | 22.28 |
| AFP | | |
| <25 ng/ml | 166 | 44.03 |
| 25–400 ng/ml | 53 | 14.06 |
| >400 ng/ml | 65 | 17.24 |
| Unknown | 93 | 24.67 |
| Ishak fibrosis score | | |
| 0 | 76 | 20.16 |
| 1–2 | 31 | 8.22 |
| 3–4 | 30 | 7.96 |
| 5 | 9 | 2.39 |

(*continued on next page*)

**Table 1** (*continued*)

| Clinical characteristic | Total ($n$ = 377) | % |
|---|---|---|
| 6 | 72 | 19.10 |
| Unknown | 159 | 42.18 |
| Alcohol consumption | | |
| Yes | 118 | 31.29 |
| No | 240 | 63.66 |
| Unknown | 19 | 5.04 |
| Hepatitis status | | |
| Yes | 156 | 41.38 |
| No | 202 | 53.58 |
| Unknown | 19 | 5.04 |
| Survival status | | |
| Living | 244 | 64.72 |
| Dead | 126 | 33.42 |
| Unknown | 7 | 1.86 |

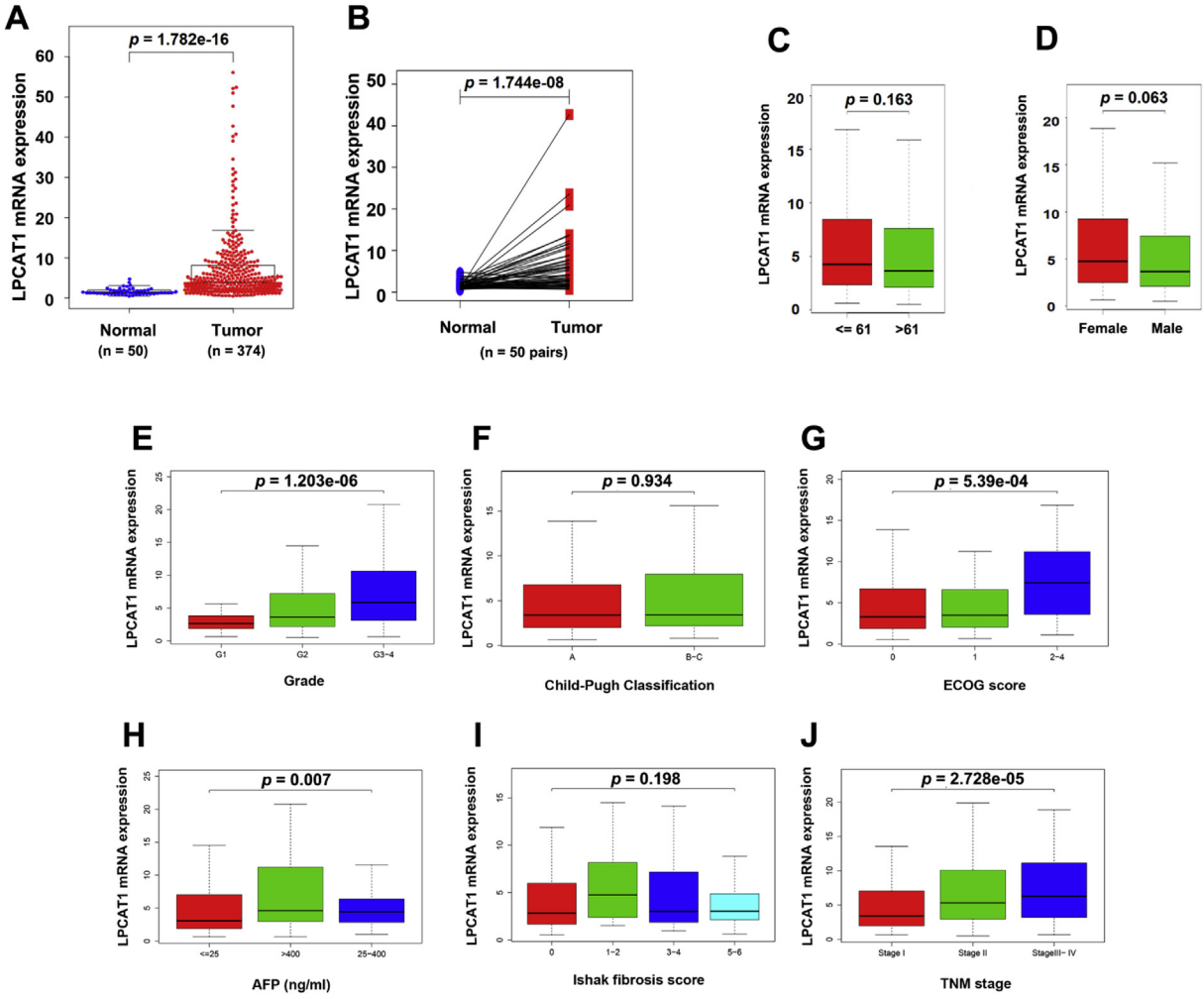


**Figure 1** Correlation between LPCAT1 expression and clinical variables. **(A)** Differential LPCAT1 expression between tumor tissues and normal tissues (normal tissues $n$ = 50; tumor tissues $n$ = 374). **(B)** Differential LPCAT1 expression between tumor tissues and normal tissues in paired samples from the same patient ($n$ = 50 pairs, 50 patients). **(C–J)** Correlation between LPCAT1 expression and age, gender, grade, Child-Pugh Classification, ECOG score, AFP, Ishak fibrosis score and TNM stage, respectively.

processed (Table 1), and 370 tumor tissues with LPCAT1 expression were obtained after removing the missing data.

### Survival analysis

LPCAT1 mRNA expression and different population survival curves in HCC patients were plotted with Kaplan–Meier method using survival packages in R program. Log-rank tests were used to analyze the differences among survival curves. The cut-off value of LPCAT1 expression was set as its median value.

