Research Article

The Role of RANBP3L in Pan-Cancer with its Significance in Hepatocellular Carcinoma

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Abstract

Background: RAN binding protein 3-like (RANBP3L), a member of the Ran-binding protein family, has been linked to various cellular functions, but the role in cancer remains underexplored. In this research we assessed the diagnosis and prognosis value about RANBP3L in pan-cancer, especially in liver hepatocellular carcinoma (LIHC).

Methods: We analyzed RANBP3L expression of 33 cancer types from TCGA data and assessed its relationship with overall survival (OS), disease-specific survival (DSS), and progression-free interval (PFI). We used TIMER2.0 and CIBERSORT to explore the correlation between RANBP3L expression and immune cells. we conducted immunohistochemistry, qRT-PCR, and western blotting by using tissue samples from LIHC patients to assess the RANBP3L's diagnostic and prognostic value of LIHC.

Results: In 18 different cancers, RANBP3L expression was found to be lower in tumor tissues compared to normal tissues, including LIHC. Lower RANBP3L expression was referred to shorter OS, DSS, and PFI in LIHC. ROC analysis and nomogram model based on RANBP3L expression demonstrated high predictive accuracy for patient diagnosis and survival. Moreover, immune infiltration analysis showed that RANBP3L related to various immune cells and impacted prognosis. Furthermore, analysis on LIHC patient tissues found that higher RANBP3L expression was related to better tumor-free survival and OS.

Conclusion: RANBP3L plays a crucial role in LIHC. Not only does its expression level correlate with patient survival, but it also plays an important role in immune modulation. RANBP3L presents a promising candidate for future therapeutic strategies and biomarker for LIHC.

Keywords: RANBP3L; liver hepatocellular carcinoma; Biomarkers; TCGA

Introduction

Cancer is an important global health challenge, with rising incidence and mortality rates each year [1]. Among those prevalent cancers, liver hepatocellular carcinoma (LIHC) is particularly associated with high mortality rates worldwide [2]. Despite ongoing advancements in cancer diagnosis and treatment, the five-year overall survival (OS) rates for many cancers remain low, highlighting the need for more effective therapeutic strategies [3]. While substantial progress has been made in utilizing cancer biomarkers for diagnosis and prognosis in certain cancers [4], the lack of effective biomarkers for liver and other cancers remains a significant barrier. Given the need for innovative diagnostic and therapeutic methods to improve patient outcomes and offer new avenues for treatment [5].

RAN binding protein 3 like (RANBP3L) is from the family of Ran-binding proteins, which featured the presence of the Ran-binding domain [6]. Ran (Ras-related nuclear protein) is a small GTPase from the Ras superfamily, which could regulate nucleocytoplasmic transport of molecules and control cell cycle progression [7]. It has been reported that RANBP3L could modulate bone morphogenetic

protein signaling and the mesenchymal stem cells differentiation [8]. There are little researches about RANBP3L in tumors, only one report shows that the immune cell enrichment score of RANBP3L combined with other seven genes can predict outcomes in endometrial cancer patients [9].

This research was to explore the RANBP3L expression and function in multiple cancers by database, especially in LIHC. Then we assessed the relationship between the RANBP3L expression and immune cells infiltration. Finally we utilized LIHC samples to investigate the RANBP3L expression and prognostic value.

Methods

Database-driven Analysis

The expression of RANBP3L in the 33 cancers (Table 1) were obtained from the Cancer Genome Atlas (TCGA) database (https://portal.gdc.cancer.gov/). The clinical data were come from the TCGA database.

Kaplan-Meier analysis with log-rank test was used to analyze prognosis included OS (overall survival), DSS (disease-specific survival) and PFI (progression-free interval).

For cancers the RANBP3L expression was linked to the prognosis, the association between clinical characteristic and RANBP3L expression was explored. We used Spearman rank test and Wilcoxon rank-sum test for clinical characteristic analysis. the ROC analysis was conducted applying the "pROC" package. The nomogram model of RANBP3L in LIHC was established according to the RANBP3L expression and the clinical stage to predict the OS. The calibration curve was used to evaluate the predictive accuracy of the nomograms for 1-year, 3-year, and 5-year survival outcomes.

We used TIMER2.0 (Tumor Immune Estimation Resource 2.0, http://timer.cistrome.org/) [10] to explore the correlation between RANBP3L expression and the immune cells infiltration of various tumors in TCGA. Multiple algorithms, including TIMER2.0 and CIBERSORT (https://cibersortx.stanford.edu/) [11], were applied for the immune cell estimation. Additionally, we explored the correlation of immune cell infiltration and OS of RANBP3L expression across different cancer types.

We draw the protein-protein interaction (PPI) network according to the STRING data (https://string-db.org/)., with the interaction threshold of 0.4. The Gene Ontology (GO) analysis containing the biological pathways (BP), the molecular functions (MF) and the cellular components (CC). The Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis was also performed meanwhile. The cluster Profiler R package and the DESeq R package were used for GESA in this study.

Patients and Samples Collection

Tissue microarrays were constructed using 70 LIHC tissue samples which were got from patients that did hepatectomy at the Hangzhou First People's Hospital. Another 6 paired of HCC tissues and the para-carcinoma tissues used for western blot and RT-qPCR were got from patients who did hepatectomy at Hangzhou First People's Hospital. Ethical Committee approved the research, and each patient signed the informed consent form. This research was carried out following the ethical principles outlined in the Declaration of Helsinki. The diagnosis of HCC was confirmed by pathological examination for every patient. The para-carcinoma tissue was defined as tissue at least 1cm away from the margin of the carcinoma tissue.

Quantitative Real-time Polymerase Chain Reaction (qRT-PCR)

The RNA extraction specific experimental steps could refer to this literature [12]. GAPDH was applied as internal standard. The following primer sequences were used: RANBP3L: Forward Primer (5′-3′), AAATCTGTCATTGCTCAACCCA and Reverse Primer (5′-3), GCTGCTTCATACAGGGTGTCTT; GAPDH: Forward Primer (5′-3′), GAACGGGAAGCTCACTGG and Reverse Primer (5′-3′), GCCTGCTTCACCACCTTCT. The results were calculated by the 2-ΔΔCt method, with each sample being tested in triplicate.

Western Blot (WB)

The extraction of protein and the specific experimental steps could refer to this article [13]. TTC39A Polyclonal antibody (No. 17875-1-AP) was purchased from Proteintech Group, Inc. GAPDH (No. 60004-1-Ig) which was used as internal standard, was also purchased from Proteintech Group, Inc. Immunodetection was performed by an enhanced chemiluminescence (ECL) detection kit. Then the grayscale values were calculated by the Image J software.

