

Research Article

Bioinformatics Analysis and Identification of the Expression and Mechanism of Immune-Related Gene MAPT in Hepatocellular Carcinoma

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Abstract

MAPT (Microtubule Associated Protein Tau) is a Protein Coding gene. Aberrant expression of MAPT has been reported to be associated with several types of tumors, such as gastric, breast, and colorectal cancer, and so on. However, the role of MAPT in HCC (Hepatic carcinoma) is still poorly understood. In our research, MAPT-related data mining and analyzing were used publicly-available data from TCGA, GEO, Oncomine, and HPA databases. The survival curve was shown and analyzed by using Kaplan Meier Plotter. Gene Set Enrichment Analysis

(GSEA), TIMER, STRING, and R package were used to explore the function and potential mechanism of MAPT in HCC. The results show that MAPT is overexpressed in HCC samples and is correlated with worse prognosis of patients with HCC. Bioinformatics analysis showed that MAPT contributed to the development of tumors through a variety of mechanisms. In conclusion, the Up-regulation of MAPT was significantly linked to poor prognosis in HCC patients, and it could be a new therapeutic target for HCC therapy.

Keywords: MAPT; Hepatocellular carcinoma; Prognosis; Bioinformatics analysis

1. Introduction

Hepatocellular carcinoma (HCC) is the most common malignancy with a high mortality rate in many parts of the world [1]. During the last few decades, significant advances have been achieved in understanding the epidemiology, risk factors, and molecular mechanisms in HCC [2]. Nevertheless, the annual mortality rate associated with HCC has increased substantially over the past two decades [3]. Determining accurate prognostic biomarkers and revealing therapeutic targets for HCC is therefore urgent. The microtubule-associated protein tau (MAPT) gene is located on chromosome 17 (17q21) and encodes for the protein Tau [4]. The MAPT gene is of central importance for several neurodegenerative diseases [5]. Interestingly, growing numbers of studies in recent years have been conducted on the function of MAPT in tumors; its expression and role in different tumors have been found to be changed. Previous research demonstrated that higher serum levels of MAPT were independently related to poor prognosis in patients with metastatic breast cancer [6]. Conversely, initial analyses, reported by Saif Zaman et al., suggested that a higher expression of MAPT associated with better overall survival in neuroblastoma [7].

However, MAPT in HCC has been rarely discussed. Zhang developed and validated a prognostic nomogram to predict the overall survival of HCC patients, in which MAPT acts as a significant variable [8]. Bioinformatics analysis by Qi revealed that MAPT serves as an upstream regulator of AMELY in HCC [9]. Despite this, the expression level, clinicopathological significance, and the

biological functions and associated mechanisms of MAPT in HCC had not reported to date. In this study, GEO, Oncomine, HPA, and TCGA databases were used to clarify the potential connection between the expression of MAPT and prognosis of HCC patients, as well as the association between MAPT and clinical parameters. Furthermore, the correlation between the expression of MAPT and prognosis of HCC patients was performed by using survival analysis based on Kaplan Meier Plotter. Finally, initial studies of the mechanisms of MAPT in HCC were carried out by a series of online databases and bioinformatics software packages, hoping to provide useful insights into the current research in HCC.

2. Methods

2.1 Data resource and description

Gene expression data (HTSeq-counts) of 424 HCC samples, including 374 primary tumors and 50 solid tissue normal samples, were downloaded from TCGA (<https://cancergenome.nih.gov/>). Gene expression analysis was performed by R(v3.6.2) using the limma [10] packages to look for the differentially expressed of MAPT between tumor and non-tumor tissue samples. A meta-analysis of MAPT expression in 5 analyses was shown by using Oncomine (<https://www.oncomine.org>) [11]. Three expression microarray series GSE25097, GSE45436, GSE55092, including HCC tumor and non-tumor tissue samples were obtained from the Gene Expression Omnibus dataset (GEO, <https://www.ncbi.nlm.nih.gov/geo/>). The Human Protein Atlas database (HPA, <https://www.proteinatlas.org/>) [12] was used to identify the difference of MAPT protein expression between HCC tissues and adjacent normal samples. A total of 2498 immune-related genes were downloaded from the ImmPort database (<http://www.immport.org/>), and 500 most differential

survival genes in HCC were obtained from Gene Expression Profiling Interactive Analysis (GEPIA) online database (<http://gepia.cancer-pku.cn/>) [13]. Additionally, survival curves of MAPT in HCC patients in different subgroups were constructed by using the Kaplan Meier plotter (<http://kmplot.com/analysis/>) [14].

2.2 Gene set enrichment analysis

Gene expression data were divided into a high and a low group based on the median level of MAPT expression to elucidate the significant function and pathway of MAPT in HCC prognosis by using GSEA software (<https://software.broadinstitute.org/gsea/>) [15]. A function or pathway term with P -value <0.05 . $FDR < 0.05$ was considered statistically significant.

2.3 Protein interaction network of MAPT and GO enrichment analyses

We perform a Protein-Protein interaction network of MAPT by using the STRING database (<https://string-db.org/>). Gene Ontology (GO) enrichment analyses were used to investigate gene sets related to MAPT by using the R package "cluster profiler" [16]. In our research. GO terms were visualized by R package "GO plot" [17], and terms with $FDR < 0.05$ were considered statistically significant.

2.4 Analysis of gene expression and tumor-infiltrating immune cells

Immune infiltration analysis of HCC was performed by TIMER2.0 (<http://timer.cistrome.org/>) [18, 19] to explore the correlation between MAPT and the infiltration levels of immune cells. The association between MAPT and six types of immune cells (B cells, CD4+ T cells, CD8+ T cells, neutrophils, macrophages, and dendritic cells) was analyzed by the Spearman's correlation, and Wilcoxon rank-sum

test was used to clarify the association of infiltration of immune cells with the different expression groups of MAPT.