### Identification of potential LPCAT1 related tumor genes

370 HCC patients were divided into high or low expression groups based on median value of LPCAT1 expression, and differentially expressed genes (DEGs) between the two groups were analyzed. In the same way, DEGs between normal tissues and tumor tissues were analyzed. Wilcoxon tests was applied for identification of DEGs.[27] Genes with | log2 fold change (FC) | $\geq$ 1 and adjusted *P* value ($P < 0.05$) were considered statistically significant for the DEGs. The potential LPCAT1 related tumor genes were identified by taking intersection of the two batches of DEGs by using "Venn Diagram" package.[28] The expression of intersection genes in these two groups were presented using heatmap obtained from R program.

### GO function and KEGG signal pathway enrichment analysis

The potential LPCAT1 related tumor genes obtained above were subjected to GO function and KEGG signal pathway enrichment analysis. GO analysis includes three parts: cellular component (CC), molecular function (MF) and biological process (BP). Bioconductor packages were used to perform GO and KEGG pathway analysis on the overlapped DEGs. Adjusted $P < 0.05$ was considered to be statistically significant.[29,30]

### PPI network and hub genes

The Search Tool for the Retrieval of Interacting Genes database (STRING) (https://string-db.org/) was a good visual platform to evaluate protein/gene function.[31] We administrated PPI Network through imputing LPCAT1 related potential candidate tumor genes to this platform. 0.9 was set as the cutoff value of interaction score. Then, Cytoscape software (3.7.1) was used for construction of PPI network.[32] Hub genes were discovered by the number of adjacent nodes in PPI network using R packages.

### Statistical analysis

Differential expression of LPCAT1 was analyzed with Wilcoxon tests. The associations between LPCAT1 expression and clinicopathologic parameters were analyzed with Wilcoxon and Kruskal tests. Survival curves were plotted with Kaplan–Meier method. Log-rank-tests were used to analyze the differences in survival curves. Univariate and multivariate Cox analyses were used to evaluate the effects of different clinicopathologic parameters on OS. All statistical analyses were performed in R (v.3.6.1). The cut-off value of LPCAT1 expression was determined by its median value.

## Results

### Clinical characteristics of HCC patients

HCC clinical sample information was obtained from TCGA official website, mainly including sex, age, race, grade, TNM stage, Child-Pugh Classification, ECOG score, alpha fetoprotein (AFP), Ishak fibrosis score, alcohol consumption, hepatitis status and survival status. These 377 HCC patients included 255 males and 122 females. The median age was 61.0 $\pm$ 11.5 years old. The detail of each clinical parameter was shown in Table 1.

### Differential mRNA expression of LPCAT1 between tumor tissues and normal tissues in HCC patients

As shown in Fig. 1A, gene expression datum of 424 tissues, including 50 (50/424, 11.79%) normal samples and 374 (374/424, 88.20%) tumor samples, were downloaded from TCGA official website on Feb 1, 2020. The range of LPCAT1 mRNA expression in 50 normal samples was from 0.52 to 4.76, and the median was 1.39, whereas in 377 tumors, LPCAT1 mRNA expression range was from 0.52 to 56.04, and the median was 3.93. To compare expression differences of LPCAT1 mRNA between tumor and normal tissue samples, we performed differential expression analysis using Wilcoxon tests. LPCAT1 mRNA expression in tumor samples was found significantly higher than that in normal samples in both unpaired and paired tissues ($P = 1.782e\text{-}16$, $P = 1.744e\text{-}08$, respectively) (Fig. 1A, B).

### Correlation between LPCAT1 mRNA expression and clinical characteristics in HCC patients

As shown in Fig. 1C–J, LPCAT1 mRNA expression was related to tumor Grade, ECOG score, AFP and TNM stage with *P* values being 0.000, 0.000, 0.007, 0.000, respectively. Age, Gender, Child-Pugh Classification and Ishak fibrosis score had no correlation with LPCAT1 mRNA expression ($P = 0.163$, $P = 0.063$, $P = 0.934$).

### Correlation between LPCAT1 mRNA expression and OS in HCC

As shown in Fig. 2A–D, Kaplan–Meier survival analysis indicated that HCC patients with high LPCAT1 mRNA expression had poorer OS than those with low LPCAT1 expression in all patients (HR 2.6, $P < 0.001$). The same survival trends were observed in 1-year, 3-year and 5-year survival probability (HR 3.52, $P < 0.001$; HR 2.96, $P < 0.001$ and HR 2.9, $P < 0.001$, respectively, Fig. 2B–D). Meanwhile, we performed a subgroup analysis in different