Immunohistochemistry

Immunohistochemistry was performed with the tissue microarrays, make by the 70 pairs of LIHC tissues and the para-carcinoma tissues. The specific experimental steps could refer to this literature [13]. TTC39A Polyclonal antibody (No.21323-1-AP) was purchased from Proteintech Group, Inc. The H-Score was used to estimate the results of immunohistochemistry, using the Visiopharm software. The H-score ranged from 0 to 300, the higher values means stronger overall positive intensity [14].
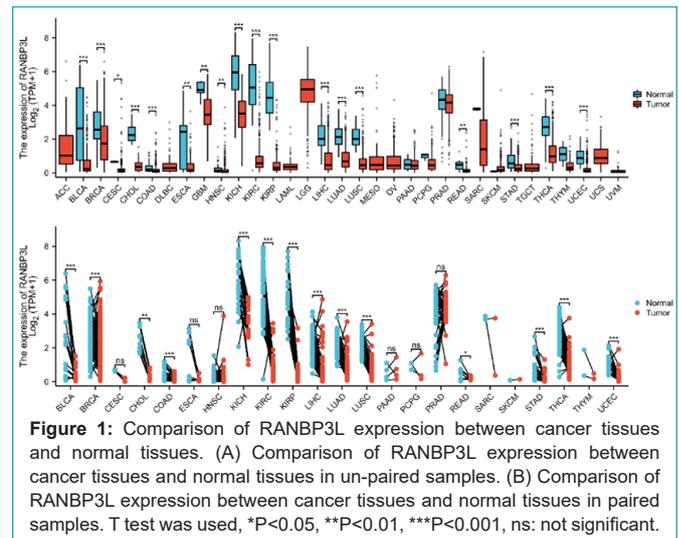
Results

Comparison of RANBP3L Expression between Normal Tissues and Cancer Tissues

RANBP3L expression for un-paired samples were displayed in 33 cancers according to the TCGA database. Among these 33 cancers, RANBP3L expression was reduced in tumor tissues compared to normal tissues in 18 cancers, including LIHC, KIRC, LUAD and so on (Figure 1A). Similarly, the expression of RANBP3L for paired samples were also found in 23 cancers according to the TCGA database. Among these 23 cancers, RANBP3L expression was reduced in tumor tissues compared to normal tissues in 14 cancers, including LIHC, KIRC, LUAD and so on (Figure 1B).

RANBP3L Expression was Correlated with the Patients' Prognosis

The RANBP3L expression was linked to patients' OS of with LIHC (Figure 2A). For LIHC patients, the lower expression of RANBP3L in cancer tissues indicated worse OS, respectively (Figure 2B).

Figure 1: Comparison of RANBP3L expression between cancer tissues and normal tissues. (A) Comparison of RANBP3L expression between cancer tissues and normal tissues in un-paired samples. (B) Comparison of RANBP3L expression between cancer tissues and normal tissues in paired samples. T test was used, *P<0.05, **P<0.01, ***P<0.001, ns: not significant.

A.

Characteristics	Total(N)	HR(95% CI) Univariate analysis	P value Univariate analysis
ACC	79	1.136 (0.540 - 2.392)	0.736
BCLA	411	1.266 (0.944 - 1.699)	0.115
BRCA	1086	1.128 (0.818 - 1.554)	0.462
CFSC	306	1.089 (0.685 - 1.732)	0.719
CHOL	35	0.869 (0.343 - 2.205)	0.768
COAD	477	1.245 (0.843 - 1.840)	0.271
DLBC	48	0.683 (0.163 - 2.865)	0.603
ESAD	81	0.779 (0.415 - 1.465)	0.439
RSCC	82	0.674 (0.303 - 1.496)	0.332
GBM	168	0.840 (0.598 - 1.180)	0.315
HNSC	503	0.998 (0.765 - 1.303)	0.99
KICH	64	1.924 (0.480 - 7.712)	0.356
KIRC	541	0.768 (0.569 - 1.037)	0.085
KIRP	290	0.876 (0.483 - 1.587)	0.661
LGG	530	0.871 (0.622 - 1.222)	0.425
LIHC	373	0.643 (0.454 - 0.912)	0.013
LUAD	530	0.793 (0.595 - 1.057)	0.114
LUSC	496	1.065 (0.812 - 1.395)	0.65
MESO	86	1.290 (0.806 - 2.063)	0.288
OSCC	329	1.091 (0.791 - 1.503)	0.596
OV	379	0.994 (0.769 - 1.286)	0.964
PAAD	179	1.230 (0.818 - 1.849)	0.32
PCPG	184	2.773 (0.559 - 13.768)	0.212
PRAD	501	1.143 (0.328 - 3.983)	0.834
READ	166	0.897 (0.406 - 1.978)	0.787
SKCM	457	0.830 (0.635 - 1.085)	0.172
SRAC	263	0.923 (0.622 - 1.369)	0.689
STAD	370	1.359 (0.977 - 1.890)	0.069
TGCT	139	0.898 (0.665 - 1.603)	0.999
THYM	119	1.060 (0.280 - 4.013)	0.932
UCEC	553	1.353 (0.901 - 2.033)	0.145
UCS	57	0.779 (0.395 - 1.537)	0.471
UVM	80	0.846 (0.363 - 1.972)	0.699

B.

RANBP3L
Low
High

Overall Survival
HR = 0.64 (0.45 - 0.91)
P = 0.013

Figure 2: The relationship between the expressi[...] respectively. (A) a forest map, which showed the relationship between the expression of RANBP3L and the OS of patients, for 33 cancers, respectively. (B) the expression of RANBP3L was significantly associated with the OS of patients with LIHC. P<0.05 was considered significant.

The RANBP3L expression was correlated with patients' DSS with KIRC, LIHC, LUAD, STAD and UCEC (Figure 3A). For KIRC, LIHC and LUAD, lower RANBP3L expression in cancer tissues was associated with poorer DSS (Figure 3B-D). For STAD and UCEC, the higher RANBP3L expression in cancer tissues indicated worse DSS, respectively (Figure 3E, F).

The RANBP3L expression was correlated with patients' PFI with KIRC, STAD and UCEC (Figure 4A). For KIRC, the lower RANBP3L expression in cancer tissues mean worse PFI (Figure 4B). For STAD and UCEC, the higher RANBP3L expression in cancer tissues mean worse PFI (Figure 4C, D).

RANBP3L Expression was Correlated with Patients' Clinical Features

For cancers that the RANBP3L expression was related to patients' prognosis, the connection between RANBP3L expression and patients' clinical profiles was further analyzed, according to the TCGA database (Figure 5). In KIRC, the RANBP3L expression was related to pathologic M stage and histologic grade. The RANBP3L expression was significantly related to pathologic M stage, tumor status, AFP (ng/ml) and histologic grade in LIHC. In LUAD, the RANBP3L expression was significantly linked with smoker. In STAD, the RANBP3L expression was significantly related to pathological grade and pathologic T stage. In UCEC, the RANBP3L expression was significantly linked with histological type and clinical stage.