3. Results

3.1 Identification of differentially expressed genes

By comparing transcriptome in HCC from TCGA, in total, 2068 differentially expressed genes were identified by limma, including 1991 up-regulated genes and 77 down-regulated genes (DEGs) (Figure 1A). To confirm immune-related genes associated with HCC, we selected all 116 immune-related genes from the DEGs that were considered statistically significant (Figure 1B).

3.2 Prognosis-associated and immune-related genes

The overlap between the 116 immune-related genes and 500 most differential survival genes in HCC contained three genes (BIRC5, MAPT, SPP1) as shown in the Venn diagram (Figure 1C), Three genes are highly expressed in HCC, and GEPIA shows that their expression has a significant relationship with the prognosis of patients. Among the three genes mentioned above, we selected MAPT, still poorly understood in HCC, to assess its diagnostic and prognostic value and the mechanisms it may involve in HCC.

3.3 MAPT expression comparison

A meta-analysis of MAPT expression in 5 analyses with verge values was determined as p -Value 0.05, fold change >1 , and the top 10% gene rank in the Oncomine database was performed in our research. The findings have shown that the expression levels of MAPT mRNA were significantly higher in human HCC samples than those in the non-tumor samples (Figure 2A). Analysis of different databases in GEO

revealed that MAPT mRNA was significantly upregulated in HCC in GSE25097, GSE45436, GSE55092, compared with that in normal liver tissues ($P < 0.001$, Figure 2B-2D). The details of the GEO series used in this analysis can be seen in Table 1. Further analysis shows that the protein expression of MAPT was significantly elevated in HCC samples compared with normal tissues in the HPA database (Figure 3).

3.4 Association between the expression of MAPT and the clinicopathology variables

In our study, gender, age, histologic grade, TNM stage, race, and other a total of 21 factors in clinical data were tested in this study to identify the relationship between MAPT and clinicopathological characteristics (Table 2). The findings indicated that MAPT overexpression was significantly associated with new tumor events after initial treatment ($P < 0.001$, Table 2). However, there is no correlation between MAPT expression and gender, age, histologic grade, TNM stage, or other clinicopathologic characteristics. A univariate analysis revealed that MAPT expression levels, pathologic stage, and TNM stage correlated with the prognosis of patients ($P < 0.05$). To further explore factors associated with patients' survival, a multivariate Cox regression analysis was performed on eight variables. The results showed that MAPT expression levels ($P < 0.001$), histologic grade ($P = 0.018$) and stage T ($P = 0.001$) and stage M ($P = 0.047$) were independent prognostic factors associated with overall survival (OS) in HCC patients (Table 3).

3.5 The relationship between MAPT expression and prognosis in HCC patients

We analyzed the overall survival (OS), disease-free survival (DSS), progression-free survival (PFS), and

relapse-free survival (RFS) rates to evaluate the prognostic value of MAPT expression in HCC. As shown in figure 4, HCC patients with high MAPT expression had shorter OS ($P = 0.00013$, Figure 4A), RFS ($P = 0.0019$, Figure 4B), DSS ($P = 0.0014$, Figure 4C) and PFS ($P = 0.0029$, Figure 4D) than those with low MAPT expression. Also, subgroup survival analysis in different populations was performed in our research. The high expression level of MAPT has significantly affected the worse OS in HCC patients with male sex, but not associated with poor prognoses in female patients (Figure 5) and MAPT overexpression was only significantly associated with worse OS in HCC patients without vascular invasion (Figure 6). In addition to this, the high expression level of MAPT was significantly correlated with poor prognosis in other groupings.

3.6 Association of MAPT expression with immune infiltration

The correlation between the expression level of MAPT and the immune infiltration in the tumor microenvironment was analyzed by Spearman correlation and then generated by TIMER. The plot shows that the MAPT was positively correlated with macrophages. Conversely, no associations were observed between MAPT and infiltration of B cells, CD4+ T cells, CD8+ T cells, neutrophils, and dendritic cells (Figure 7).

3.7 PPI and GO enrichment

Protein-protein interaction network of MAPT revealed that ten genes, including CDK5R1, APP, CASP3, CDK5, GSK3B, CAMK2A, BRSK2, MAPK2, MAPK8, and TUBA1B, were interacted with MAPT (Figure 8A). Peptidyl-serine phosphorylation, peptidyl-serine modification, regulation of autophagy, neuron death, etc. were the

most enriched GO biological process of MAPT interactive genes. Additionally, protein serine/threonine kinase activity, tau-protein kinase activity, tau protein binding, protease binding, etc. was the most enriched GO molecular functions of MAPT interactive genes (Figure 8B).

3.8 Result of the GSEA tool reporting the most significant KEGG pathways

Subsequent single-gene GSEA analysis confirmed high expression of MAPT was linked to the Wnt signaling pathway, the Notch signaling pathway, the VEGF signaling pathway, pathways in cancer, and promoted the development of bladder cancer, small cell lung cancer, thyroid cancer and so on. The results confirmed that MAPT was tightly associated with tumors (Figure 8C).

