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Original Article

Prognostic significance of LRPPRC and its association with immune infiltration in liver hepatocellular carcinoma

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Abstract: Background: Leucine rich pentatricopeptide repeat containing (LRPPRC) protein is a multifunctional protein involved in cell cycle progression and tumor development. However, its prognostic significance and association with immune infiltration in Liver hepatocellular carcinoma (LIHC) remain unclear. Methods: We utilized transcriptomic and clinical data from The Cancer Genome Atlas (TCGA) and Genotype Tissue Expression (GTEx) databases of LIHC patients to investigate the potential pro-cancer role of LRPPRC, including differential expression of LRPPRC in LIHC, prognostic value, clinicopathological features, immune cell infiltration relevance and function enrichment analysis. Results: Our findings suggest that LRPPRC is upregulated in LIHC and exhibits correlations with survival, clinical stage, and tumor grade in LIHC patients. Additionally, immune infiltration analysis revealed significant negative correlations between LRPPRC expression and multiple tumor-infiltrating immune cells, including CTLs, DCs, pDCs, B cells, Th17 cells, neutrophils, T cells, Mast cells, Th1 cells, Tregs, and NK cells, whereas a significant positive correlation was observed with infiltration of Th2 cells, T helper cells and Tcms. Furthermore, functional enrichment analysis indicated that LRPPRC may be involved in G2m checkpoint, mitotic spindle, E2f targets, Wnt Beta catenin signaling, spermatogenesis and other processes.

Keywords: LRPPRC, liver hepatocellular carcinoma (LIHC), prognostic value, immune infiltration

Introduction

Liver hepatocellular carcinoma (LIHC) is one of the most common and aggressive malignancies, with high morbidity and mortality rates [1, 2]. According to the Global Cancer Statistics report, there will be approximately 906,000 new liver cancer cases and 830,000 deaths globally in 2020, and the type of 75%-85% primary liver cancer cases was LIHC [3, 4]. The development of LIHC is recognized as a multistep complex biological process involving a multifactorial etiology and the interplay of multiple genes, culminating in tumorigenesis, progression, recurrence and metastasis [5, 6]. Despite the availability of various target biomarkers for the diagnosis and treatment of LIHC, the specific molecular mechanisms governing cell proliferation and metastasis remain largely elusive for this highly heterogeneous tumor [7, 8]. Thus, the search for novel biomarkers becomes imperative to achieve a more comprehensive understanding of LIHC development and prognosis.

Leucine rich pentatricopeptide repeat containing (LRPPRC) protein, belonging to the PPR motif-containing family of proteins, is a multifunctional proteins found in multiple cellular compartments, including the outer and inner nuclear membranes, the nucleoplasm, the endoplasmic reticulum, the cytoskeleton and the mitochondrion, performing a wide range of functions involving homeostasis, microtubule

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alterations, DNA/RNA binding, mitochondrial gene expression and function, cell-cycle progression, metabolic processes, and tumorigenesis and progression [9, 10]. Previous studies have indicated that LRPPRC expression is increased in different tumor tissues, such as prostate and gastric cancers, lung adenocarcinomas, colon cancers, breast and endometrial adenocarcinomas, and lymphomas [11]. Given that normal cells rarely or lowly express LRPPRC, the protein may be a potential molecular target for cancer diagnosis, prognosis, and treatment. Recent reports have revealed the correlation between high LRPPRC expression and stages, grades and poor prognosis of tumor patients [12, 13]. However, the correlation between LRPPRC expression in LIHC and clinicopathological features as well as the immune cell infiltration are poorly understood. Therefore, we are keen to explore the potential role of LRPPRC in LIHC.

In this study, we comprehensively assessed the differences in LRPPRC expression between LIHC tumor tissues and normal tissues and its correlation with patient prognosis using RNA-seq data from The Cancer Genome Atlas (TCGA) and Genotype Tissue Expression Project (GTEx) databases. In addition, we investigated the correlation between LRPPRC expression and the level of immune cell infiltration to explore the possible mechanisms by which LRPPRC induces LIHC occurrence and progression. Eventually, to reveal its potential function, we performed Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Set Enrichment Analyses (GSEA) of differentially expressed genes (DEGs) between LRPPRC high and low expression groups.

Materials and methods

Data collection and expression analysis of LRPPRC

Transcriptomic gene expression data and clinical information from TCGA (https://portal.gdc.cancer.gov) and the GTEx (https://gtexportal.org/) were downloaded from the UCSC Xena database (https://xenabrowser.net/datapages/) for 33 tumors differential gene expression analysis [14]. Including adrenocortical carcinoma (ACC), bladder urothelial carcinoma (BLCA), breast invasive carcinoma (BRCA), cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), cholangiocarcinoma (CHOL), colon adenocarcinoma (COAD), lymphoid neoplasm diffuse Large B-cell lymphoma (DLBC), esophageal carcinoma (ESCA), glioblastoma multiforme (GBM), head and neck squamous cell carcinoma (HNSC), kidney chromophobe (KICH), kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP), acute myeloid leukemia (LAML), brain lower grade glioma (LGG), liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), mesothelioma (MESO), ovarian serous cystadenocarcinoma (OV), pancreatic adenocarcinoma (PAAD), pheochromocytoma and paraganglioma (PCPG), prostate adenocarcinoma (PRAD), rectum adenocarcinoma (READ), sarcoma (SARC), skin cutaneous melanoma (SKCM), stomach adenocarcinoma (STAD), testicular germ cell tumors (TGCT), thyroid carcinoma (THCA), thymoma (THYM), uterine corpus endometrial carcinoma (UCEC), uterine carcinosarcoma (UCS), uveal melanoma (UVM).