The ROC Curve and Nomogram Model According to the Expression of RANBP3L in LIHC

Among the 33 cancers, the RANBP3L expression was linked to the LIHC patients' OS. Then, ROC analysis and nomogram model were established from the expression of RANBP3L in LIHC. The ROC analysis showed RANBP3L could be a diagnostic indicator for LIHC, with an Area Under Curve about 0.859 (Figure 6A). The nomogram model demonstrated high precision in estimating the 1-year, 3-year, and 5-year survival probabilities for LIHC patients, as evidenced by the well-calibrated survival prediction curves for these time points. (Figure 6B, C).
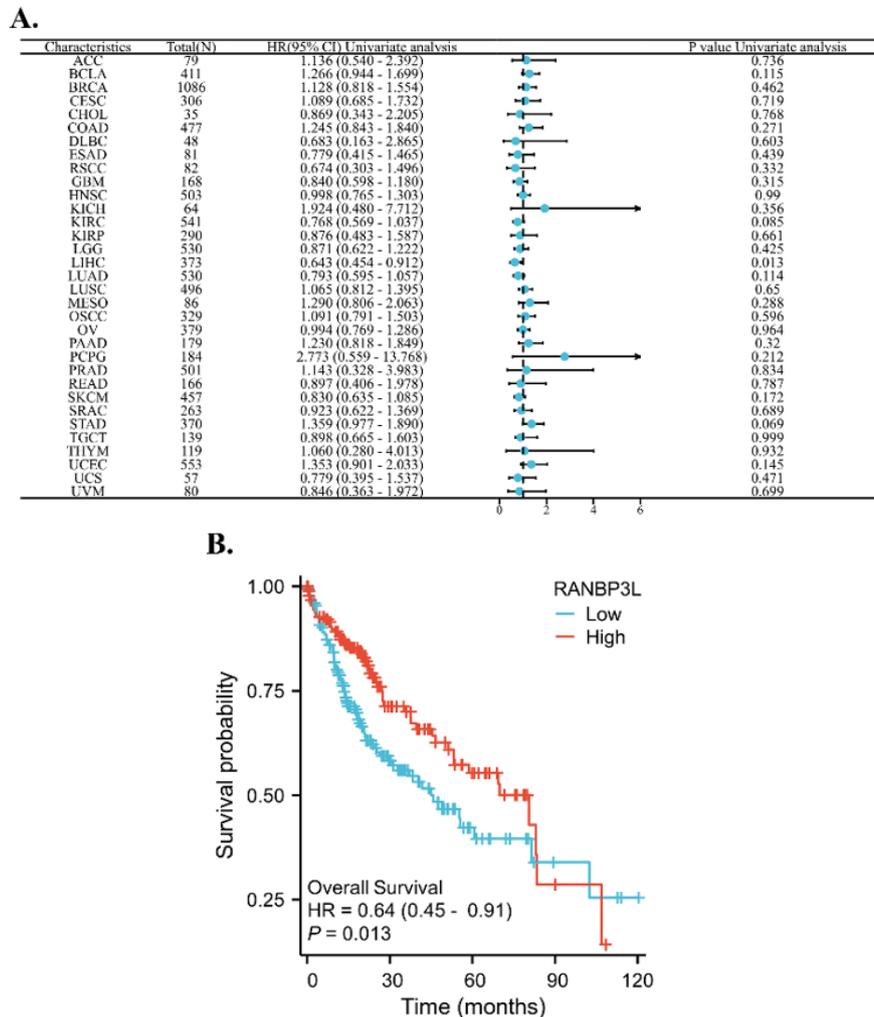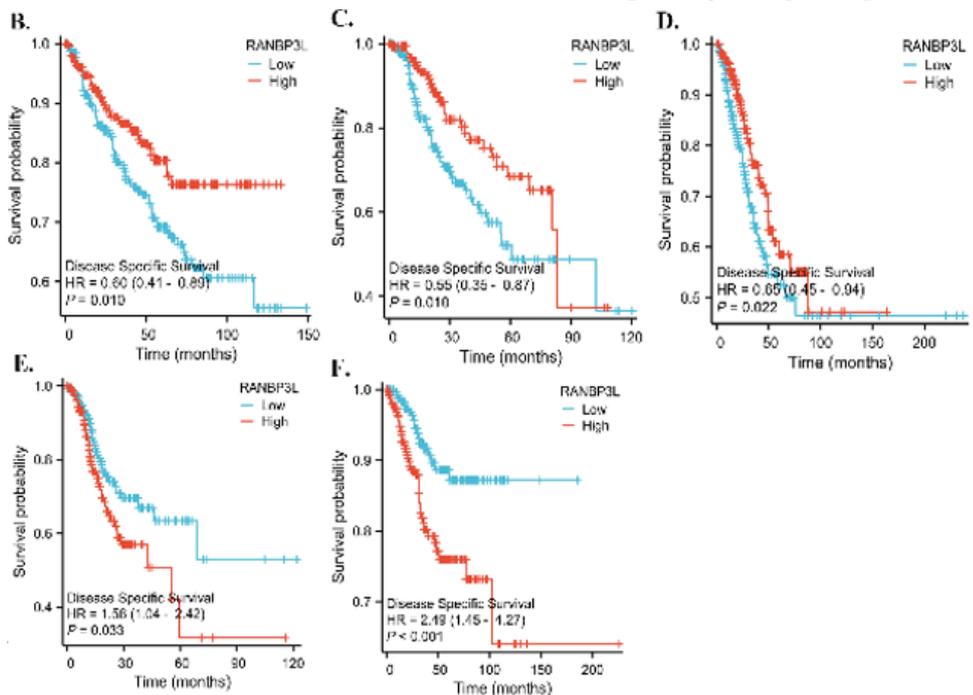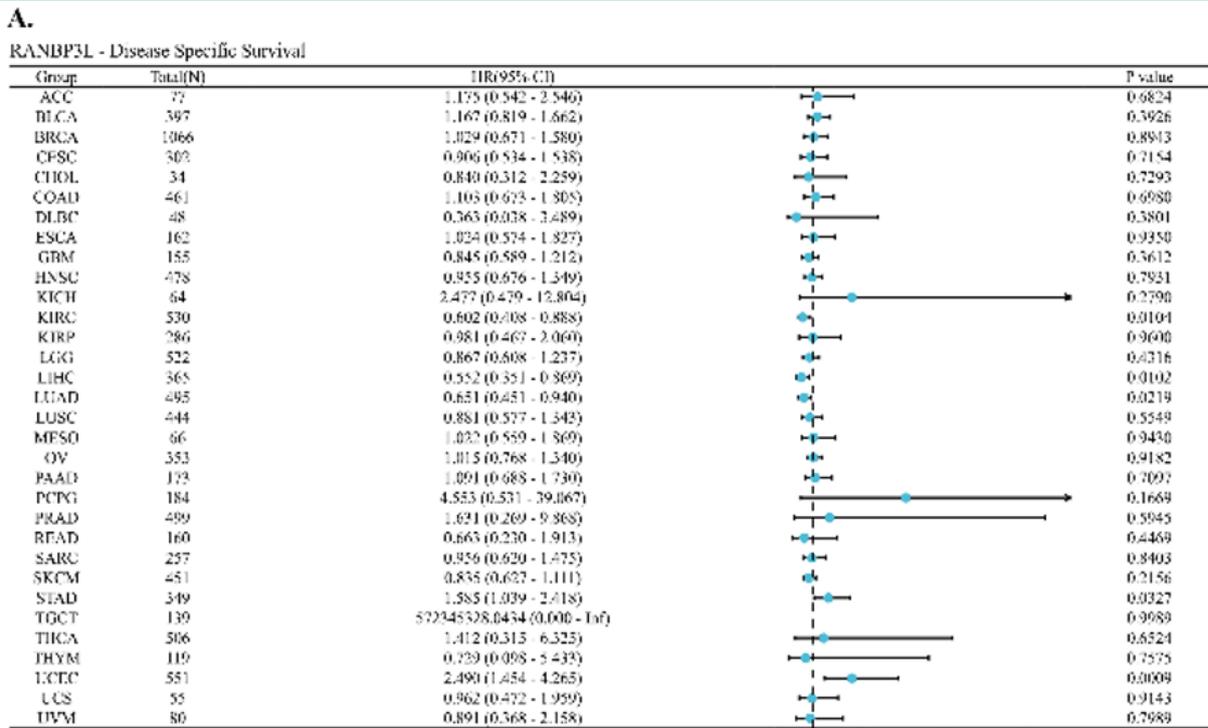
Figure 3: The relationship between the expression of RANBP3L and the DSS of patients with 33 cancers, respectively. (A) a forest map, which showed the relationship between the expression of RANBP3L and the DSS of patients, for 33 cancers, respectively. (B-F) the expression of RANBP3L was significantly associated with the DSS of patients with KIRC, LIHC, LUAD, STAD and UCEC, respectively. P<0.05 was considered significant.