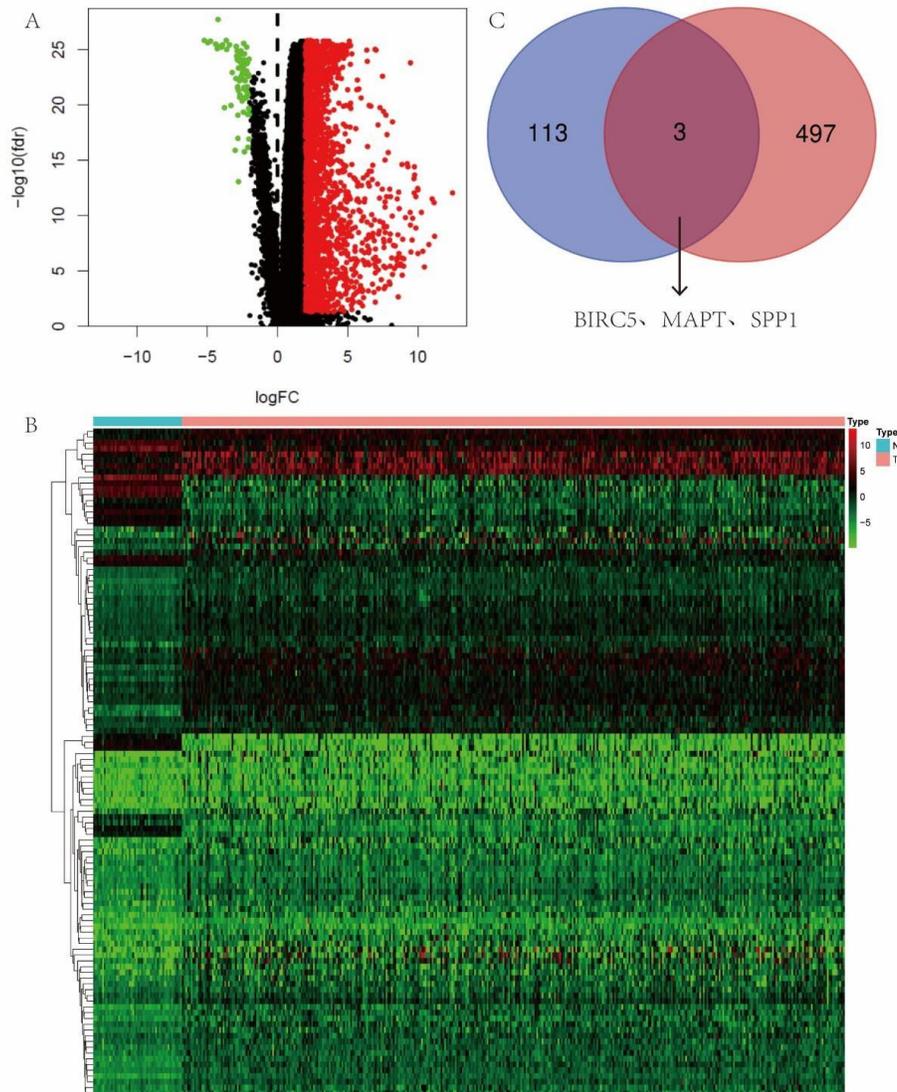


Figure 1: (A) 1991 up-regulated genes and 77 down-regulated genes were identified in HCC. (B) 116 immune-related genes from the DEGs that were considered statistically significant. (C) The overlap between the 116 immune-related genes and 500 most differential survival genes in HCC contained 3 genes.

