Proceedings of Anticancer Research, 2025, Volume 9, Issue 1
http://ojs.bbwpublisher.com/index.php/PAR
ISSN Online: 2208-3553
ISSN Print: 2208-3545

The Predictive Value of *SPP1* Gene Expression for the Survival of Advanced Liver Cancer Treated with Transarterial Chemoembolization

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Abstract: *Objective:* To evaluate the predictive value of *secreted phosphoprotein 1* (*SPP1*) gene expression for postoperative survival in patients with advanced liver cancer undergoing hepatic artery interventional chemoembolization treatment. *Method:* Bioinformatics methods, including gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis, were used to identify genes related to survival prognosis in hepatocellular carcinoma (HCC) patients. A retrospective analysis of 115 advanced liver cancer patients treated between January 2016 and October 2017 was conducted. Patients were categorized into *SPP1* high-expression (n = 89) and low-expression groups (n = 26). Additionally, 115 healthy individuals served as the control group. The relationship between *SPP1* expression and clinical pathological features was analyzed. A 60-month follow-up and logistic regression analysis identified risk factors affecting survival. *Results:* SPP1 mRNA expression was significantly higher in liver cancer patients compared to healthy controls (P < 0.05). *SPP1* expression levels were significantly associated with tumor size, Child-Pugh grading, lymph node metastasis, and BCLC staging (P < 0.05). High *SPP1* expression, along with tumor size, Child-Pugh grading, lymph node metastasis, and BCLC staging, were independent risk factors for survival (P < 0.05). The 60-month survival rate was 17.39%, with a median survival of 40 months in the low-expression group versus 18 months in the high-expression group (P < 0.05). *Conclusion:* SPP1 expression is significantly upregulated in advanced liver cancer patients and has predictive value for postoperative survival following hepatic artery chemoembolization treatment. SPP1, combined with clinical indicators such as tumor size, Child-Pugh grading, lymph node metastasis, and BCLC staging, may serve as a prognostic biomarker for interventional treatment outcomes.

Keywords: *SPP1*; Transarterial chemoembolization; Advanced liver cancer; Survival period; Predictive value

Online publication: February 13, 2025

1. Introduction

Liver cancer is one of the most prevalent malignant tumors worldwide, characterized by high incidence and mortality rates. However, most patients with liver cancer seek medical attention only after the disease has progressed to an advanced stage. Consequently, early diagnosis is of critical importance for effective treatment [1]. Currently, alpha-fetoprotein (AFP) serves as a diagnostic biomarker for liver cancer, but it has limitations in diagnostic accuracy. Studies indicate that 32% to 59% of liver cancer patients exhibit normal AFP levels. Moreover, understanding the prognosis of cancer patients is crucial for improving their quality of life and optimizing treatment strategies. This underscores the necessity of identifying novel, more accurate biomarkers to enhance patient survival and prognosis.

Secretory phosphoprotein 1 (SPP1) is a chemokine-like glycoprotein secreted by cells and is recognized as a significant mediator of tumor-associated inflammation. In prostate cancer research, SPP1 expression has been shown to be significantly upregulated, contributing to the development of multidrug resistance and complicating clinical management. Additionally, bioinformatics analyses have revealed that SPP1 expression is markedly elevated in hepatocellular carcinoma tissues. However, the relationship between SPP1 expression and postoperative survival in patients with advanced liver cancer remains unclear. This study aims to assess the predictive value of *SPP1* gene expression for postoperative survival in patients with advanced liver cancer undergoing hepatic artery interventional chemoembolization treatment.

2. Methods

2.1. Expression difference analysis

R software version 4.13 was used to process and convert the downloaded data for analysis. The "ggpuber" R package was employed to analyze the differential expression of SPP1 mRNA between HCC tissue and normal tissue. Statistical significance was considered at $P < 0.05$.

2.2. Survival analysis and clinical feature correlation analysis

SPP1 was divided into high-expression and low-expression groups based on the median SPP1 mRNA expression in HCC tissue (median = 5.32768). The "survival" and "survivminer" R packages, along with Kaplan-Meier curves, were used to analyze the relationship between *SPP1* expression levels and the survival of HCC patients. Univariate Cox regression analysis was conducted to evaluate the relationship between *SPP1* expression levels and patient prognosis, and receiver operating characteristic (ROC) curves were plotted. Statistical significance was defined as $P < 0.05$.