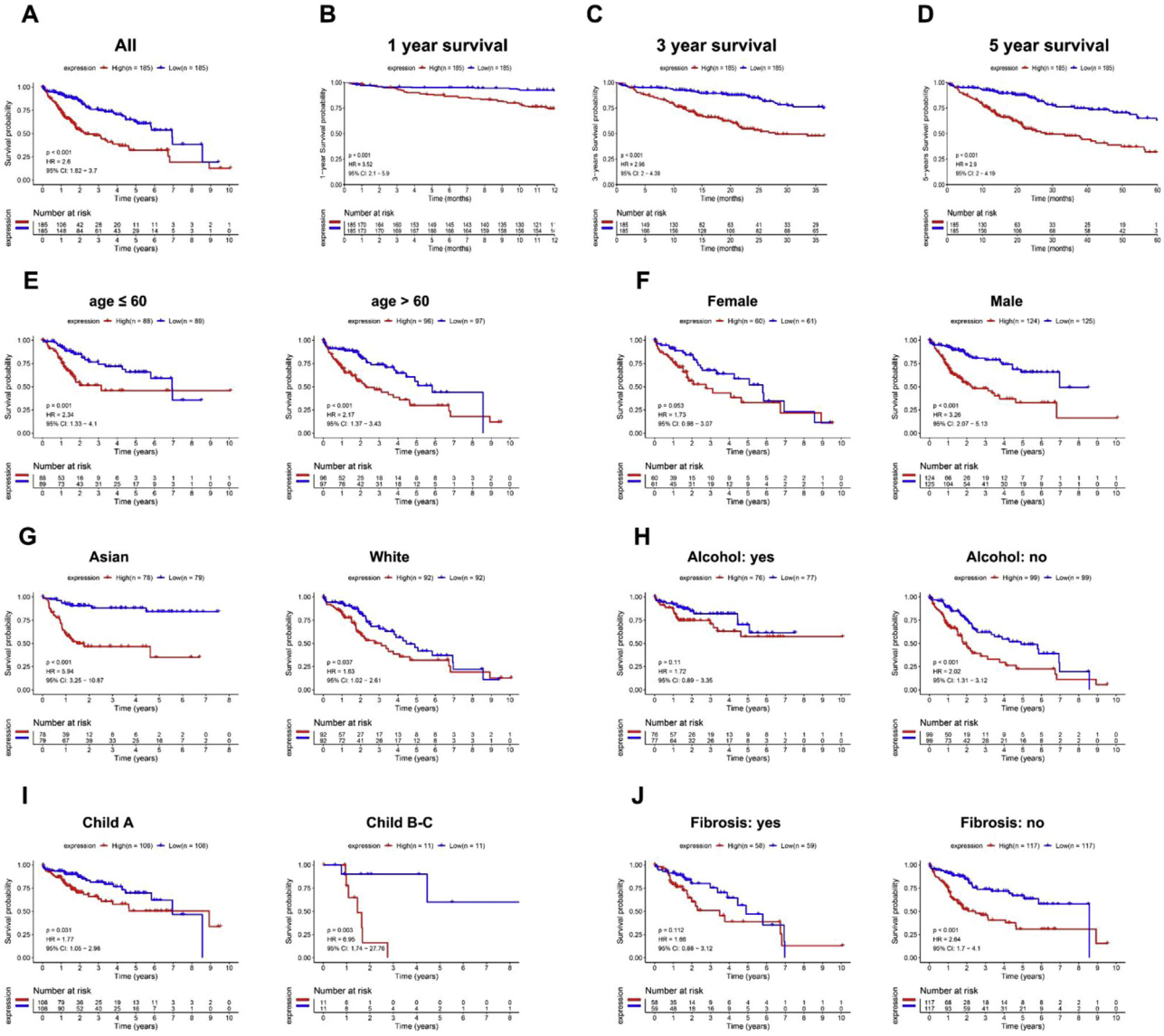


**Figure 2** Correlation between LPCAT1 mRNA expression and OS in HCC. **(A)** Impact of LPCAT1 expression on OS in all patients in this TCGA cohort. **(B—D)** Impact of LPCAT1 expression on 1, 3, 5-year survival. **(E)** Impact of LPCAT1 expression on OS in patients with different age stage. **(F)** Impact of LPCAT1 expression on OS in patients with different gender. **(G)** Impact of LPCAT1 expression on OS in different ethnic groups. **(H)** Impact of LPCAT1 expression on OS in patients with or without a history of alcohol consumption. **(I)** Impact of LPCAT1 expression on OS in patients with different Child-Pugh Classification. **(J)** Impact of LPCAT1 expression on OS in patients with or without hepatic fibrosis. **(K)** Impact of LPCAT1 expression on OS in patients with different ECOG status. **(L)** Impact of LPCAT1 expression on OS in patients with different AFP level. **(M)** Impact of LPCAT1 expression on OS in patients with different Grade Classification. **(N)** Impact of LPCAT1 expression on OS in patients with different TNM Stage.