The RANBP3L Expression was Associated with the Immune Cells Infiltration and could Affect the LIHC Patients' OS Combined with the Immune Infiltration Score

CIBERSORT analysis showed that in some of cancer types, a relationship was observed between the levels of immune cell infiltration and RANBP3L expression (figure 7). RANBP3L expression had a relation with infiltrating B cells, CD8 T cells, Macrophages, Neutrophils, NK cells, pDC, T cells, Tcm, TFH, Th17 cells, and Th2 cells in LIHC. Neutrophils, macrophage, macrophage/monocyte and common lymphoid progenitor infiltration was related to OS in LIHC.

The Potential Functions of RANBP3L in LIHC

The top 100 genes associated with the RANBP3L gene were

A.

| Characteristics	Total(N)	HR(95% CI) Univariate analysis	P value Univariate analysis	X5
ACC	79	0.738 (0.398 - 1.370)	0.336	
BLCA	412	1.077 (0.803 - 1.444)	0.62	
BRCA	1086	0.955 (0.689 - 1.322)	0.781	
CESC	306	1.124 (0.707 - 1.787)	0.621	
CHOL	35	0.650 (0.264 - 1.599)	0.348	
COAD	477	1.135 (0.801 - 1.609)	0.475	
DLBC	48	0.631 (0.184 - 2.159)	0.463	
ESAD	81	0.877 (0.480 - 1.602)	0.67	
ESCC	82	1.016 (0.532 - 1.942)	0.961	
GBM	168	0.984 (0.701 - 1.380)	0.923	
HNSC	503	0.909 (0.686 - 1.206)	0.51	
KICH	64	1.829 (0.533 - 6.279)	0.337	
KIRC	539	0.680 (0.496 - 0.932)	0.017	
KIRP	289	0.890 (0.529 - 1.495)	0.659	
LGG	530	0.924 (0.704 - 1.212)	0.567	
LIHC	373	0.851 (0.637 - 1.138)	0.277	
LUAD	530	0.903 (0.693 - 1.177)	0.45	
LUSC	497	0.911 (0.659 - 1.260)	0.574	
MESO	84	1.090 (0.649 - 1.832)	0.744	
OSCC	329	0.929 (0.662 - 1.302)	0.669	
OV	379	1.005 (0.794 - 1.273)	0.965	
PAAD	179	0.712 (0.480 - 1.055)	0.09	
PCPG	184	1.088 (0.470 - 2.520)	0.844	
PRAD	501	1.314 (0.875 - 1.973)	0.189	
READ	166	0.996 (0.514 - 1.930)	0.99	
SKCM	458	0.841 (0.673 - 1.052)	0.13	
SRAC	263	1.272 (0.913 - 1.772)	0.155	
STAD	372	1.470 (1.028 - 2.101)	0.035	
TGCT	139	1.144 (0.612 - 2.135)	0.674	
THYM	119	1.016 (0.431 - 2.400)	0.97	
UCEC	553	1.621 (1.139 - 2.308)	0.007	
UCS	57	0.878 (0.458 - 1.681)	0.694	
UVM	79	1.263 (0.591 - 2.697)	0.547	
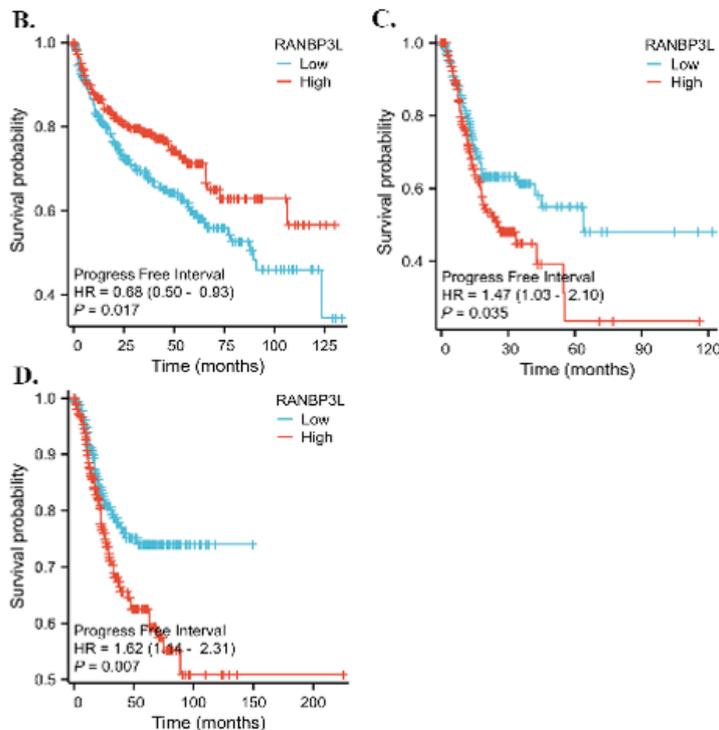
Figure 4: The relationship between the expression of RANBP3L and the PFI of patients with 33 cancers, respectively. (A) a forest map, which showed the relationship between the expression of RANBP3L and the PFI of patients, for 33 cancers, respectively. (B-D), the expression of RANBP3L was significantly associated with the PFI of patients with KIRC, STAD and UCEC, respectively. P<0.05 was considered significant.