2.3. Differential gene analysis and functional enrichment analysis

Differential genes between the *SPP1* high-expression and low-expression groups were identified using the "limma" R package. Upregulated and downregulated genes underwent Gene Ontology (GO) biological function annotation and Kyoto Encyclopedia of Genes and Genomes (KEGG) signaling pathway enrichment analysis using the "circularize" and "clusterProfiler" R packages. Statistical significance was defined as $P < 0.05$, with the adjusted P-value (P_{adj}) and false discovery rate (FDR) q-value less than 0.05.

2.4. Research subjects

A retrospective analysis was conducted on 115 patients with advanced liver cancer treated at the First Affiliated Hospital of Xi'an Medical College from January 2016 to October 2017.

Inclusion criteria: (1) Patients meeting diagnostic and treatment criteria for liver cancer [4], aligned with the American College of Hepatology or the European College of Hepatology guidelines; (2) Barcelona Clinic Liver Cancer (BCLC) staging Phase B or C; (3) Underwent hepatic artery interventional chemoembolization; (4) Possessed basic language and hearing abilities, with informed consent obtained from patients and families; (5) No prior treatment before the study; (6) Karnofsky performance status exceeding 60 points.

Exclusion criteria: (1) Combined malignancies (e.g., gastric or lung cancer); (2) Severe abnormalities in liver, kidney, or heart function; (3) Intolerance to hepatic artery chemoembolization; (4) Abnormal coagulation function or infectious diseases.

Based on the optimal ROC-determined threshold value (SPP1 = 2.03), patients were divided into two groups: the *SPP1* low-expression group (26 cases, SPP1 ≤ 2.03) and the *SPP1* high-expression group (89 cases, SPP1 > 2.03). A control group of 115 healthy individuals was also included. The study was approved by the hospital ethics committee and adhered to relevant medical ethics principles.

2.5. Hepatic artery interventional chemoembolization

Patients received traditional hepatic artery interventional chemoembolization [5]. An emulsion of 2–20 mL iodized oil, doxorubicin (10–40 mg), and mitomycin (2–10 mg) was injected selectively into the tumor's feeding artery via a hepatic artery catheter. Gelatin sponge or PVA particles were used for arterial embolization until blood flow to the main feeding artery ceased. Enhanced CT scans were performed 4–8 weeks post-procedure. Patients with residual active lesions and adequate liver function underwent repeated treatment as necessary.

2.6. Real-time fluorescence quantitative PCR (RT-PCR) for SPP1 detection

Peripheral blood mononuclear cells were collected from 8 mL of fasting venous blood from liver cancer patients three days post-surgery and from healthy controls during physical exams. Density gradient centrifugation was used for separation. RNA was extracted using the TRIZOL method, and RNA purity was assessed via UV spectrophotometry (acceptable range: 1.8–2.1). Primer design was completed using Primer5 software, and SPP1 mRNA expression was quantified using the $2^{-\Delta\Delta CT}$ method, with GAPDH serving as the internal reference.

2.7. Observational indicators

The relationship between *SPP1* expression and clinical-pathological characteristics was analyzed, including age, gender, smoking history, tumor size, Child-Pugh grading [6], lymph node metastasis, BCLC staging, and cirrhosis presence.

2.8. Follow-up

Patients were followed up through telephone or outpatient visits. The follow-up period began after surgical treatment and lasted 60 months. Factors influencing patient survival were analyzed.

2.9. Statistical analysis

SPSS 24.0 software was used for data analysis. Metric data were expressed as mean ± standard deviation (SD) and analyzed using *t*-tests. Count data were expressed as [*n* (%)] and analyzed using χ^2 tests. Logistic regression

models identified risk factors influencing survival, while Kaplan-Meier survival curves assessed the relationship between *SPP1* expression and prognosis. Statistical significance was defined as $P < 0.05$.

3. Results

3.1. Expression of SPP1 mRNA in HCC and normal tissues

The results demonstrated that the expression level of SPP1 mRNA was significantly increased in HCC tissues compared to normal tissues ($P < 0.05$), as illustrated in **Figure 1**.