Differences of LRPPRC expression in tumor and normal tissues were analyzed in TCGA samples, TCGA + GTEx samples, TCGA paired samples and unpaired samples, respectively. R packages “stats” and “car” were used for statistical analysis, Log2(value+1) transformation and Wilcoxon rank sum test were performed on the expression data in TPM format.

Prognostic value of LRPPRC for LIHC

R package “forestplot” was utilized to demonstrate the correlation between LRPPRC expression and pan-cancer survival. Kaplan-Meier (KM) survival analysis was performed to assess the differences in overall survival (OS), disease specific survival (DSS), progress free interval (PFI) between high and low LRPPRC expressing groups in LIHC samples. KM curves were plotted using R packages “survival” and “survminer”. Subsequently, time-dependent receiver operating characteristic (ROC) was conducted by R package “timeROC” and ROC curves were plotted to predict OS in LIHC patients.

Association of LRPPRC with clinical features

Selected clinical variables involving patient age, race, BMI, OS event, AFP (ng/ml), tumor status, pathologic stage, pathologic T stage and histologic grade to investigate the correlation with LRPPRC expression.

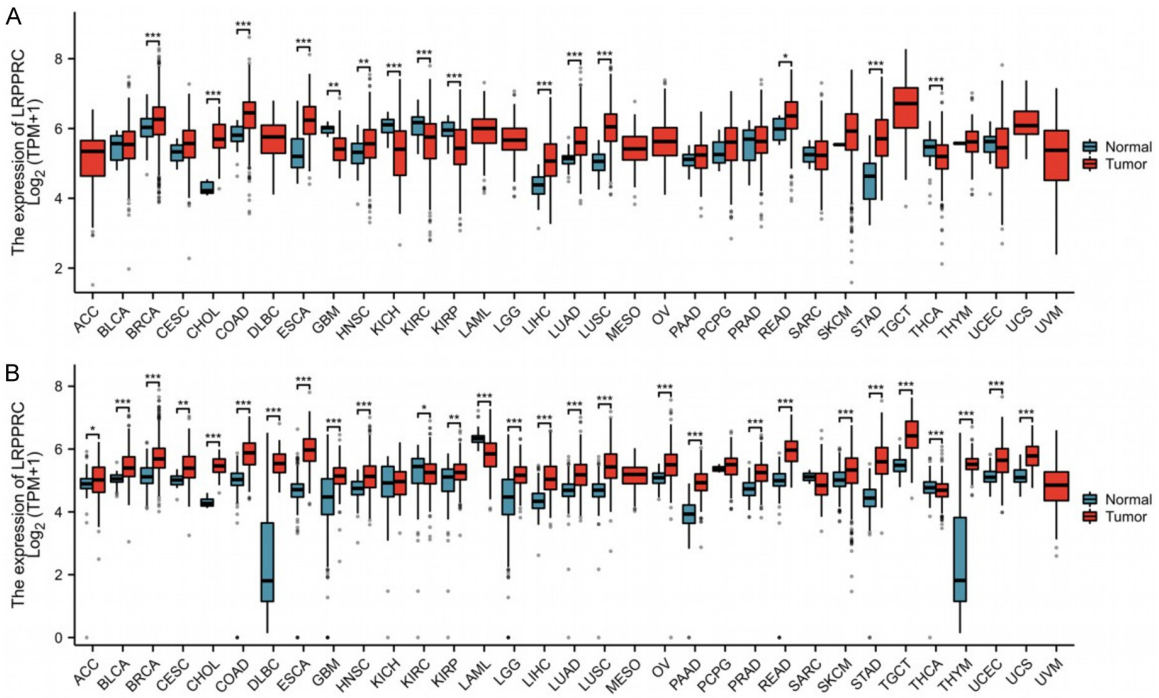

Figure 1. Expression of LRPPRC in pan-cancer. A. Expression levels of LRPPRC in 33 different human cancers in TCGA. B. Expression levels of LRPPRC in 33 different human cancers in TCGA + GTEx. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Tumor immune cell infiltration analysis

Immune infiltration in LIHC was evaluated through single-sample gene set enrichment analysis (ssGSEA) utilizing the "GSVA" package [15, 16]. The expression profiles of 24 immune cell types were examined to quantify the extent of infiltration. Spearman's correlation analysis was used to examine the association between LRPPRC expression and these immune cells. Wilcoxon rank sum test was then performed to assess differences in the level of immune infiltration between high and low LRPPRC expression groups.

Functional enrichment analysis

According to the LRPPRC expression value, LIHC samples were divided into high and low expression groups, and the difference analysis between the two groups was performed using the DESeq2 package. DEGs were collected with the criteria of adjusted *p*-value (*P*) < 0.05 and |log2fold change (FC)| > 1. Analysis of co-expressed genes associated with LRPPRC expression in TCGA-LIHC samples using Spearman's rank correlation coefficient. Based on the DEGs between LRPPRC high- and low-expression groups, GO, KEGG and GSEA were performed using the R package "clusterProfiler" [17].

Statistical analysis

R software (version 4.2.1) was used to perform all statistical analyses. Wilcoxon rank sum tests were performed for analysis of differences. Correlations were assessed using Spearman's correlation coefficients, and all data were visualized using the ggplot2 package. Statistical significance was set at $P < 0.05$.