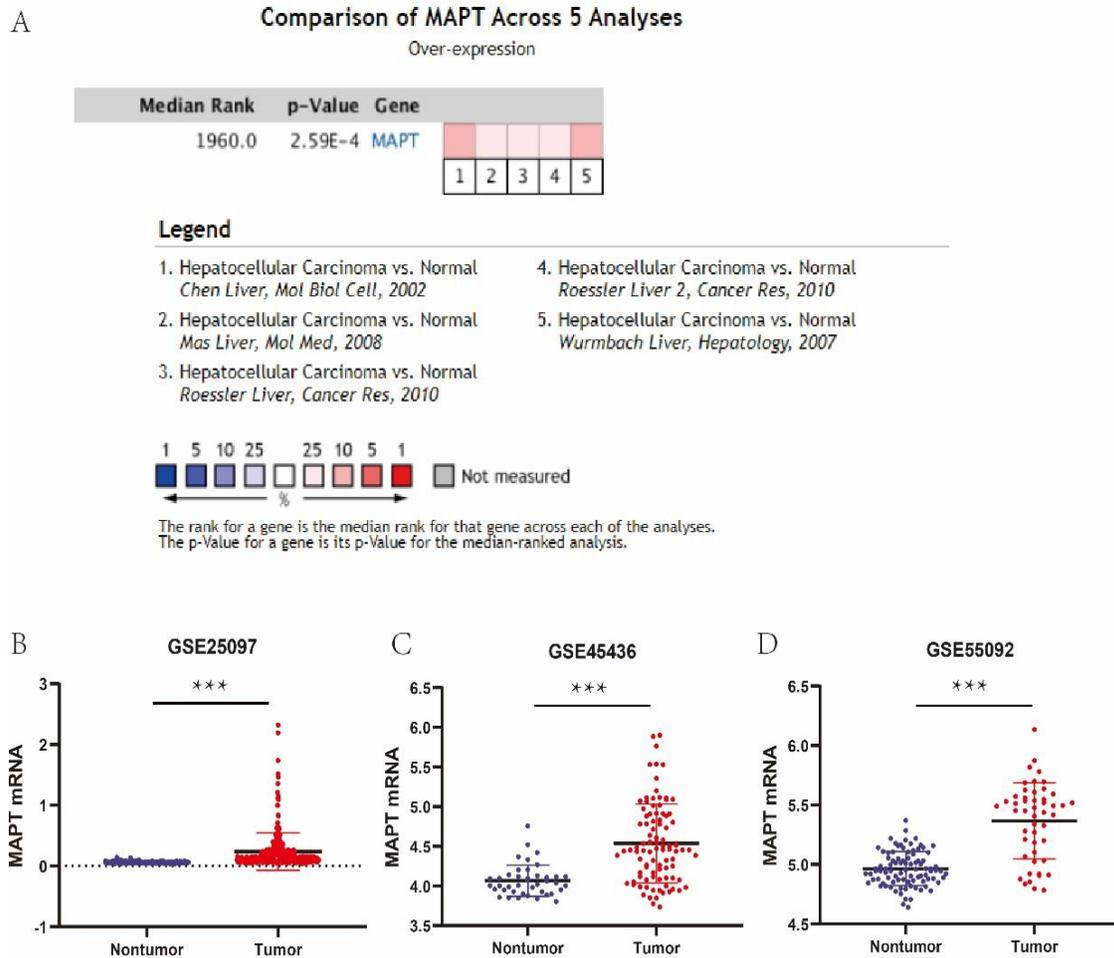


Figure 2: (A) OncoPrint analysis of MAPT expression in HCC. (B) MAPT mRNA expression levels between tumor and nontumor tissues in HCC patients in GEO database series.

GEO series	Contributor(s)	Tumor	Nontumor	Platform
GSE25097	Zhang C, 2010	268	243	Rosetta/Merck Human RSTA Affymetrix 1.0 microarray, Custom CDF
GSE45436	Hsieh J, 2013	93	42	Affymetrix Human Genome U133 Plus 2.0 Array
GSE55092	Melis M et al, 2014	49	91	Affymetrix Human Genome U133 Plus 2.0 Array

Table 1: Details of GEO series included in this analysis.

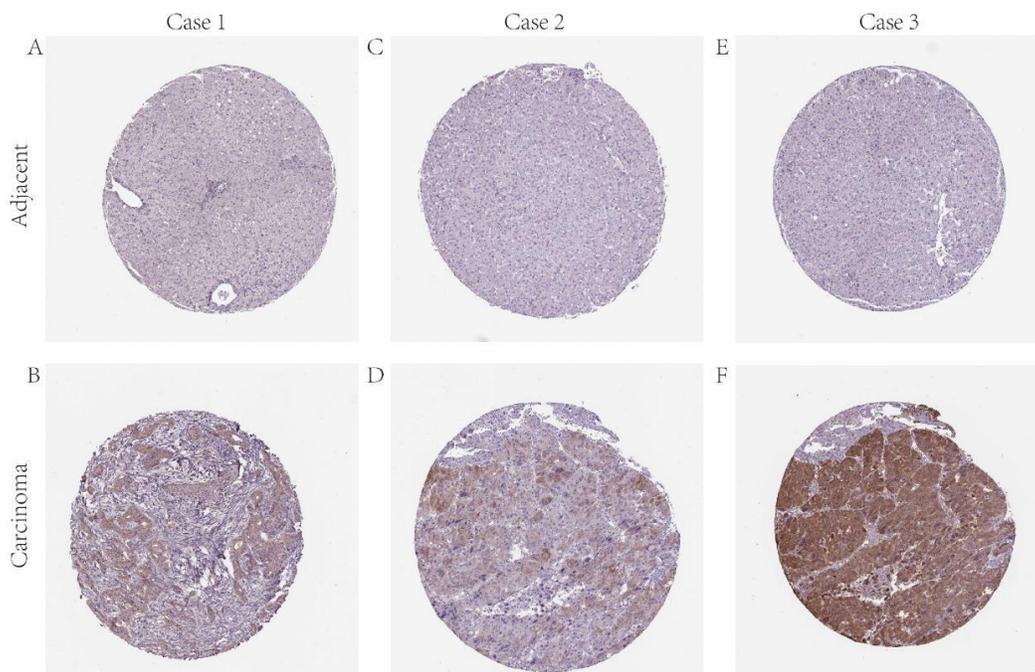


Figure 3: IHC staining of MAPT protein in HCC (HPA database). Representative images of IHC staining of MAPT expression in HCC samples and matched adjacent normal tissues (A-F).

Variables	MAPT expression level		P value
	Low (n = 185)	High (n = 185)	
Age			0.754
<60	83	86	
≥60	102	99	
Gender			0.74
Male	123	123	
Female	59	62	
Pathologic stage			0.797
I	88	79	
II	43	46	
III	52	57	
IV	2	3	
Histologic grade			0.166
G1	28	27	
G2	98	83	
G3	56	66	
G4	3	9	

T classification			0.704
T1	94	87	
T2	47	48	
T3	38	42	
T4	5	8	
TX	1	0	
N classification			0.582
N0	127	126	
N1	3	1	
NX	55	58	
M classification			0.973
M0	134	134	
M1	2	2	
MX	51	49	
New Event			0.795
No occurrent	97	97	
Extrahepatic Recurrence	14	17	
Intrahepatic Recurrence	42	36	
Locoregional Recurrence	27	32	
New Primary Tumor	5	3	
New tumor event after initial treatment			<0.001
Yes	39	56	
No	73	101	
NA	73	28	
Relative family cancer history			0.366
Yes	62	50	
No	100	107	
NA	23	28	
Vascular tumor cell type			0.633
Macro	9	7	
Micro	42	50	
None	108	98	
NA	26	30	
Cancer Status			0.546
With tumor	58	51	
Tumor free	112	122	
NA	15	12	