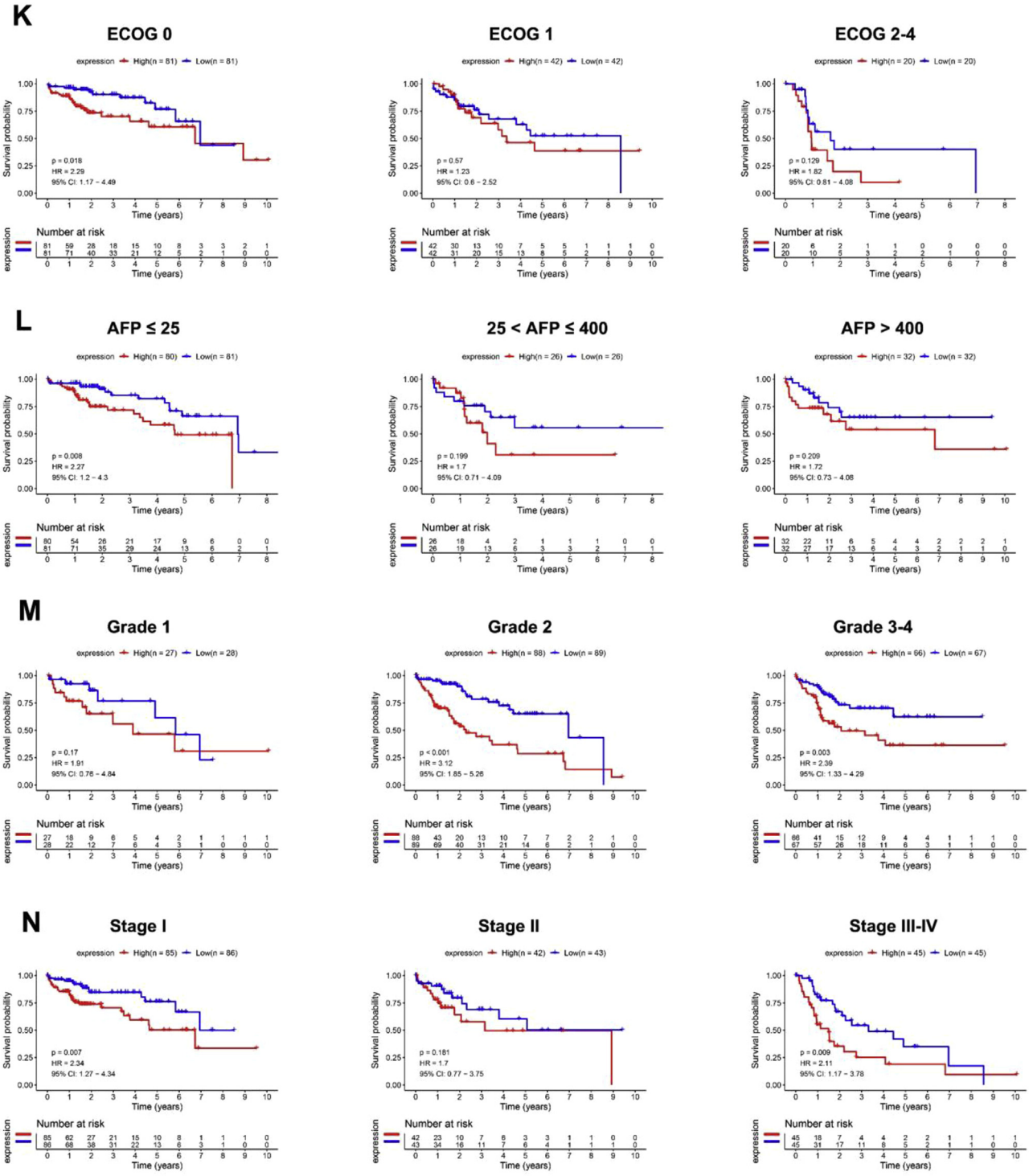


**Figure 2** (*continued*).

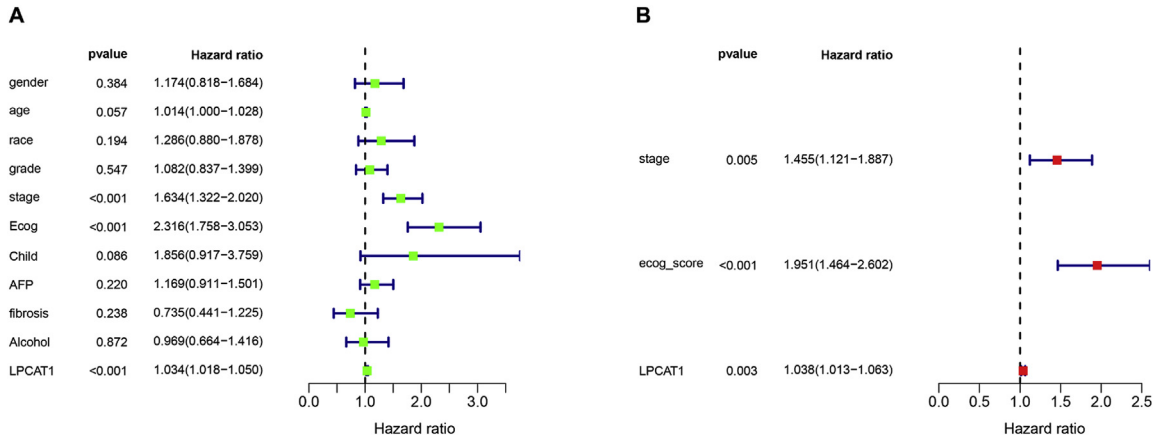


**Figure 3** Forest plot of the influence of each clinical variable on OS. **(A)** Univariate analysis. **(B)** Multivariate analysis.

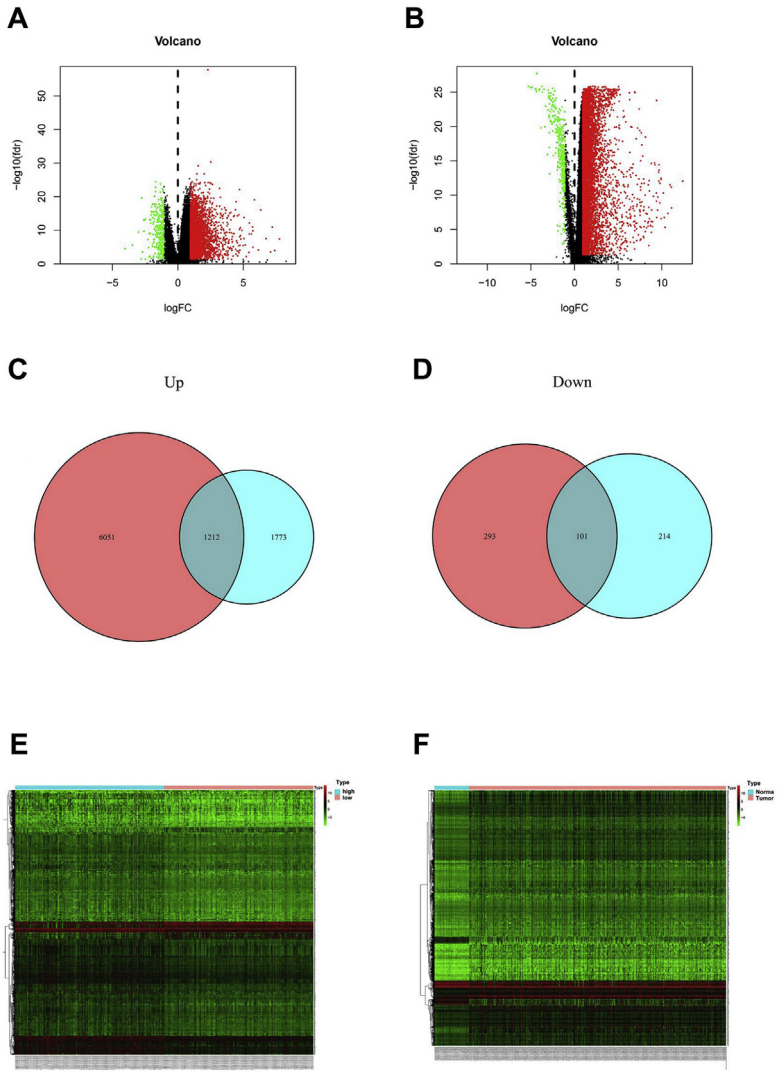


**Figure 4** The identification of potential LPCAT1 related tumor genes. **(A)** The volcano figure of DEGs between LPCAT1 high expression group and low expression group. **(B)** The volcano figure of DEGs between tumor tissues and normal tissues. **(C)** The Venn diagram of significantly up-regulated DEGs in intersection of "normal *vs.* tumor" and "LPCAT1 high expression *vs.* LPCAT1 low expression". **(D)** The Venn diagram of significantly down-regulated DEGs in intersection of "normal *vs.* tumor" and "LPCAT1 high expression *vs.* LPCAT1 low expression". **(E)** The heatmap of overlapped DEGs in LPCAT1 high expression and low expression tumor tissues. **(F)** The heatmap of overlapped DEGs in tumor tissues and normal tissues.