Results

Correlation of LRPPRC with pan-cancer

To elucidate the potential role of LRPPRC in cancer, we initiated an analysis of its expression in 33 human tumors by extracting gene expression data from the TCGA database. The box plot clearly shows that LRPPRC expression levels were significantly elevated in 10 tumor types compared to normal tissues, including BRCA, CHOL, COAD, ESCA, HNSC, LIHC, LUAD, LUSC, READ, and STAD (**Figure 1A**). Regrettably, a comprehensive analysis was hampered by

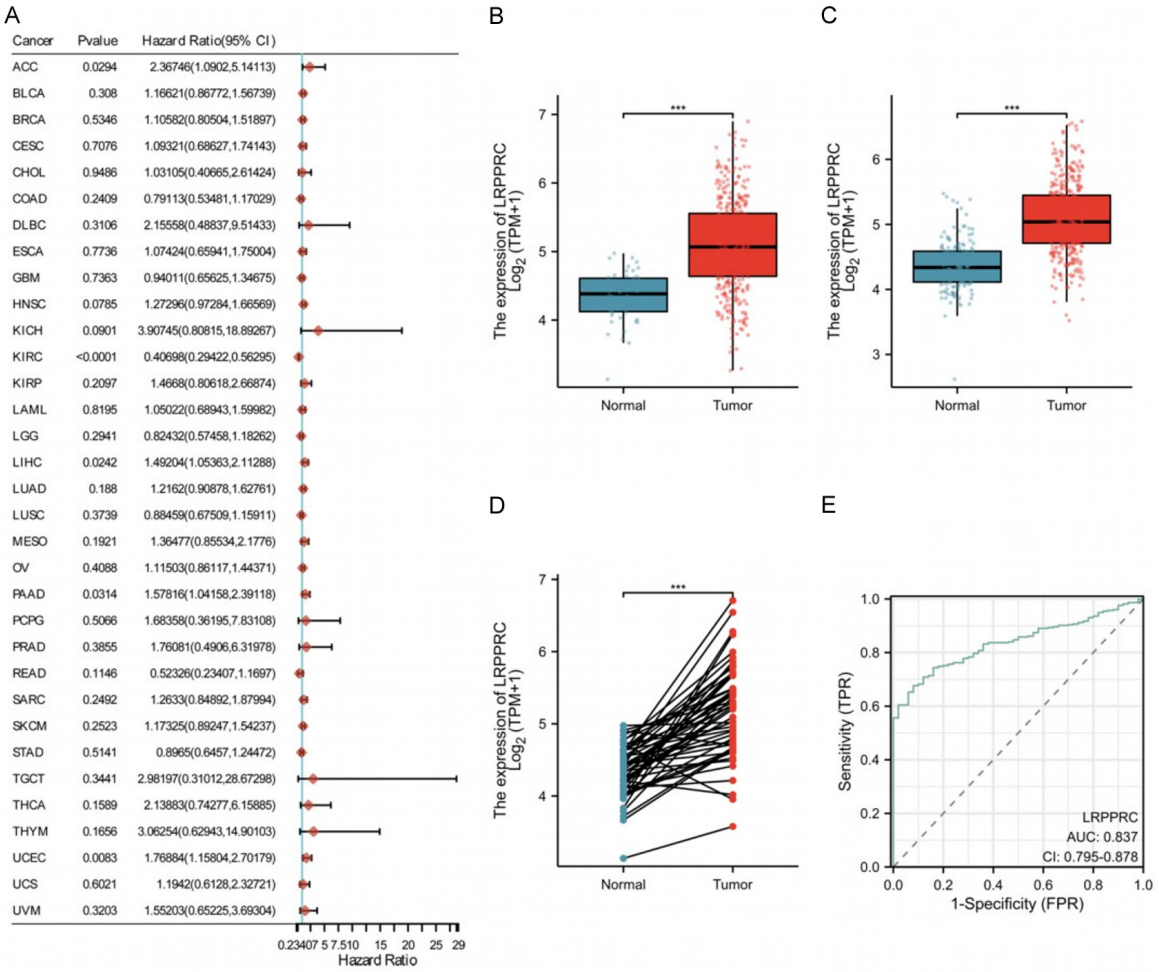

Figure 2. Expression of LRPPRC in LIHC. A. Forest plot of OS associations in 33 types of tumor. B. The expression levels of LRPPRC in 374 LIHC tissues and 50 normal tissues in TCGA LIHC dataset. C. The expression levels of LRPPRC in 371 LIHC tissues and 160 normal tissues in TCGA + GTEx dataset. D. 50 paired LIHC tissues and normal tissues in TCGA LIHC dataset. E. Diagnostic ROC curves in TCGA + GTEx dataset. *P < 0.05; **P < 0.01; ***P < 0.001.

the lack of certain normal tissue data in the TCGA database. Therefore, TCGA and GTEx were merged for a more thorough analysis. The results showed that in the majority of tumors, LRPPRC expression in tumor tissues exceeded that in corresponding normal tissues (**Figure 1B**), spanning 25 tumor types: ACC, BLCA, BRCA, CESS, CHOL, COAD, DLBC, ESCA, GBM, HNSC, KIRP, LGG, LIHC, LUAD, LUSC, OV, PAAD, PRAD, READ, SKCM, STAD, TGCT, THYM, UCEC, and UCS.

Upregulation of LRPPRC in LIHC

Subsequently, we extended our investigation to pan-cancer prognosis of LRPPRC and identified it as a high-risk adverse prognostic factor for LIHC (P < 0.05, Hazard ratio (HR) 95% confidence interval (CI) > 1) (**Figure 2A**). In both the TCGA cohort and the merged TCGA, GTEx cohort, LRPPRC levels were elevated in LIHC samples compared to normal samples (**Figure 2B**, **2C**). In the TCGA cohort, LRPPRC was statistically significantly higher expressed in LIHC tissues compared to paired adjacent normal tissues (P < 0.001) (**Figure 2D**). In addition, the ROC curve highlighted the commendable predictive and diagnostic capabilities of LRPPRC, with an area under the curve (AUC) of 0.837 (95% CI = 0.795-0.878), effectively discriminating LIHC tissues from normal counterparts (**Figure 2E**).