Hepatic inflammation			0.156
None	63	54	
Mild	49	50	
Severe	12	5	
NA	61	76	
Albumin result specified value			0.481
<3.5	38	31	
3.5~5.1	109	108	
>5.1	6	4	
NA	32	42	
Child-pugh classification			0.062
A	106	110	
B	16	5	
C	1	0	
NA	62	70	
Ishak fibrosis status			0.384
No Fibrosis	44	30	
Portal Fibrosis	16	15	
Fibrous Speta	11	17	
Nodular Formation and Incomplete Cirrhosis	5	4	
Established Cirrhosis	36	33	
NA	73	86	
Race			0.279
American Indian or Alaska Native	2	0	
Asian	70	87	
Black or African American	9	8	
White	98	86	
NA	6	4	
Prothrombin time result value			0.65
<11	134	126	
11~13	15	13	
>13	2	3	
NA	34	43	
Platelet result count			0.475
<100	11	6	
100~300	103	109	
>300	40	34	

NA	31	36	
Creatinine value in mg/dl			0.297
<0.5	2	3	
0.5~1.2	131	118	
>1.2	23	21	
NA	29	43	
Residual tumor			0.124
R0	164	159	
R1	11	6	
R2	1	0	
RX	6	16	
NA	3	4	

Table 2: Clinicopathological characteristics of HCC patients between MAPT high and low groups.

Patients						
Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age	1.213	0.855-1.721	0.278	1.143	0.790-1.652	0.478
Gender	1.226	0.861-1.747	0.259	1.086	0.757-1.558	0.655
Histologic grade	1.122	0.890-1.415	0.330	1.347	1.052-1.725	0.018
Pathologic stage	1.283	1.170-1.407	< 0.001	1.026	0.861-1.222	0.777
Stage T	1.245	1.159-1.338	< 0.001	1.234	1.088-1.400	0.001
Stage N	1.222	1.016-1.469	0.033	1.123	0.872-1.447	0.370
Stage M	1.273	1.058-1.531	0.010	1.293	1.004-1.665	0.047
MAPT	1.497	1.223-1.833	< 0.001	1.542	1.233-1.929	< 0.001

Table 3: Univariate and multivariate Cox regression analyses of overall survival in 370 HCC patients form TCGA.

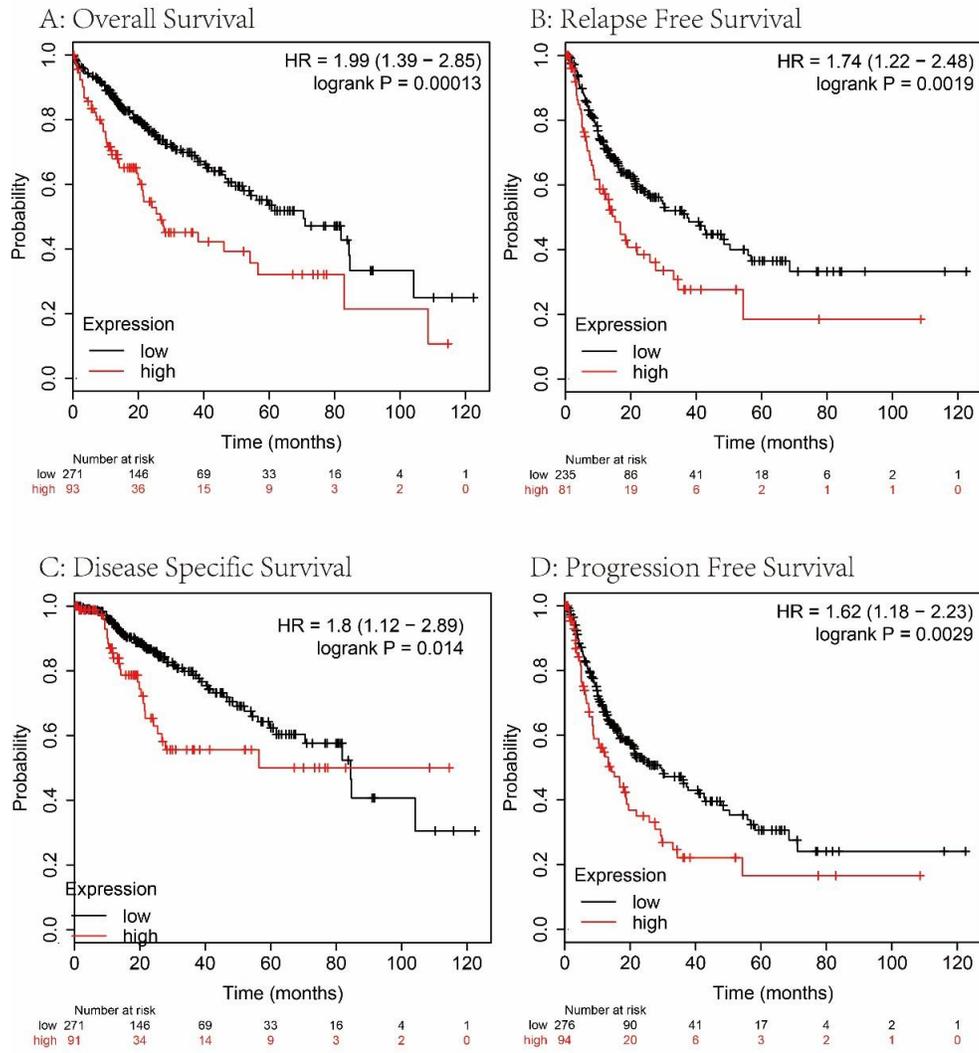


Figure 4: The effect of low vs. high MAPT expression in patients with HCC on OS, RFS, DSS and PFS time (A-D).