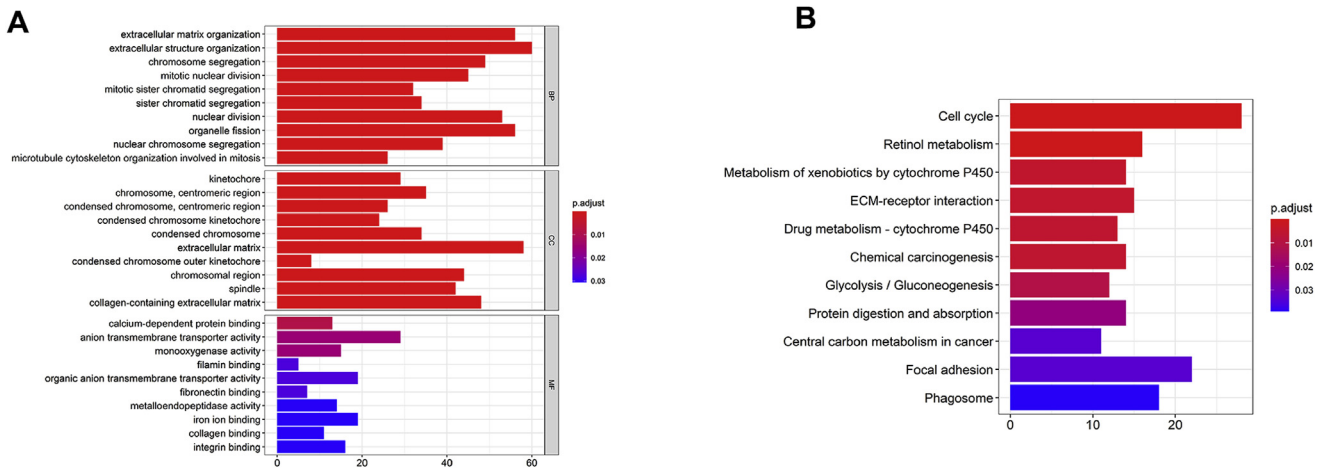


**Figure 5** Functional enrichment analysis of overlapped DEGs. **(A)** GO analysis. **(B)** KEGG pathway analysis.

**Table 2** GO and KEGG enrichment analysis of potential LPCAT1 related tumor genes in HCC ranked by *P* value (TOP 5).

| Category | GO or KEGG ID | GO or KEGG term | *P*.adjust | Count |
|---|---|---|---|---|
| BP | GO:0030198 | Extracellular matrix organization | 4.87E-11 | 56 |
| BP | GO:0043062 | Extracellular structure organization | 5.58E-11 | 60 |
| BP | GO:0007059 | Chromosome segregation | 5.58E-11 | 49 |
| BP | GO:0140014 | Mitotic nuclear division | 5.58E-11 | 45 |
| BP | GO:0000070 | Mitotic sister chromatid segregation | 2.08E-10 | 32 |
| CC | GO:0000776 | Kinetochore | 8.39E-09 | 29 |
| CC | GO:0000775 | Chromosome, centromeric region | 8.39E-09 | 35 |
| CC | GO:0000779 | Condensed chromosome, centromeric region | 1.16E-08 | 26 |
| CC | GO:0000777 | Condensed chromosome kinetochore | 3.33E-08 | 24 |
| CC | GO:0000793 | Condensed chromosome | 9.14E-08 | 34 |
| MF | GO:0048306 | Calcium-dependent protein binding | 0.008772 | 13 |
| MF | GO:0008509 | Anion transmembrane transporter activity | 0.015186 | 29 |
| MF | GO:0004497 | Monooxygenase activity | 0.015186 | 15 |
| MF | GO:0031005 | Filamin binding | 0.027735 | 5 |
| MF | GO:0008514 | Organic anion transmembrane transporter activity | 0.027735 | 19 |
| KEGG | hsa04110 | Cell cycle | 1.91E-08 | 28 |
| KEGG | hsa00830 | Retinol metabolism | 5.64E-05 | 16 |
| KEGG | hsa00980 | Metabolism of xenobiotics by cytochrome P450 | 0.004853 | 14 |
| KEGG | hsa04512 | ECM-receptor interaction | 0.005052 | 15 |
| KEGG | hsa00982 | Drug metabolism — cytochrome P450 | 0.005754 | 13 |

populations. High LPCAT1 mRNA level indicated poorer survival probability in Male (HR 3.26, $P < 0.001$, Fig. 2F), Asian (HR 5.94, $P < 0.001$, Fig. 2G), AFP≤25 (HR 2.27, $P = 0.008$, Fig. 2L), Grade 3—4 (HR 2.39, $P = 0.003$, Fig. 2M), Stage I (HR 2.34, $P = 0.007$, Fig. 2N). There were no relationships between LPCAT1 mRNA expression and prognosis in Female (HR 1.73, $P = 0.053$, Fig. 2F), Alcohol consumption (HR 1.72, $P = 0.11$, Fig. 2H), Fibrosis (HR 1.66, $P = 0.112$, Fig. 2J), ECOG 1 and ECOG 2—4 (HR 1.23, $P = 0.57$; HR 1.82, $P = 0.129$, Fig. 2K), $25 < AFP \leq 400$ and $AFP > 400$ (HR 1.7, $P = 0.199$; HR 1.72, $P = 0.209$, Fig. 2L), Grade 1 (HR 1.91, $P = 0.17$, Fig. 2M), Stage II (HR 1.7, $P = 0.181$, Fig. 2N).