LRPPRC is a potential prognostic biomarker in LIHC

The KM method was applied to calculate the relevance of LRPPRC expression to the progno-

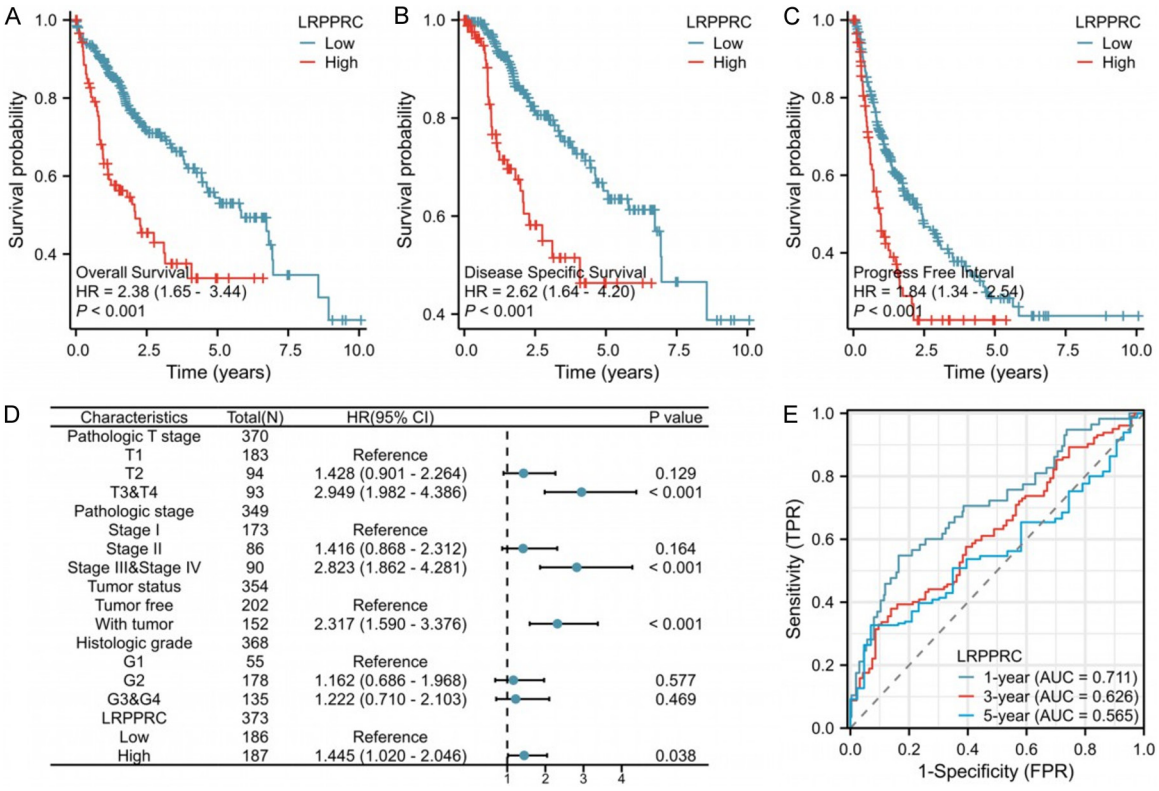

Figure 3. Prognostic significance in LIHC. KM survival curves of LRPPRC high and low expression patients in OS (A), DSS (B), PFI (C). (D) Univariate Cox regression model. (E) Predictive ability of LRPPRC for 1-, 3-, and 5-year OS in LIHC.

sis of LIHC patients. Patients were categorized into high and low LRPPRC expression groups using the median LRPPRC expression as the critical score. KM survival analysis revealed that the OS, DSS, and PFI of the LRPPRC high-expression group showed significantly worse prognosis compared to the LRPPRC low-expression group, suggesting that LRPPRC is an oncogene (**Figure 3A-C**). Subsequently, pathologic stage, T-stage, tumor status, histologic grade, and LRPPRC expression level were subjected to univariate Cox regression analysis to further identify factors correlated with different prognoses. The forest plot showed that LRPPRC was a detrimental prognostic factor for OS in LIHC patients (**Figure 3D**). Furthermore, the prognostic value of LRPPRC was confirmed by ROC curve analysis (**Figure 3E**). The AUC was greater than 0.5 at 1, 3 and 5 years, implying that the LRPPRC expression level has a moderate prognostic value.

LRPPRC expression and clinicopathological characteristics

LRPPRC expression levels were dramatically correlated with various clinical parameters in LIHC patients, including age, race, BMI, AFP levels, OS, tumor status, histologic grade, T stage and pathologic stage. Notably, the younger age group (age ≤ 60 years) showed higher LRPPRC expression compared to the older age group (age > 60 years) ($P < 0.05$). Furthermore, LRPPRC expression was significantly increased in Asian patients compared to individuals of other races. In addition, LIHC patients with a BMI of less than 25, AFP levels greater than 400, poor OS and advanced cancer stage also exhibited higher LRPPRC levels.