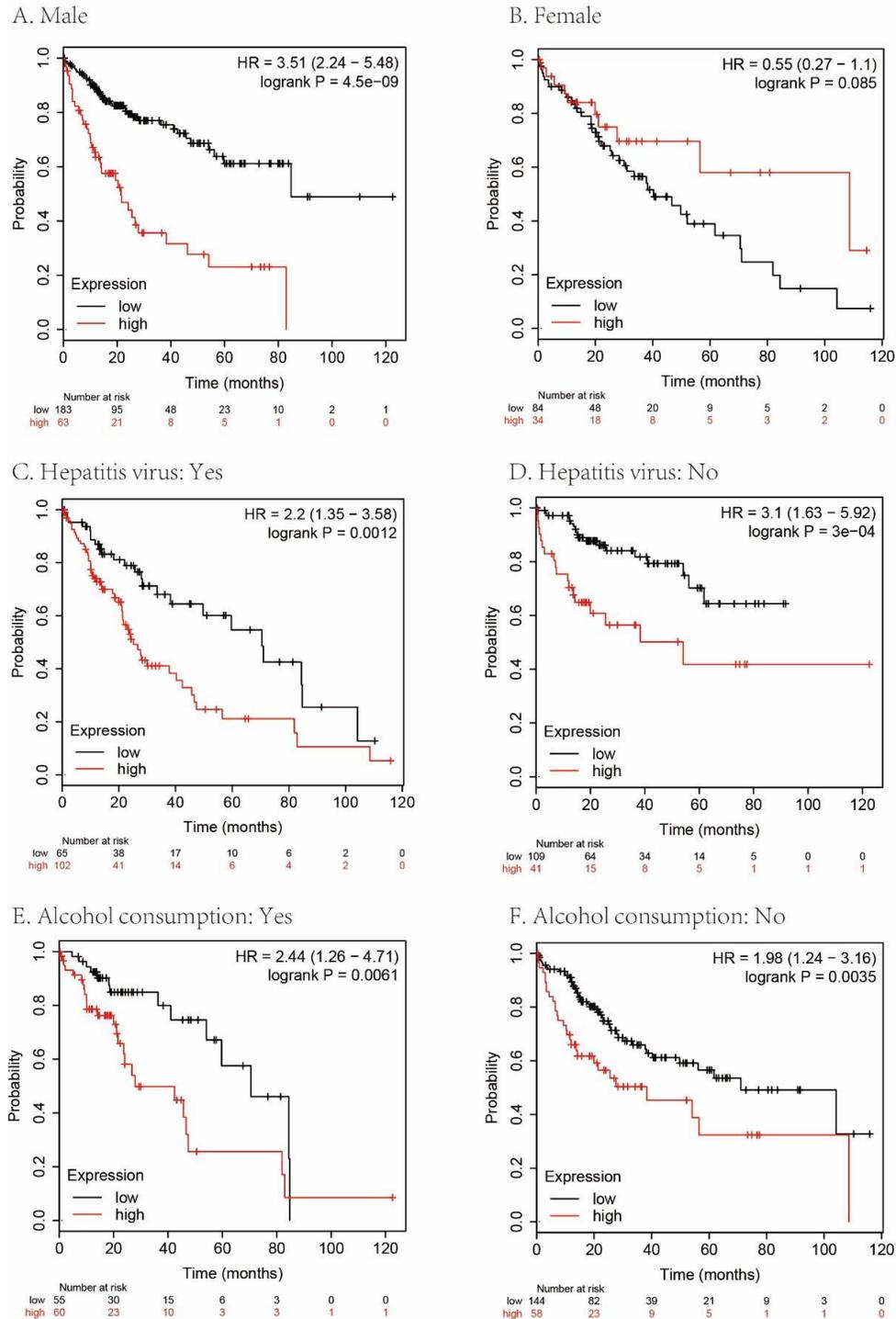


Figure 5: Subgroup analyses of overall survival comparison in different population [gender (A, B), gender hepatitis virus (C, D) and alcohol consumption (E, F)] with MAPT median cutoffs in HCC patients.