Univariate analysis revealed that, in addition to the expression of LPCAT1, stage and ECOG score were significantly correlated with poor OS. While age, gender, race, grade, Child score, alpha fetoprotein, Ishak fibrosis score and alcohol consumption had no relationship with OS. Multivariate analysis demonstrated that stage, ECOG score and LPCAT1 expression were independently associated with OS (Fig. 3).

## Identification of potential LPCAT1 related tumor genes

There were altogether 1987 DEGs between LPCAT1 high expression group and low expression group, consisting of 1773 significantly up-regulated DEGs and 214 significantly down-regulated DEGs. The volcano figure of these DEGs

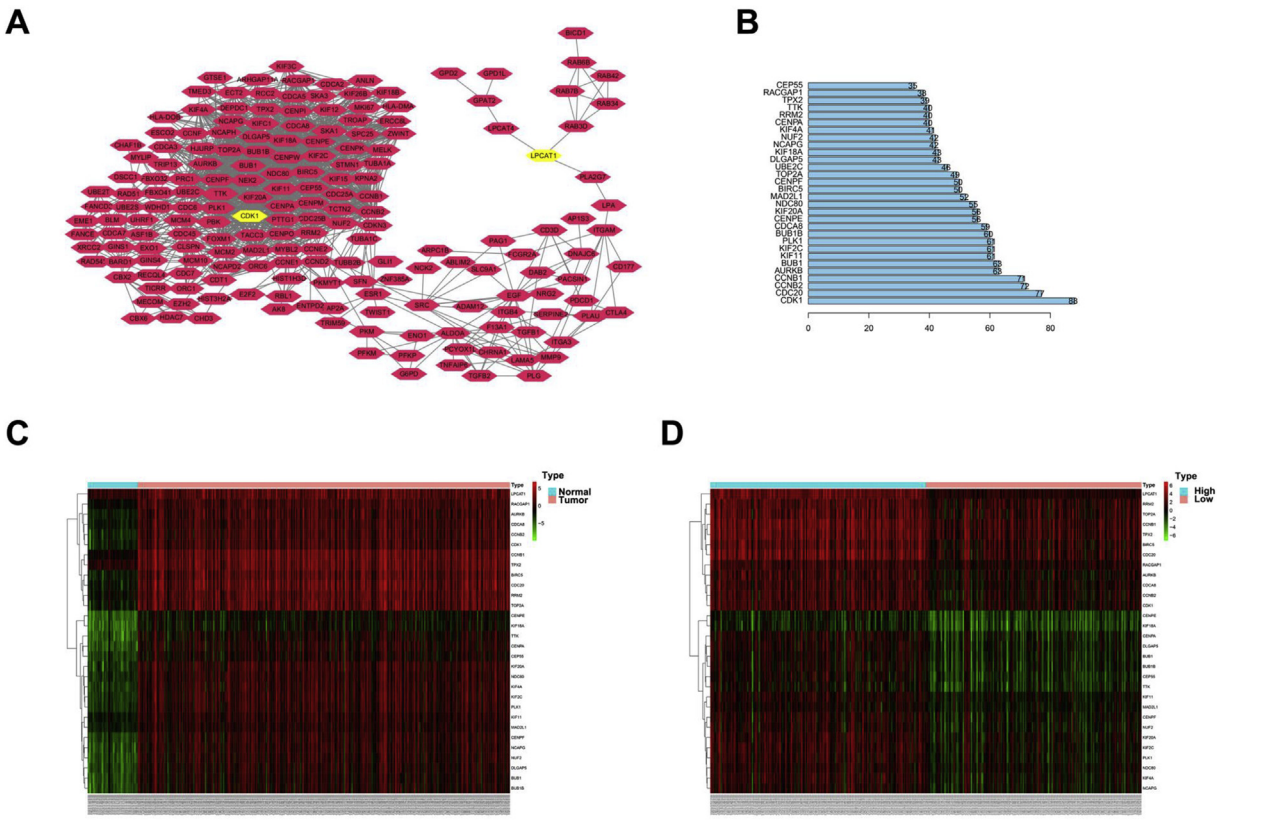


**Figure 6** PPI network analysis and hub genes. **(A)** The PPI network of overlapped DEGs. **(B)** Barplot of the top 30 genes with largest number of adjacent nodes. **(C)** Heatmap of the top 30 genes with largest number of adjacent nodes in tumor tissues and normal tissues. **(D)** Heatmap of the top 30 genes with largest number of adjacent nodes in LPCAT1 high expression and low expression tumor tissues.

was shown in Fig. 4A. A total of 6344 differentially expressed genes were found in tumor tissues ($n = 374$) when compared with normal tissues ($n = 50$). The volcano figure of these DEGs was shown in Fig. 4B. Among them, 6051 genes were found significantly up-regulated, while 293 down-regulated. Then, we selected intersection of the two sets of genes for subsequent bioinformatics analysis. Finally, we got 101 overlapped genes in down-regulated DEGs (Fig. 4C) and 1212 overlapped genes in up-regulated DEGs (Fig. 4D). The expression levels of DEGs between LPCAT1 high expression and low expression patients were displayed in Fig. 4E. The expression levels of DEGs between normal and tumor tissues were displayed in Fig. 4F.

## GO and KEGG pathway enrichment analysis

A total of 1313 DEGs including 101 significantly down-regulated overlapped DEGs and 1212 significantly up-regulated overlapped DEGs were classified according to GO term. As to BP, CC, MF, extracellular matrix organization, kinetochore, calcium-dependent protein binding was most significantly enriched respectively (Fig. 5A). As shown in Fig. 5B, KEGG pathway enrichment analyses showed overlapped DEGs mainly participate in cell cycle, retinol metabolism, metabolism of xenobiotics by cytochrome P450, etc. (Table 2).