Association between LRPPRC expression and tumor immune cell infiltration

Subsequently, we evaluated the extent of immune cell infiltration in LIHC patients. Using

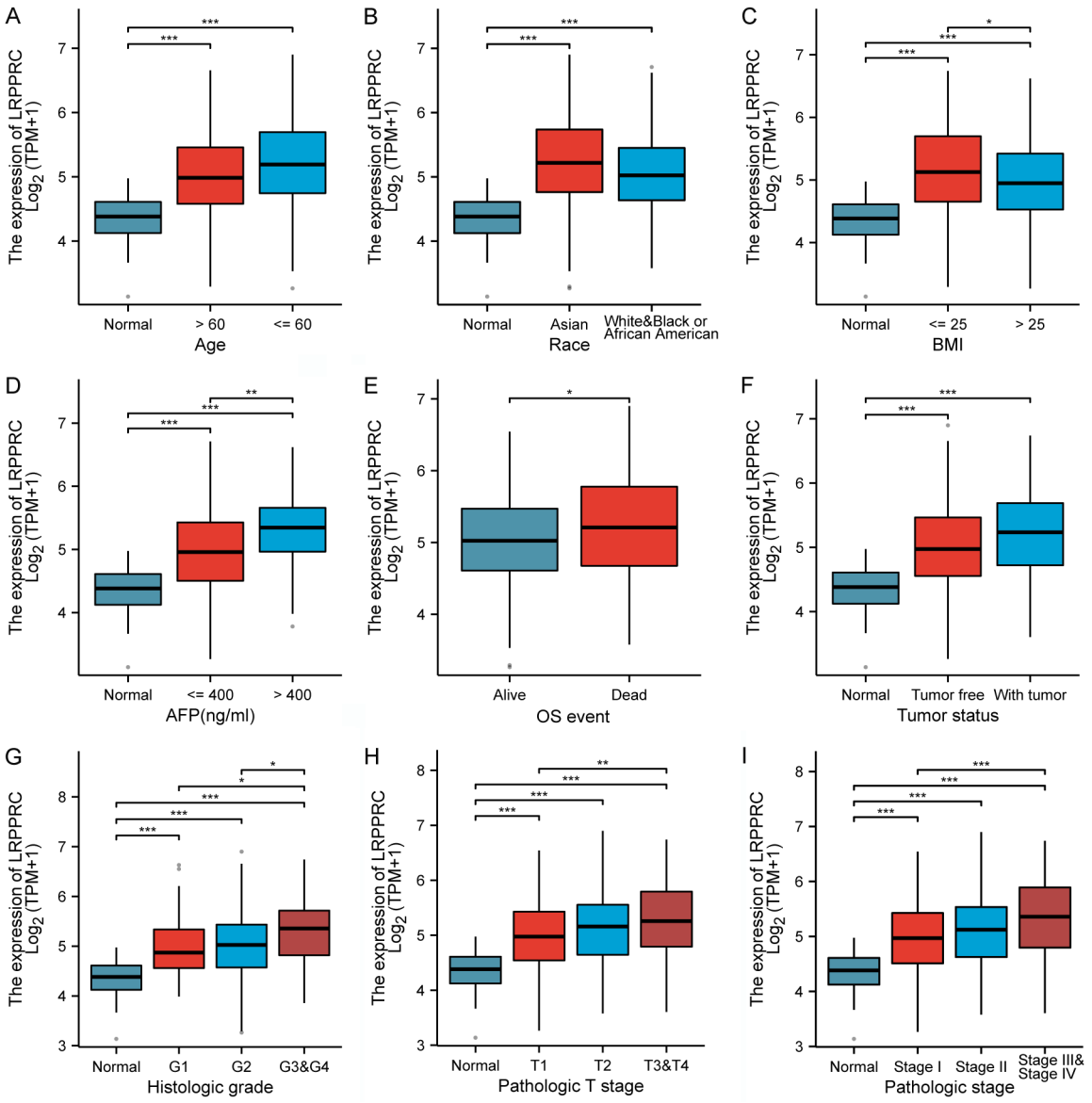

Figure 4. The correlation of LRPPRC expression in LIHC with clinical features. Association of LRPPRC expression with age (A), race (B), BMI (C), AFP (ng/ml) (D), OS event (E), tumor status (F), histologic grade (G), pathologic T stage (H) and pathologic stage (I) in LIHC patients. *P < 0.05; **P < 0.01; ***P < 0.001.

the ssGSEA algorithm, we explored the distribution of 24 immune cell types in both high and low LRPPRC expression groups within LIHC tissues. Notably, 14 immune cell subtypes, including cytotoxic T cells (CTLs), dendritic cell (DCs), plasmacytoid dendritic cells (pDCs), B cells, T helper cell 17 (Th17) cells, neutrophils, T cells, Natural Killer (NK) cells, NK CD56dim cells, Th1 cells, Mast cells, regulatory T cells (Tregs), immature dendritic cells (iDC), gammadelta T cells (Tgd) showed higher infiltration in the low expression group compared to the high expression group, whereas 3 immune cell subtypes (Th2 cells, T helper cells, central memory T cells (Tcms)) showed higher infiltration in the high expression group (**Figure 5A**, **5B**). In addition, we performed correlation analyses to further elucidate the relationship between LRPPRC expression and specific immune cell types. LRPPRC expression showed a positive correlation with Tcm cells (r = 0.295, P < 0.001; **Figure 5C**), T helper cells (r = 0.267, P < 0.001; **Figure 5D**), Th2 cells (r = 0.234, P < 0.001; **Figure 5E**). In contrast, LRPPRC expression showed a neg-