presented as a PPI network in Figure 8A. According to the 100 genes, GO enrichment analysis was conducted including BP analysis, CC analysis and MF analysis (Figure 8B). The BP analysis indicated that RANBP3L might play roles in the process of cellular hormone metabolic, isoprenoid metabolic, terpenoid metabolic and retinoic acid metabolic. The CC analysis indicated that RANBP3L might play

roles in microbody and peroxisome. The MF analysis suggested that RANBP3L could be involved in functions such as oxidoreductase activity (utilizing NAD or NADP as acceptors), oxidoreductase activity (targeting CH-OH group of donors), CoA-ligase activity and NAD binding. According to the 100 genes, KEGG pathway analysis was also conducted. The results indicated that RANBP3L might be involved in
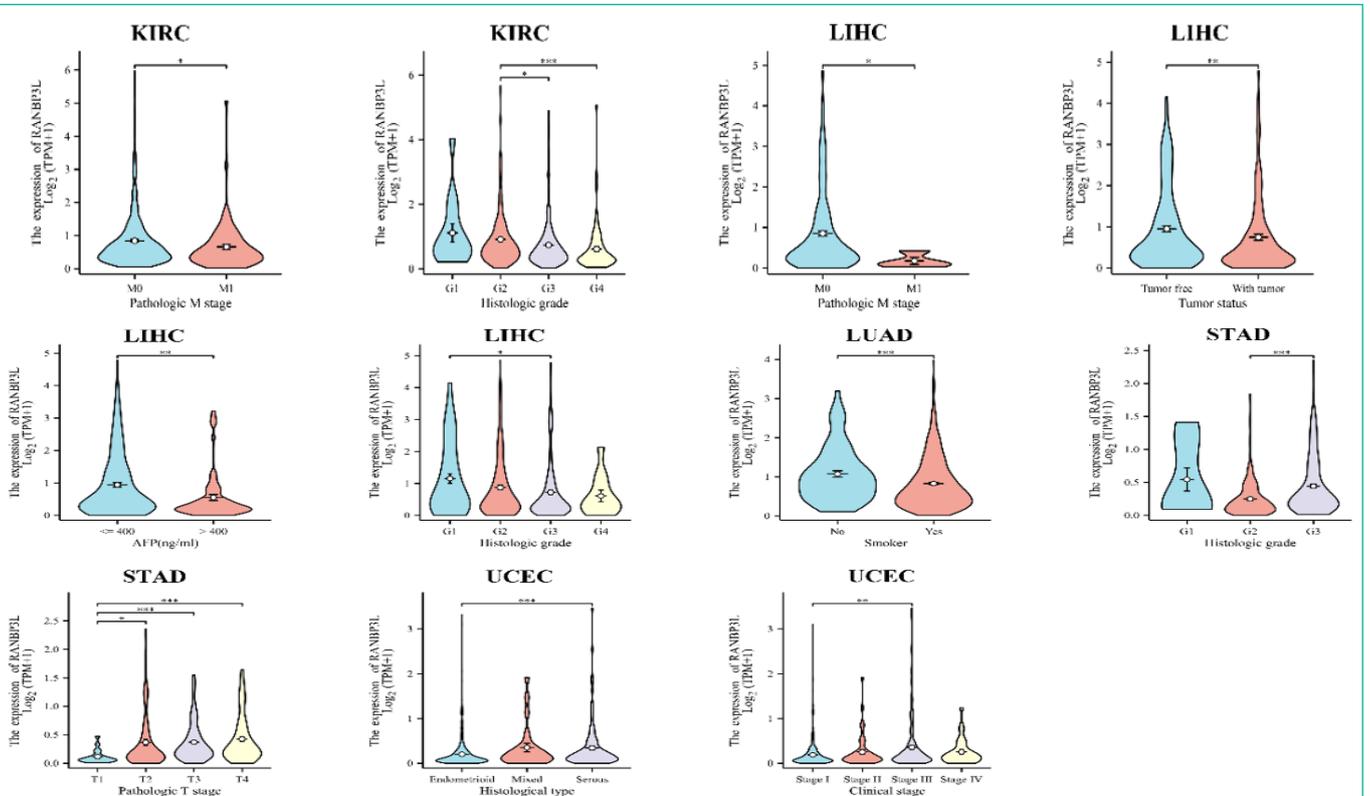
Figure 5: The expression of RANBP3L was associated with some clinical characteristics for patients with KIRC, LIHC, LUAD, STAD and UCEC, respectively. *P<0.05, **P<0.01, ***P<0.001.
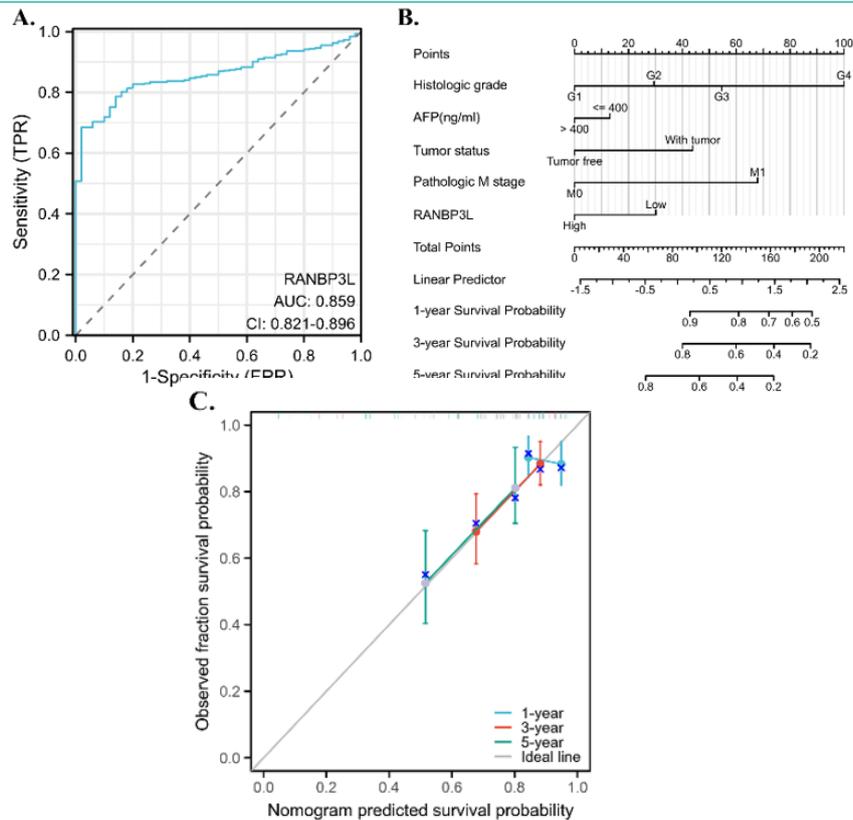