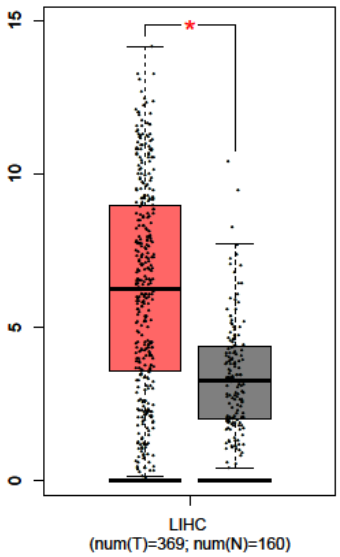

Figure 1. SPPI expression level significantly increased in HCC tissue ($P < 0.05$)

3.2. Relationship between SPP1 expression levels and survival prognosis in HCC patients

Kaplan-Meier curve analysis revealed that the OS of HCC patients with low *SPP1* expression was significantly higher than that of patients with high *SPP1* expression ($P < 0.005$, **Figure 2A**). Univariate Cox regression analysis demonstrated that the *SPP1* expression level (OS:HR = 1.127, 95% CI: 1.072–1.184, $P < 0.005$) was an independent risk factor for poor prognosis in HCC patients, as shown in **Figure 2B**.

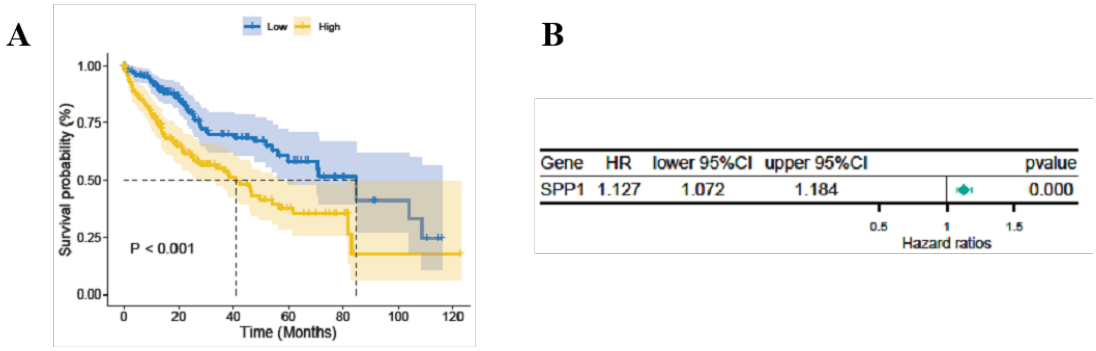

Figure 2. Relationship between *SPP1* expression level and survival prognosis of HCC patients. **(A)** Kaplan-Meier analysis of *SPP1* survival curve. **(B)** Univariate Cox regression analysis of the relationship between *SPP1* expression level and prognosis in HCC patients.

3.3. Differentially expressed genes and functional enrichment analysis

A total of 455 differentially expressed genes (DEGs) were identified between the high and low *SPP1* expression groups, including 380 upregulated and 75 downregulated genes (**Figure 3A**). GO enrichment analysis indicated that these DEGs were enriched in biological processes (BP) such as hormone metabolism, cellular components (CC) including extracellular matrix containing collagen, and molecular functions (MF) such as receptor-ligand activity (**Figures 3B–3D**). KEGG pathway analysis demonstrated significant enrichment in pathways related to neuroactive ligand-receptor interactions, bile secretion, and retinol metabolism (**Figure 3E**).