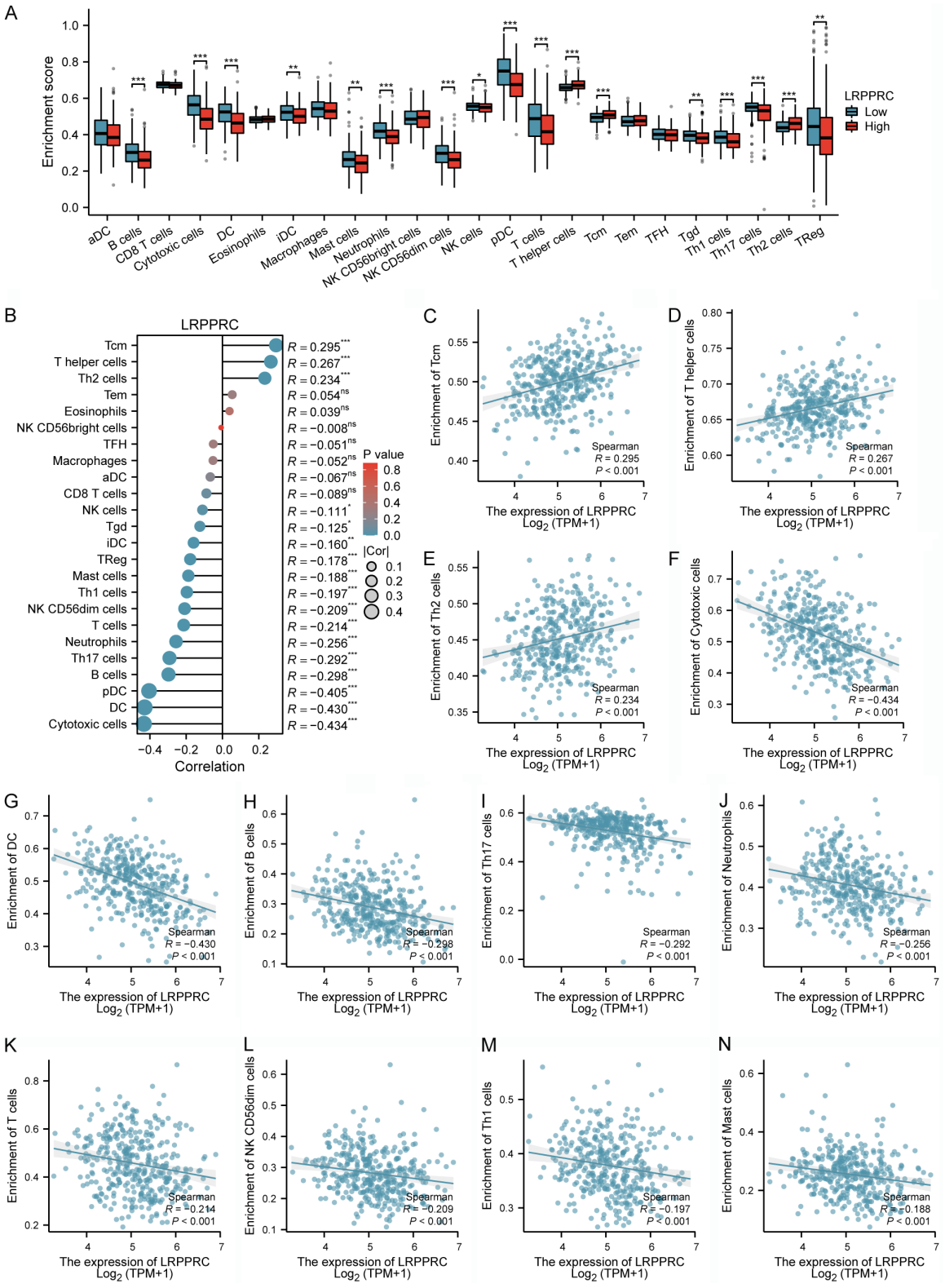

Figure 5. LRPPRC is closely associated with immune cells infiltration in HCC. (A) Difference in enrichment scores of 24 immune cells between patients with high and low LRPPRC. (B) Correlation of LRPPRC expression with relative infiltration of 24 immune cells in LIHC. (C) Scatter plots demonstrating the association between LRPPRC expression levels and Tcm cells (C), T helper cells (D), Th2 cells (E), cytotoxic cells (F), DCs (G), B cells (H), Th17 cells (I), neutrophils (J), T cells (K), NK CD56dim cells (L), Th1 cells (M), and mast cells (N). *P < 0.05; **P < 0.01; ***P < 0.001.

ative correlation with cytotoxic cells (r = -0.434, P < 0.001; **Figure 5F**), DCs (r = -0.430, P < 0.001; **Figure 5G**), B cells (r = -0.298, P < 0.001; **Figure 5H**), Th17 cells (r = -0.292, P < 0.001; **Figure 5I**), neutrophils (r = -0.256, P < 0.001; **Figure 5J**), T cells (r = -0.214, P < 0.001; **Figure 5K**), NK CD56dim cells (r = -0.209, P < 0.001; **Figure 5L**), Th1 cells (r = -0.197, P < 0.001; **Figure 5M**), and mast cells (r = -0.188, P < 0.001; **Figure 5N**).