Figure 6: Diagnostic and prognostic effect of RANBP3L in LIHC. (A) RANBP3L could be a good diagnostic indicator for LIHC patients. (B) and (C) RANBP3L could accurately predict the 1-year, 3-year and 5-year survival probability for LIHC patients.
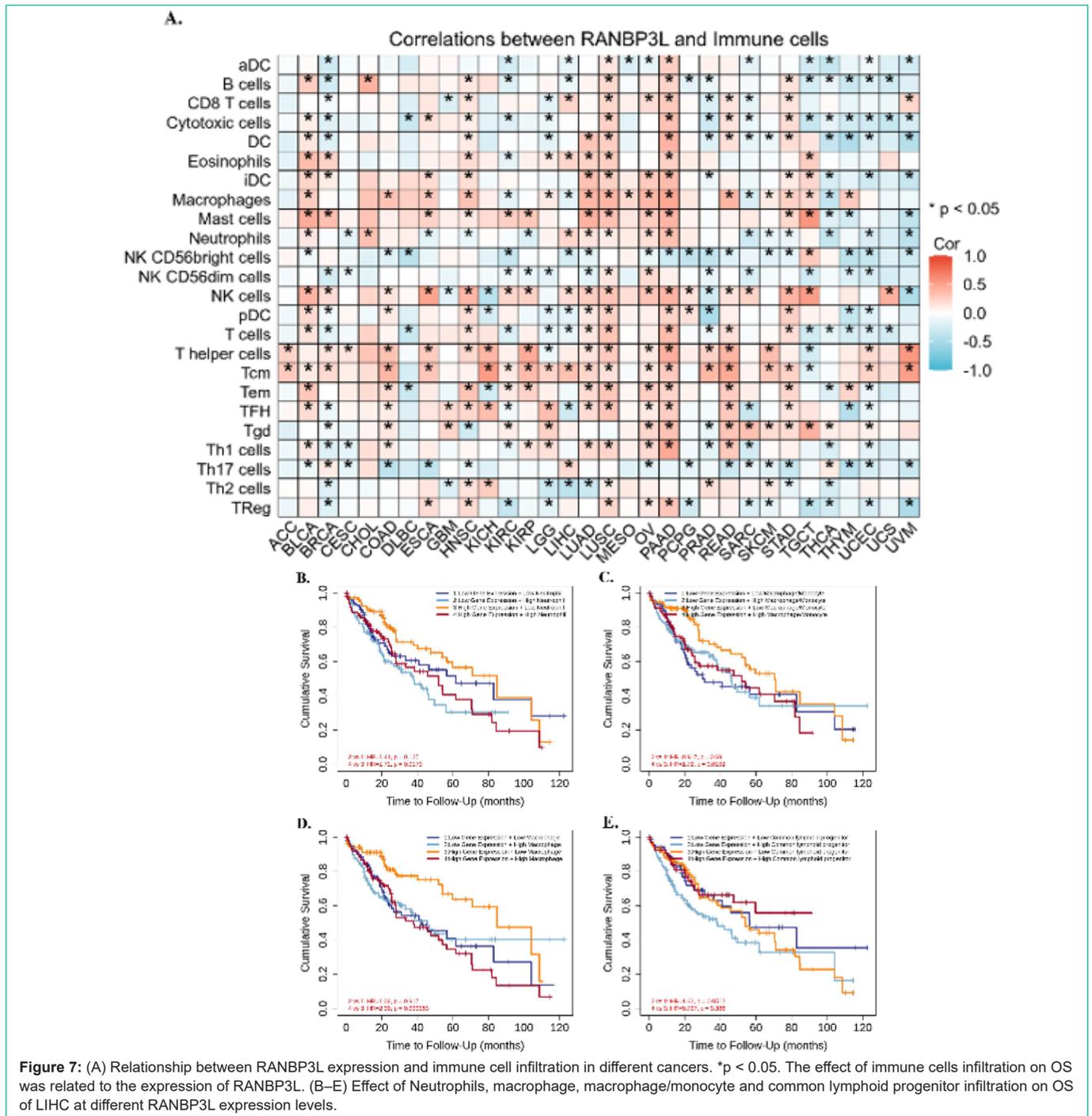
Figure 7: (A) Relationship between RANBP3L expression and immune cell infiltration in different cancers. *p < 0.05. The effect of immune cells infiltration on OS was related to the expression of RANBP3L. (B–E) Effect of Neutrophils, macrophage, macrophage/monocyte and common lymphoid progenitor infiltration on OS of LIHC at different RANBP3L expression levels.

the process of fatty acid degradation, metabolism of xenobiotics by cytochrome P450, drug metabolism - cytochrome P450 and retinol metabolism(Figure 8C). Furthermore, the potential functions of RANBP3L in LIHC were explored via the GSEA. The result showed that RANBP3L might paly roles in ' Fatty Acid Metabolism ' and ' Biological Oxidations ' (Figure 8D).

The Expression and Survival of RANBP3L in LIHC Patients

Immunohistochemistry was conducted in 70 LIHC tissues of tissue microarray. We use 235 as the cutoff value of H-Score

to distinguish high and low expression of RANBP3L. RANBP3L expression is elevated in para-carcinoma tissues in comparison with LIHC tissues (Figure 9A). Higher RANBP3L expression in LIHC tissues indicated better OS and TFS for LIHC patients (Figure 9B and 9C). Furthermore, the mRNA and protein level of para-carcinoma tissues is higher than LIHC tissues in another 6 LIHC patients (Figure 10).