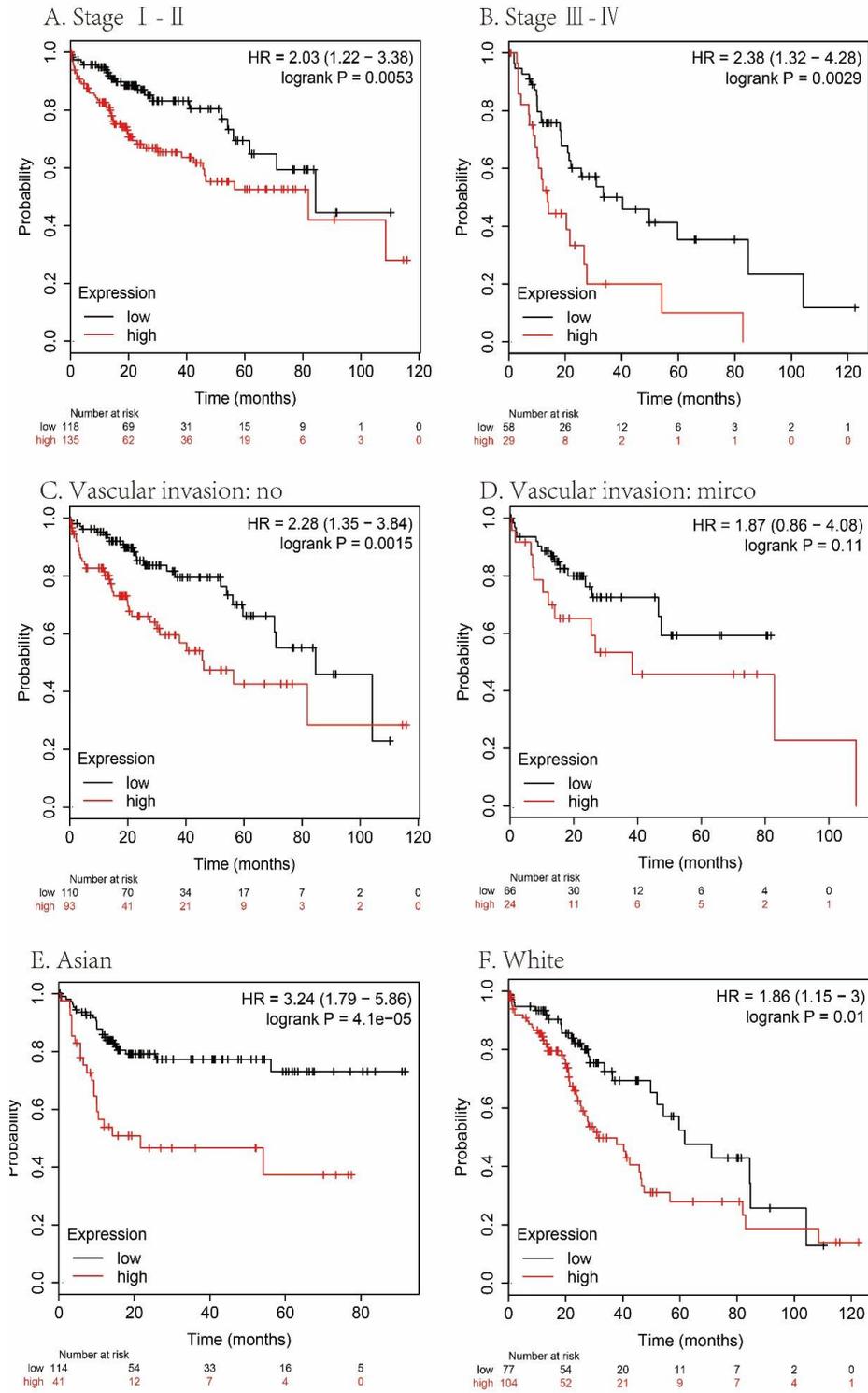


Figure 6: Subgroup analyses of overall survival comparison in different population [stage (A, B), vascular invasion (C, D) and race (E, F)] with MAPT median cutoffs in HCC patients.

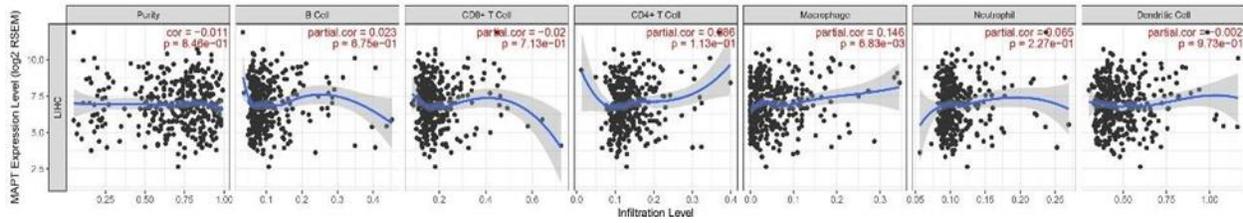


Figure 7: Association of MAPT expression with immune infiltration in HCC.