## Protein—protein interaction network analysis and hub genes

As shown in Fig. 6A, the PPI network of overlapped DEGs including 468 nodes and 2249 edges was constructed by Cytoscape software, based on STRING database. Top 30 genes with largest number of adjacent nodes were visualized. These genes were *CDK1*, *CDC20*, *CCNB2*, *CCNB1*, *AURKB*, *BUB1*, *KIF11*, *KIF2C*, *PLK1*, *BUB1B*, *CDCA8*, *CENPE*, *KIF20A*, *NDC80*, *MAD2L1*, *BIRC5*, *CENPF*, *TOP2A*, *UBE2C*, *DLGAP5*, *KIF18A*, *NCAPG*, *NUF2*, *KIF4A*, *CENPA*, *RRM2*, *TTK*, *TPX2*, *RACGAP1*, *CEP55* (Fig. 6B). *CDK1*, with maximum number of adjacent nodes, was selected as hub gene. CDK1 has been reported to act on cell cycle, which was consistent with the result of KEGG enrichment analysis. The expression of these genes in normal-tumor groups and LPCAT1 high expression-low expression groups were shown in Fig. 6C and D. As shown in Fig. 7, Kaplan—Meier survival curve of these 30 genes was drawn to further evaluate their impact on 5-year survival rate of HCC patients. The results showed that HCC patients with high expression of all 30 genes showed significantly worse prognosis than those with low expression ($P < 0.05$).

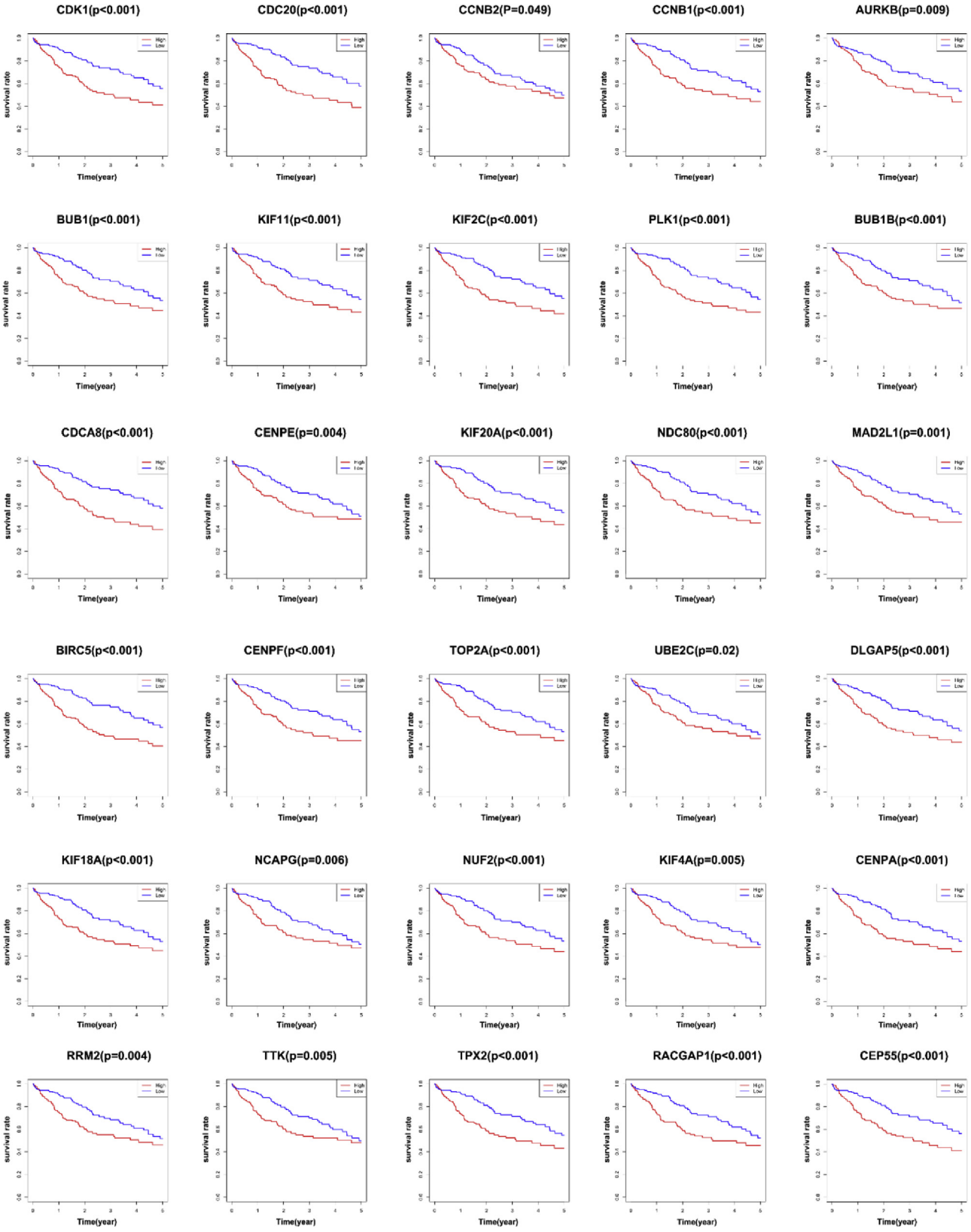


**Figure 7** Survival analysis of genes with potential prognostic function in the top 30 genes.

## Discussion

LPCAT1, an important enzyme in phosphatidylcholine metabolism, can alter the phospholipid composition of the plasma membrane and affect breathing by regulating the level of saturated phosphatidylcholine.[33] It plays an important role in the occurrence and development of various cancers. Recent studies have demonstrated that LPCAT1 is expressed at high levels in breast cancer, colorectal cancer, prostate cancer and HCC. The function of LPCAT1 has been investigated by knockdown and overexpression in HCC, and LPCAT1 has been confirmed to increase cell proliferation and invasion capacity.[26] Regarding the relationship between LPCAT1 and clinical parameters, some researchers have found that LPCAT1 is associated with T stage, estrogen receptor negativity, progesterone receptor negativity, amplification of HER2 and OS in breast cancer, and that upregulation of LPCAT1 is linked to poor prognosis.[34] LPCAT1 is therefore considered an independent predictor of early tumor recurrence in breast cancer.[24] Genetic variant in *LPCAT1* is also associated with the prognosis of lung cancer.[35] However, the relationship between LPCAT1 and clinical characteristics in patients with HCC is still unclear.