Discussion

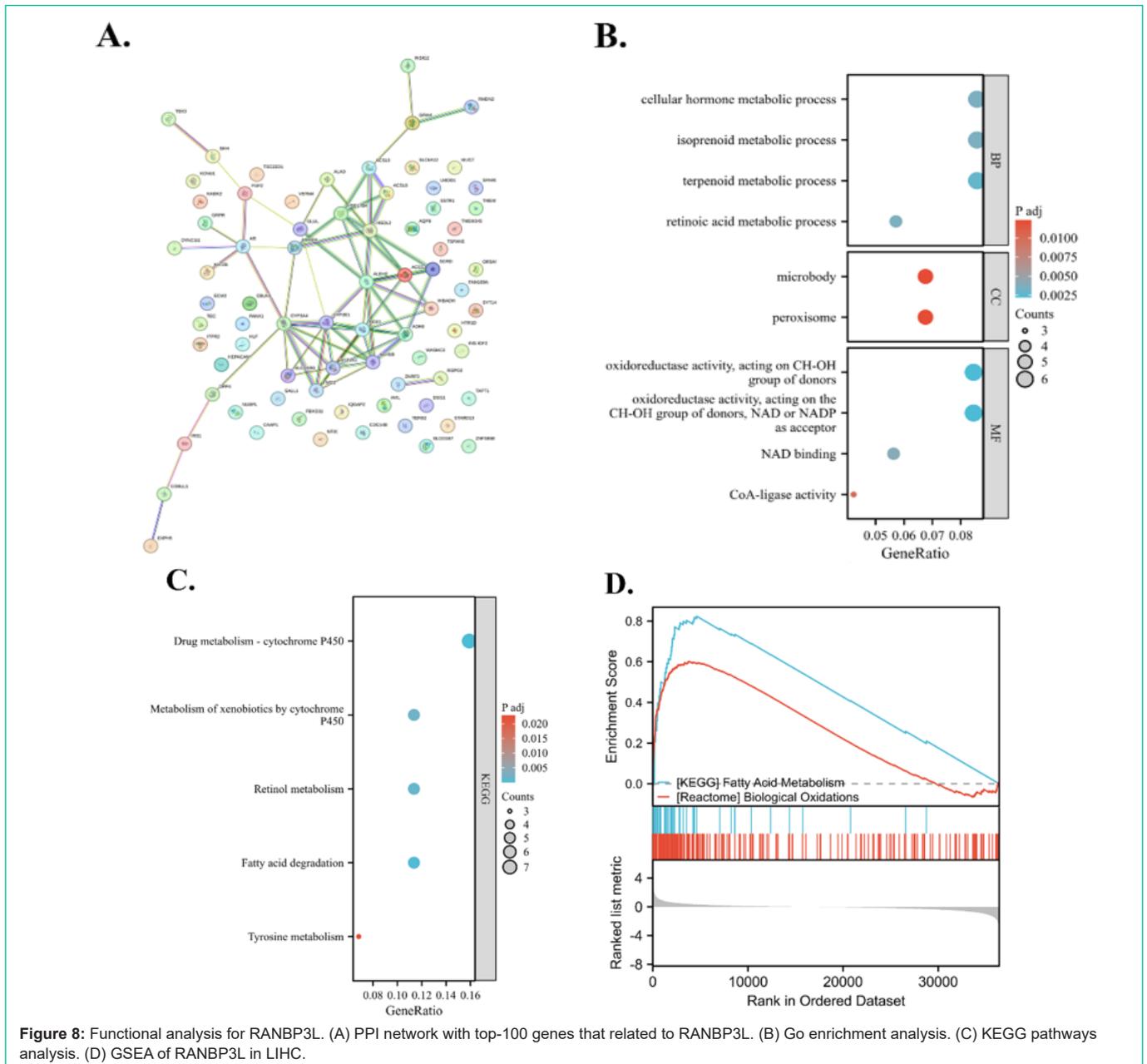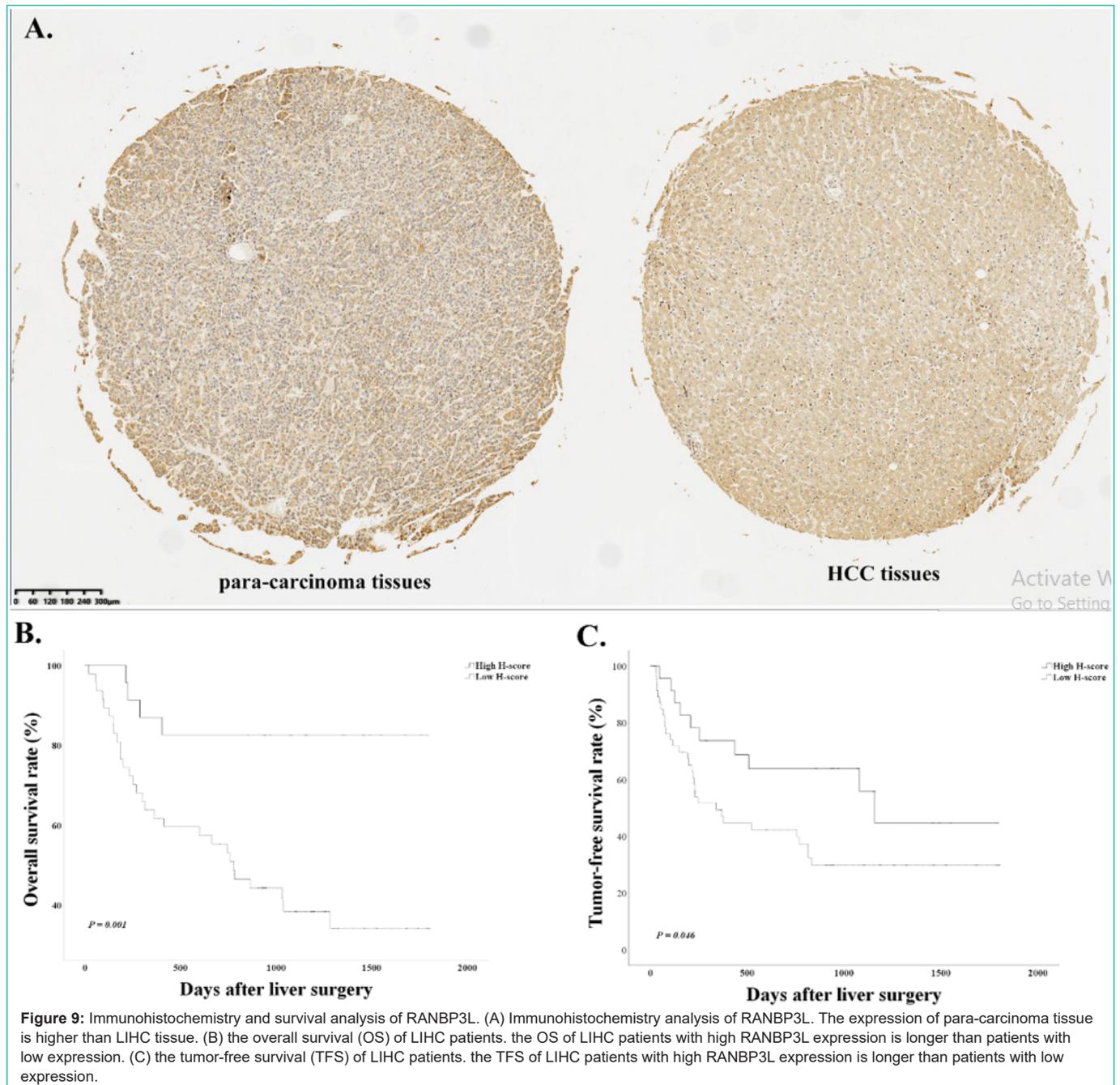LIHC is still a leading cancer-related mortality globally, and the

Figure 8: Functional analysis for RANBP3L. (A) PPI network with top-100 genes that related to RANBP3L. (B) Go enrichment analysis. (C) KEGG pathways analysis. (D) GSEA of RANBP3L in LIHC.

development of effective biomarkers for diagnosis and prognosis should be an area of intense research [3]. We analyzed the expression trends and prognostic relevance of RANBP3L across multiple cancers, particularly focus on LIHC to found the role of RANBP3L in the LIHC progress.