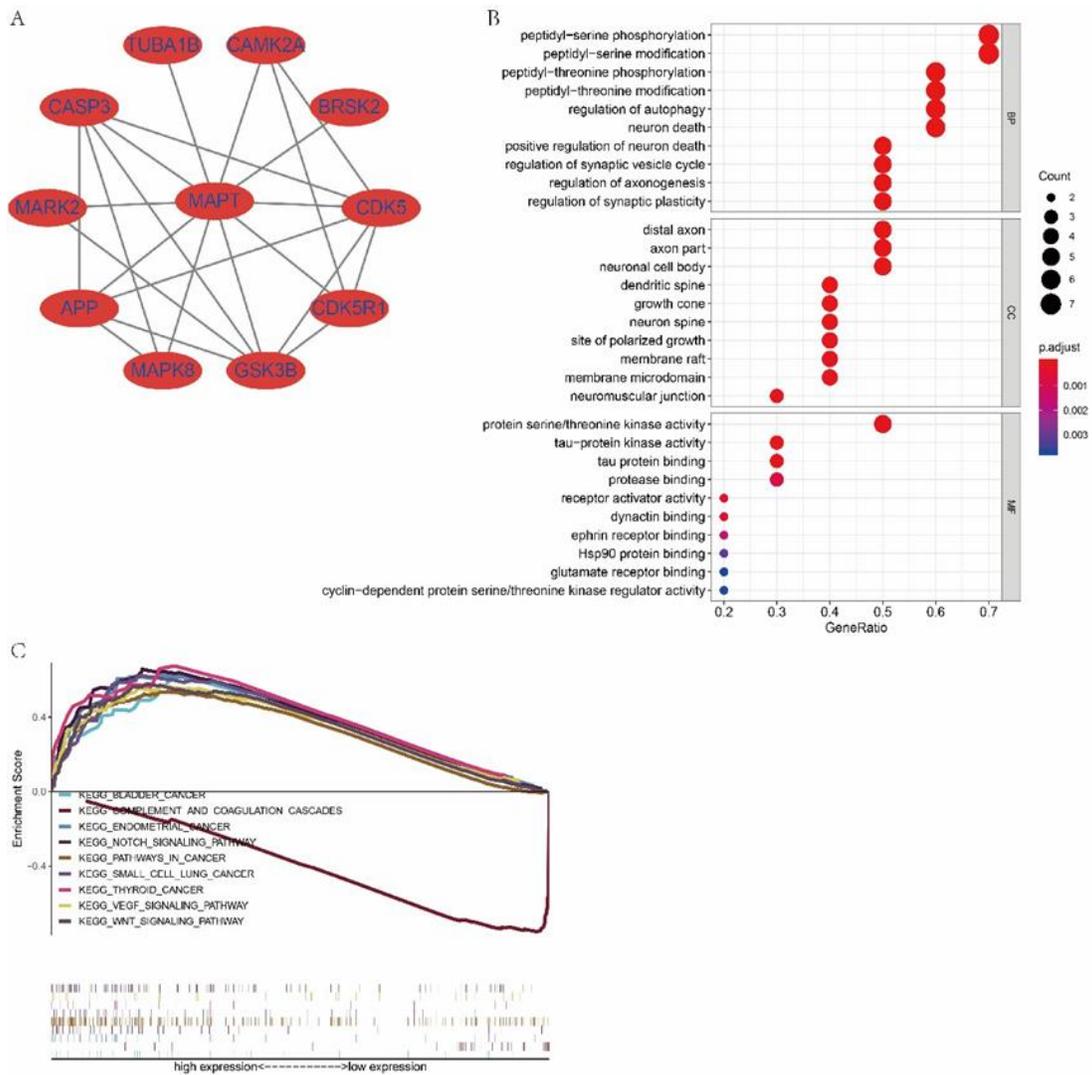


Figure 8: (A) Protein-protein interaction of MAPT using String analysis. (B) GO enrichment of its interactive genes. (C) Representative signal pathways of MAPT single-gene GSEA analysis.

4. Discussion

Previous studies about MAPT related diseases mainly focused on neurological disorders such as Dementia, Alzheimer's Disease, Parkinson's Disease, and so on [20-23]. However, recent studies have drawn much attention to its role in the tumor over the past few years. Analysis by Ricardo Gargini et al. suggests that MAPT is aberrantly expressed in a number of tumor types and shows a general association with prognosis [24], although its exact molecular mechanism and function in cancer have not yet been elucidated. Besides, many studies showed that the aberrant expression of MAPT in many cancers, such as neuroblastoma, breast, and prostate cancer [6, 7, 25]. Nonetheless, the survey about MAPT in HCC was still lacking. In light of the previous studies mentioned above, we undertook this research to investigate the potential value of MAPT in HCC. In this research, we found that overexpression of MAPT is significantly in HCC, and the high expression levels of MAPT in HCC were significantly associated with worse OS. This conclusion was in general agreement with that in breast cancer. Regrettably, the serum MAPT levels in HCC patients were not collected in the present study. In addition, MAPT expression was associated with recurrence after initial treatment. It indicates that HCC patients with high MAPT expression are more likely to relapse. Furthermore, a weak positive correlation was observed between MAPT and macrophages in HCC. Liver macrophages play a significant role in acute and chronic hepatic diseases, and they orchestrate inflammation, fibrosis, tumor progression, and angiogenesis, as well as tissue repair and tumor surveillance [26]. The result suggests that there are subtle correlations between MAPT and HCC.

Functionally, among gastric cancer and epithelial

ovarian cancer patients, lower expression of MAPT is correlated with increased susceptibility to paclitaxel therapy [27, 28]. This suggests that MAPT levels might be a marker for predicting the sensitivity of tumors to chemotherapy. More than that, MAPT promotes microtubule assembly and stability [29]. However, MAPT was aberrantly expressed in various tumors. Due to the different microtubule composition of different cell types, a tentative inference on the result is that MAPT-induced microtubule dynamics changes may have different effects on cell behavior, depending on the origin of the cell tissue [25]. A complete description of a protein's function requires an understanding of all the chaperones to which it specifically binds. KEGG and GO enrichment analysis was performed on the genes in the protein-protein interaction network, and the results demonstrated that MAPT might participate in several tumor-associated pathways and oxidation-reduction processes in our research. GO enrichment analysis of genes that show MAPT is mainly involved in biological processes such as peptidyl-threonine phosphorylation and peptidyl-serine phosphorylation. Its molecular function is primarily related to the regulation of serine-threonine protein kinase activity. Serine-threonine protein kinase involves a variety of proteins and plays a wide range of molecular features in many tumors [30, 31, 32]. The above results show that MAPT may function as an upstream regulatory factor to participate in the regulation of serine-threonine protein kinase activity and participate in both tumor initiation and progression of human cancers. Unfortunately, no experimental study has been carried out to find the potential oncogenic mechanisms of MAPT in HCC development.

Accordingly, further experiments are required to

demonstrate the specific mechanism of its cancer-promoting effect. Taken together, this study provides the first detailed analysis of evaluating the expression level of human MAPT protein and mRNA in HCC. The expression of MAPT was significantly overexpressed compared with that in non-tumor liver tissues in HCC based on TCGA, Oncomine, HPA, and GEO databases. MAPT was remarkably overexpressed in HCC tissues and was inversely associated with OS and RFS of HCC patients. Furthermore, our initial analyses also show the signaling pathways that MAPT may be involved in, and the molecular functions, biological processes that MAPT may participate in. We will inform the design of future experimental studies in light of our results. In summary, MAPT may be useful as a predictive diagnostic factor in HCC and as a possible therapeutic target.

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