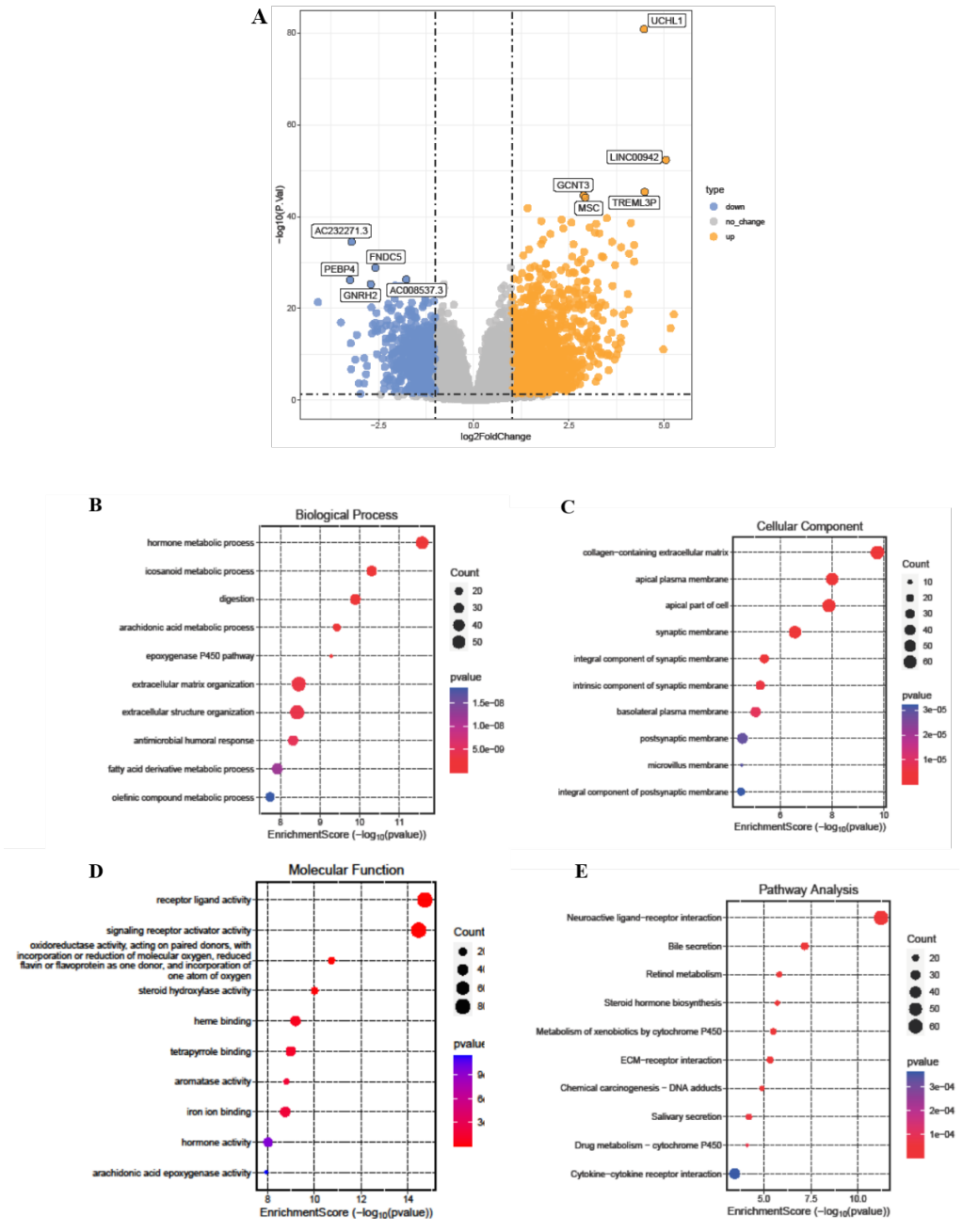

Figure 3. Functional enrichment analysis of *SPP1*-related DEGs in HCC based on the GO and KEGG methods. **(A)** Differential gene expression. **(B–D)** GO enrichment analysis. **(E)** KEGG pathway enrichment analysis.

3.4. Comparison of SPP1 mRNA expression between patients with liver cancer and the control group

The expression level of SPP1 mRNA in peripheral blood mononuclear cells of patients with liver cancer was significantly higher than that of the healthy control group (P<0.05), as presented in **Table 1**.

Table 1. Comparison of SPP1 mRNA expression between liver cancer patients and the healthy control group

Group	*n*	SPP1 mRNA
Liver cancer group	115	5.15 ± 1.23
Healthy control group	115	1.38 ± 0.20
t		32.443
P		< 0.001

3.5. Correlation between SPP1 expression and clinicopathological characteristics

Patients in the high-expression group of *SPP1* demonstrated statistically significant differences in tumor size, Child-Pugh grading, lymph node metastasis, and BCLC staging ($P < 0.05$). No statistically significant differences were observed for age, gender, smoking history, or cirrhosis ($P > 0.05$), as shown in **Table 2**.

Table 2. Relationship between SPP1 expression and clinicopathological characteristics of advanced HCC patients.