We got the RANBP3L is corrected with LIHC clinical characteristics such as pathologic M stage, tumor status, AFP (ng/ml) and histologic grade. Further research found the foundation of a prognostic model incorporating RANBP3L expression and clinical features demonstrated its predictive accuracy for survival outcomes in LIHC. The nomogram with LIHC clinical characteristics provides a promising tool for individualized prognosis prediction, and this reduction correlates with poor OS and TFS in LIHC patients. we found RANBP3L is linked to important biological pathway such as

oxidoreductase activity and attend cytochrome metabolism which may regulated by phosphatidylinositol 3 kinase (PI3K)/Akt, EMT or TGF-β signaling pathways [15]. Furthermore, this study is the first research to explore the RANBP3L protein and mRNA in clinical LIHC samples. The result showed that RANBP3L might function as a candidate tumor suppressor and the function of tumor suppressor may be achieved through regulating BMP-driven lineage-specific differentiation of mesenchymal stem cells [8].

Immunotherapy of LIHC is attracted more and more attention and become very important in the LIHC treatment in recent years [16,17]. In this research, we found the link between RANBP3L and immune cell infiltration. Immune environment signature parameters can assess prognosis in some kind of cancer types [18], including LIHC [19]. These parameters can be used as prognostic elements

Figure 9: Immunohistochemistry and survival analysis of RANBP3L. (A) Immunohistochemistry analysis of RANBP3L. The expression of para-carcinoma tissue is higher than LIHC tissue. (B) the overall survival (OS) of LIHC patients. the OS of LIHC patients with high RANBP3L expression is longer than patients with low expression. (C) the tumor-free survival (TFS) of LIHC patients. the TFS of LIHC patients with high RANBP3L expression is longer than patients with low expression.

after immunotherapy [20]. The infiltration of immune cells has been shown to significantly affect LIHC prognosis, assuming its possible regulating LIHC development by the tumor microenvironment remodeling [21].

However, our research has several limitations. Firstly, this study mainly depends on retrospective cohorts and database, and further validation is required. Secondly, the mechanistic pathways about RANBP3L influences immune cell infiltration and LIHC progression still unclear and need further investigation through more basic experiment.

Conclusion

The RANBP3L expression was lower in multiple cancer tissues relative to the normal tissues and significantly associated the LIHC patients' OS according to the TCGA database. The ROC curve and nomogram model according to the expression of RANBP3L in LIHC could be a good diagnostic indicator. Analysis of LIHC samples revealed that patients exhibiting high RANBP3L expression showed a better prognosis compared to those with low expression. This research found RANBP3L may provide a suspected therapeutic target and predictive biomarker of LIHC.
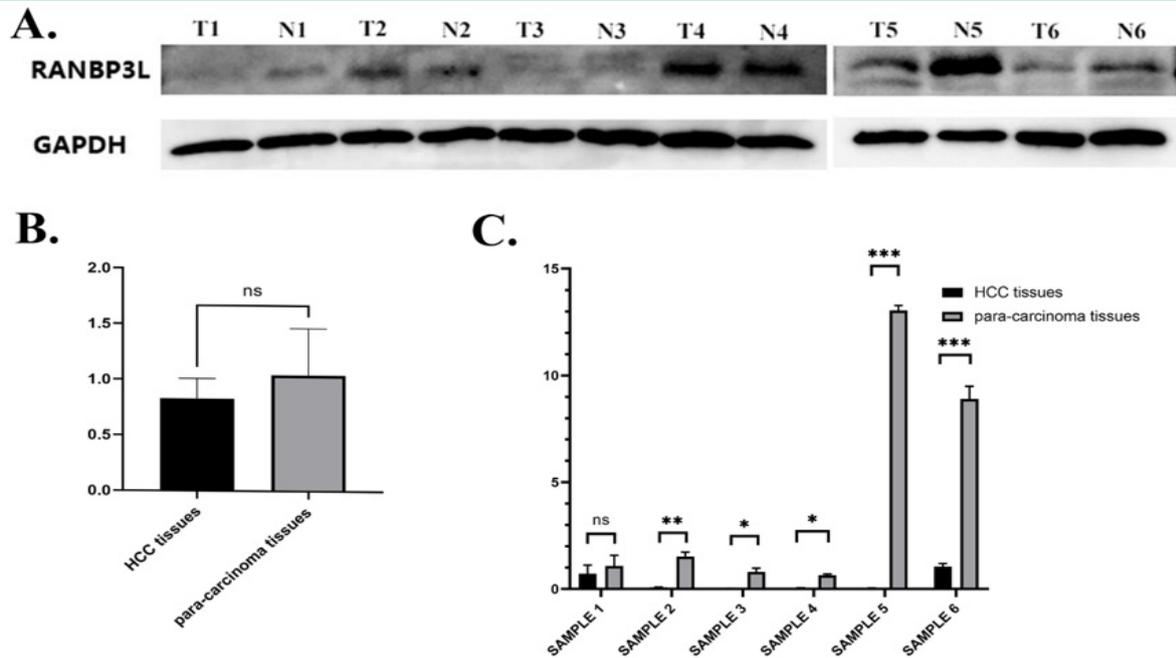
Figure 10: The protein and mRNA expression of RANBP3L in LIHC patients. (A) the protein expression of RANBP3L in LIHC patients, the expression of para-carcinoma tissue is higher than LIHC tissue. (B) Gray value of western blot, the expression of para-carcinoma tissue is higher than LIHC tissue without significance. (C) the mRNA expression of RANBP3L in LIHC patients. *P<0.05, **P<0.01, ***P<0.001.

Declarations

Conflicts of Interest

The authors stated that they had no competing interests.

Authors' contributions

The main manuscript text was written and figures were prepared by Chao Wang. This research was designed and the article was revised by Jie Li. All authors reviewed the manuscript.

Funding

Availability of Data and Materials

The data utilized are publicly accessible and can be found in the TCGA and UCSC databases.

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