Co-expressed genes and functional enrichment analysis

LIHC patients were categorized into LRPPRC high and low expression groups and screened for DEGs, with a total of 794 up-regulated and 360 down-regulated genes identified. Volcano plots were demonstrated for an in-depth understanding of the DEGs (**Figure 6A**). Correlations between LRPPRC and the top 20 DEGs were visualized by heatmap (**Figure 6B**). Subsequently, functional and pathway enrichment analyses were applied to gain a comprehensive understanding of DEGs (**Figure 6C**). It can be seen that most biological process (BP) terms were associated with regulation of hormone levels, signal release, embryonic organ development, pattern specification process, regionalization. The enriched cellular components (CC) terms were related to postsynaptic membrane, apical plasma membrane, synaptic membrane, apical part of cell, neuronal cell body. In terms of molecular function (MF), DEGs were predominantly enriched in receptor ligand activity, signaling receptor activator activity, hormone activity, growth factor activity, and passive transmembrane transporter activity. We also performed KEGG pathway enrichment analysis, which showed that high LRPPRC expression was mainly connected with Neuroactive ligand-receptor interaction, Bile secretion, Nicotine addiction. To further understand the LRPPRC expression involved in the LIHC signaling pathway, GSEA was performed. The top 5 HALLMARK-related annotations positively associated with high LRPPRC expression were G2m checkpoint, mitotic spindle, E2f targets, Wnt Beta catenin signaling, Spermatogenesis (**Figure 6D**). The top 5 HALLMARK terms negatively associated with high LRPPRC expression were fatty acid metabolism, interferon Gamma response, xenobiotic metabolism, oxidative phosphorylation, interferon Alpha response (**Figure 6E**).

Discussion

Given the complex nature of LIHC pathogenesis and the suboptimal results of existing therapies, there is a critical need to focus on preventing tumorigenesis, improving diagnostic approaches, and identifying novel therapeutic targets [18]. LRPPRC was identified as a downstream protein of P53. Recently, LRPPRC has attracted attention due to its significant correlation with the pathogenesis and progression of various tumors. However, the specific biological functions and molecular mechanisms by which LRPPRC contributes to LIHC development remain largely unexplored.

Numerous studies have consistently reported elevated LRPPRC expression in a spectrum of tumors, including gastric cancer [19], prostate cancer [13], colorectal cancer [20] suggesting its role as an oncogene. Based on this evidence, we hypothesized that LRPPRC plays a pivotal role in the initiation and progression of LIHC. Our results, which are shown in **Figures 1-3**, demonstrate the overexpression of LRPPRC in LIHC and establish a positive correlation with adverse clinical outcomes, which is consistent with previous research [21-23]. Furthermore, our analysis of LRPPRC expression in relation to clinicopathological features (**Figure 4**) demonstrates a significant association between high LRPPRC expression and higher histological grade, more advanced clinical stage, and larger tumor size. Taken together, these results underscore the critical role of LRPPRC in the development and progression of LIHC.

Tumor initiation, growth, metastasis, and treatment are intricately linked to the immune microenvironment, comprising a diverse array of infiltrating immune cells [24, 25]. The presence of tumor-infiltrating immune cells significantly influences the prognosis of LIHC and the efficacy of anti-tumor immunotherapy [26, 27]. In a study by Wang et al, LRPPRC showed a negative correlation with CD8+ and CD4+ T cells in LIHC patients, with tumors from the LRPPRC knockout group showing higher infiltration of these T cells [21]. This initial finding suggests a negative association between LRPPRC and anti-tumor immunity in LIHC. Our study builds on this and sheds light on the correlation between LRPPRC expression and various immune infiltrating cells in LIHC. **Figure 3** illus-