In our study, bioinformatic analysis using high throughput RNA-sequencing data from TCGA indicated that the expression of LPCAT1 was significantly higher in HCC tissues than in normal tissues. The differential expression of LPCAT1 between HCC tissues and normal tissues suggested that it may be a potential diagnostic biomarker. In addition, our study found that LPCAT1 expression was related to tumor grade, ECOG score, AFP and TNM stage. This implies an important role in the development and progression of HCC. Significantly different survival results were found in male and Asian subgroups, which are the main populations affected by HCC worldwide. The most striking result was that LPCAT1 was significantly associated with 1-year, 3-year and 5-year survival probability in patients with HCC, which indicates that LPCAT1 can be regarded as a good prognostic marker for these patients. Although it is an independent factor affecting the prognosis of HCC, whether LPCAT1 can be combined with other biomarkers or clinical parameters to build a predictive risk model remains to be further studied in the future.

Mechanisms of LPCAT1 action in tumor cells have been studied in previous papers, and it is involved in the EGFRvIII pathway through alteration of the composition of the plasma membrane. Mischel found that the cell membrane phospholipids were altered in EGFR gene aberrant glioblastoma multiforme (GBM) cells. LPCAT1 plays a key role in the process of reshaping lipid membrane structure, converting lysophosphatidylcholine (LPC) to phosphatidylcholine (PC). This change allows oncogenic receptors to be fixed more firmly to the plasma membrane, thereby transmitting and amplifying growth signals.[36–38] For example, in renal clear cell carcinoma, LPCAT1 promotes the occurrence and development of tumor by transforming LPC into PC.[39] A study of lung adenocarcinomas showed that patients with brain metastases had higher expression of LPCAT1 than those without brain metastasis. Moreover, LPCAT1 can upregulate the PI3K/AKT/MYC pathway, demonstrating that high expression of LPCAT1 is closely related with poor clinical outcome.[40] Non-coding RNA targeting LPCAT1 has also been discovered; the miR-205-LPCAT1 axis highlights an essential role of LPCAT1 in miR-205-regulated cancer cell proliferation.[41]

In order to further explore the mechanisms of LPCAT1 in tumorigenesis of HCC, 1313 DEGs were obtained by intersection of tumor tissue-normal tissue group DEGs and LPCAT1 high expression group-low expression group DEGs, which ensured that these genes were not only related to high expression of LPCAT1, but also to tumorigenesis. GO, KEGG and PPI construction and searching for hub genes were used to analyze potential LPCAT1 related genes in HCC. The DEGs obtained were mainly enriched in the cell cycle pathway. *CDK1*, *CDC20*, *BUB1* and some other key node genes are involved in the regulation of the cell cycle; CDK1 is the monitoring site of G2/M in the cell cycle.[42] And cyclinB1/CDK1 can regulate mitochondrial bioenergetics.[43] Recently, researchers have found that MYC can regulate the cell cycle by activating CDK1.[44] In studies of lung adenocarcinoma, LPCAT1 has been shown to upregulate MYC and activate the PI3K/AKT pathway.[40] Based on the above results, combined with bioinformatics analysis, it was considered that LPCAT1 may stimulate cell cycle procession by upregulating MYC and its downstream molecule CDK1. CDC20 has been found to be associated with poor prognosis in breast cancer, colorectal cancer, glioma and other malignant tumors.[45–48] It regulates separation of chromosomes and the end of mitosis.[49] Whether it is a downstream molecule of LPCAT1 acting on the cell cycle requires further investigation. BUB1 is a checkpoint for spindle assembly in late mitosis and also plays an important role in separating chromosomes of normal cells from those of cancer cells.[50] Numerous studies have confirmed that BUB1 mutation and differences in expression are related to tumor development.[51–55] BUB1 is also associated with CDC20 during the cell cycle, and BUB1 has been reported to inhibit the formation of the APC/C-CDC20 complex by regulating CDC20 phosphorylation, thereby inhibiting spindle assembly.[56] The experimental verification and analysis of hub genes can further explain the function and mechanism of LPCAT1 in HCC.

To summarize, our study demonstrated that LPCAT1 was an independent prognostic marker, which may cause tumorigenesis by altering the membrane phospholipid structure and, further, affecting the cell cycle in HCC. This research was limited by relying only on online data analysis, therefore more in-depth studies need to be conducted for confirmation.

## Conclusions

LPCAT1 is significantly up-regulated and was a novel independent prognosis predictor in HCC.

## Ethics approval and consent to participate

The ethical approval did not refer to this study and this study did not need the informed consent.

## Funding

This study was supported by National Natural Science Foundation of China (No. 81872380), Natural Science Foundation of Chongqing (No. cstc2018jscx-mszdX0039).

## Author contributions

Tingxiu Xiang, Shu Zhang and Hongbin Zhang: Conceptualization, Methodology, Software. Benxu Tan, Ping Ju, XiuFu Lan, Yi Liu and Jian Zhang: Data curation. Zheng Fu, Chao Li, Jinzhi Wang, Jixiang Song and Yun Xiao: Visualization, Investigation. Ke Xu, Qin Xiang, Lijuan Zhao, Zhaobo Cheng and Yan Wang: Writing — Original draft preparation.

## Availability of data and materials

The datasets generated and analyzed during the current study are available in TCGA official website repository (https://portal.gdc.cancer.gov/). We analyzed the functional protein association network with STRING database (https://string-db.org/).

## Conflict of interests

The authors declare no potential conflicts of interest.

## Acknowledgements

This study was supported by National Natural Science Foundation of China (No. #81872380), Natural Science Foundation of Chongqing (No. cstc2018jscx-mszdX0039).

## Abbreviations

| | |
|---|---|
| LPCAT1 | lysophosphatidylcholine acyltransferase 1 |
| HCC | hepatocellular carcinoma |
| OS | overall survival |
| DEGs | differentially expressed genes |
| GO | Gene Ontology |
| KEGG | Kyoto Encyclopedia of Genes and Genomes |

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