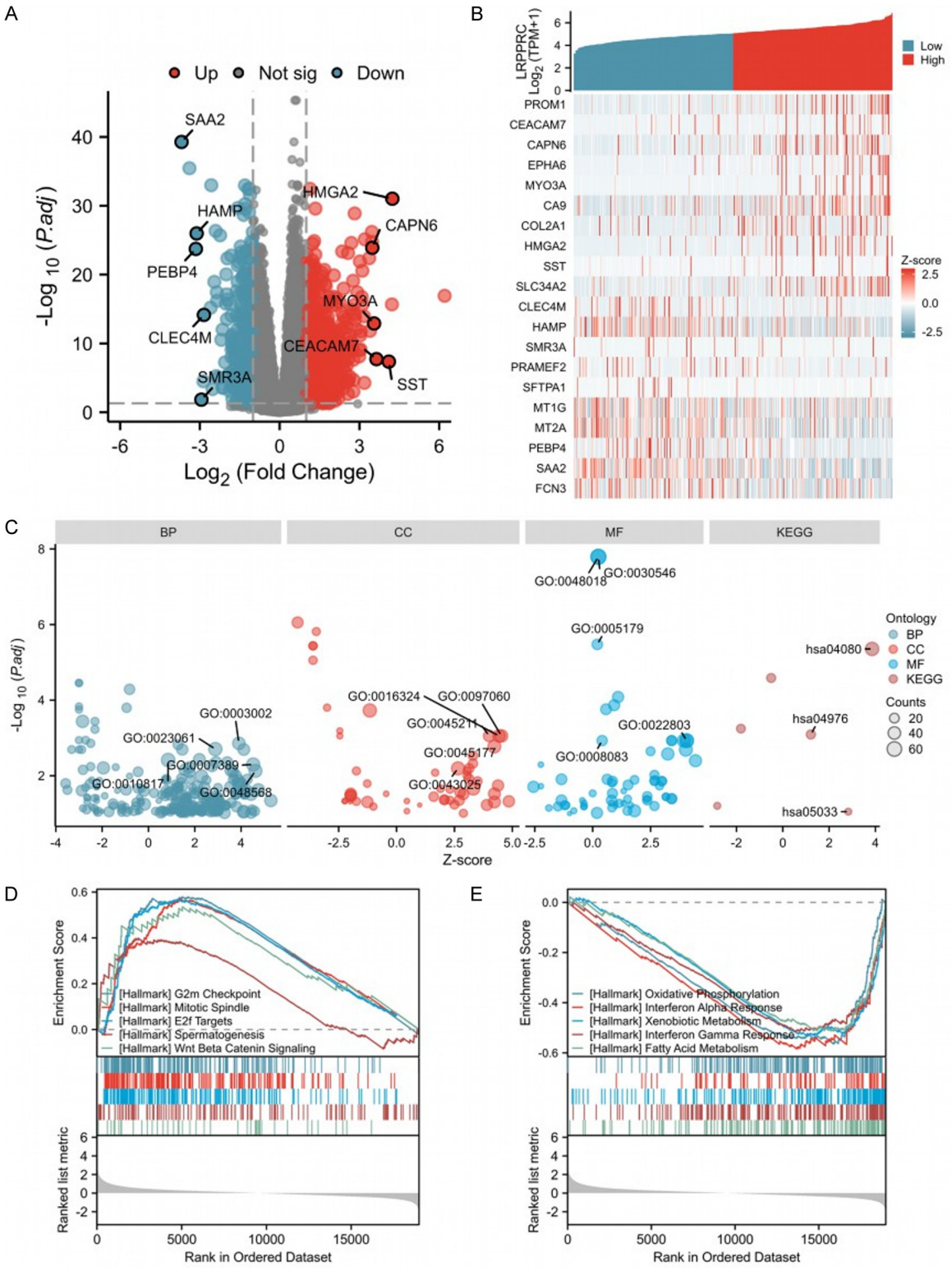

Figure 6. Identification and functional annotation of DEGs. (A) Volcano map showing the DEGs between LRPPRC high and low expression groups. (B) Heatmap showing the top 20 positively correlated genes and negatively correlated genes of LRPPRC in LIHC dataset. (C) Function enrichment analysis based on four aspects, including BP, CC, MF and KEGG. GSEA enrichment plots showing the top five (D) positively and (E) negatively associated HALLMARK pathways.

trates a negative correlation between LRPPRC expression and numerous tumor-infiltrating immune cells, including CTLs, DCs, pDCs, B cells, Th17 cells, neutrophils, T cells, Mast cells, Th1 cells, Tregs, and NK cells. These cells play pivotal roles in LIHC immune escape and anti-tumor therapy. CTLs, being the primary lymphocytes responsible for killing cancer cells [28], might face limitations in infiltrating LIHC due to LRPPRC overexpression. DCs, key antigen-presenting cells crucial for initiating anti-tumor immunity by activating CD8+ T cells [29], may also be affected. Similarly, NK cells, important in immune surveillance of malignant tumors [28], might experience modulation. However, previous studies have found that neutrophils can promote LIHC progression by suppressing anti-cancer immunity [30]. Taken together, this suggests that LRPPRC may have a modulatory effect on immune escape and the tumor immune microenvironment by regulating these cells, making it a promising target for improving the efficacy of LIHC immunotherapy.

Lastly, we delved into exploring the potential biological role of LRPPRC in LIHC. GSEA analysis indicated that LRPPRC is implicated in crucial pathways, including the G2/M checkpoint, mitotic spindle, E2F targets, and Wnt beta-catenin signaling. The G2/M checkpoint is a central control point in the cell cycle that prevents DNA-damaged cells from entering M phase. This regulatory mechanism allows for DNA repair, which is controlled by the RB-E2F complex that fine-tunes the timing and accuracy of cell cycle replication [31-33]. Simultaneously, the Wnt beta-catenin signaling pathway, known for its regulatory roles in embryonic development, cell proliferation, and differentiation, emerges as a significant player in the genesis and progression of LIHC [34, 35]. In light of these findings, it is plausible to propose that LRPPRC potentially promotes cell cycle progression and mitosis by modulating these intricate processes and pathways. This regulatory role may, in turn, contribute to the promotion of LIHC occurrence and proliferation. In conclusion, LRPPRC emerges as a potential oncogene and biomarker in LIHC, influencing immune infiltration, tumor-related biological processes, and cancer-associated signaling pathways. Despite these promising findings, our study acknowledges certain limitations, necessitating further exploration through additional fundamental experiments and a broader collection of clinical samples. These additional efforts are critical to unravel the direct functional mechanisms by which LRPPRC shapes the progression and prognosis of LIHC.

Conclusion

LRPPRC exhibited a significant upregulation in LIHC, and high expression of LRPPRC was correlated with poorer OS, DSS, and PFI in LIHC patients which showed a better diagnostic and prognostic ability. Therefore, LRPPRC is proposed as a dependable biomarker for both diagnosis and prognosis in LIHC, representing a promising therapeutic target.

Disclosure of conflict of interest

None.

Abbreviations

LRPPRC, Leucine rich pentatricopeptide repeat containing; TCGA, The Cancer Genome Atlas; GTEx, Genotype Tissue Expression; ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; DLBC, lymphoid neoplasm diffuse Large B-cell lymphoma; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LAML, acute myeloid leukemia; LGG, brain lower grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; TGCT, testicular germ cell tumors; THCA, thyroid carcinoma; THYM, thymoma; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma; UVM, uveal melanoma; OS, overall survival; DSS, disease specific survival; PFI, progress free interval; HR, Hazard ratio; KM, Kaplan-Meier; ROC, receiver operating characteristic; AUC, area under the curve; BMI, Body Mass Index; AFP, Alpha-fetoprotein; DEGs, Differential expressed

genes; CTLs, cytotoxic T cells; DCs, dendritic cell; pDCs, plasmacytoid dendritic cells; Th17, T helper cell 17; NK, Natural Killer; Tregs, regulatory T cells; iDC, immature dendritic cells; Tgd, gammadelta T cells; Tcms, central memory T cells; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; GSEA, Gene Set Enrichment Analyses; BP, biological process; CC, cellular components; MF, molecular function.

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