Indicator	*n*	SPP1		χ^2	*P*
		Low expression group (*n* = 26)	High expression group (*n* = 89)		
Age (years)				1.663	0.197
< 55	67	18 (69.23)	49 (55.06)		
≥ 55	48	8 (30.77)	40 (44.94)		
Gender				0.087	0.768
Female	56	12 (46.15)	44 (49.44)		
Male	59	14 (53.85)	45 (50.56)		
Smoking history				1.311	0.252
Yes	55	15 (57.69)	40 (44.94)		
No	60	11 (42.31)	49 (55.06)		
Tumor size (cm)				11.440	0.001
≤ 5	39	16 (61.54)	23 (25.84)		
> 5	76	10 (38.46)	66 (74.14)		
Child-Pugh Classification				7.443	0.006
A	71	22 (84.62)	49 (55.06)		
B+C	44	4 (15.38)	40 (44.94)		
Lymphatic metastasis				5.151	0.023
Yes	44	5 (19.23)	39 (43.82)		
No	71	21 (80.77)	50 (56.18)		

Table 2 (Continued)

Indicator	*n*	SPP1		χ^2	*P*
		Low expression group (*n* = 26)	High expression group (*n* = 89)		
BCLC Staging				6.169	0.013
Stage B	55	18 (69.23)	37 (41.57)		
Stage C	60	8 (30.77)	52 (58.43)		
Liver cirrhosis				0.530	0.467
Yes	46	12 (46.15)	34 (38.20)		
No	49	14 (53.85)	55 (61.80)		

3.6. Univariate analysis of survival in patients with advanced liver cancer

Univariate analysis revealed statistically significant differences ($P < 0.05$) between the survival and death groups in terms of tumor size, Child-Pugh grading, lymph node metastasis, BCLC staging, and *SPP1* expression, as detailed in **Table 3**.

Table 3. Univariate analysis of survival in patients with advanced liver cancer

Indicator	*n*	Survival group (*n* = 20)	Death group (*n* = 95)	*t*	*P*
Age (years)				0.452	0.501
< 55	67	13 (65.00)	54 (56.84)		
≥ 55	48	7 (35.00)	41 (43.16)		
Gender				0.017	0.898
Female	56	10 (50.00)	46 (48.42)		
Male	59	10 (50.00)	49 (51.58)		
Smoking history				0.594	0.441
Yes	55	8 (40.00)	47 (49.47)		
No	60	12 (60.00)	48 (50.53)		
Tumor size (cm)				7.351	0.007
≤ 5	39	12 (40.00)	27 (28.42)		
> 5	76	8 (60.00)	68 (71.58)		
Child-Pugh Classification				5.546	0.019
A	71	17 (85.00)	54 (56.84)		
B+C	44	3 (15.00)	41 (43.16)		
Lymphatic metastasis				8.186	0.004
Yes	44	2 (10.00)	42 (44.21)		
No	71	18 (90.00)	53 (55.79)		
BCLC staging				4.771	0.029
Stage B	55	14 (70.00)	41 (43.16)		
Stage C	60	6 (30.00)	54 (56.84)		

Table 3 (Continued)

Indicator	*n*	Survival group (*n* = 20)	Death group (*n* = 95)	*t*	*P*
Liver cirrhosis				1.009	0.315
Yes	46	6 (30.00)	40 (42.11)		
No	69	14 (70.00)	55 (57.89)		
SPP1				19.345	< 0.001
Low expression	26	12 (60.00)	14 (14.74)		
High expression	89	8 (40.00)	81 (85.26)		

3.7. Multivariate analysis of survival in patients with advanced liver cancer

Logistic regression analysis identified tumor size, Child-Pugh grading, lymph node metastasis, BCLC staging, and high *SPP1* expression as independent risk factors affecting survival ($P < 0.05$), as summarized in **Table 4**.

Table 4. Multivariate analysis of survival in patients with advanced liver cancer

Indicator	*B*	*SE*	Wald	*P*	OR (95% CI)
Tumor size (cm)	1.213	0.415	6.605	0.023	3.751 (1.375–10.215)
Child-Pugh Classification	2.112	0.649	11.107	0.004	8.189 (2.267–18.233)
Lymphatic metastasis	1.112	0.469	4.718	0.012	2.771 (1.115–7.027)
BCLC Staging	0.998	0.511	3.781	0.026	2.752 (1.995–7.382)
SPP1 high expression	1.326	0.570	7.852	0.033	5.412 (1.236–10.749)

3.8. SPP1 expression and survival prognosis

Follow-up was conducted over a 60-month period for the 115 patients included in the study, resulting in a survival rate of 17.39% (20/115). Kaplan-Meier survival curve analysis revealed that the median survival time for the low *SPP1* expression group was 40 months, significantly longer than the 18 months observed for the high-expression group ($P < 0.05$), as shown in **Figure 4**.

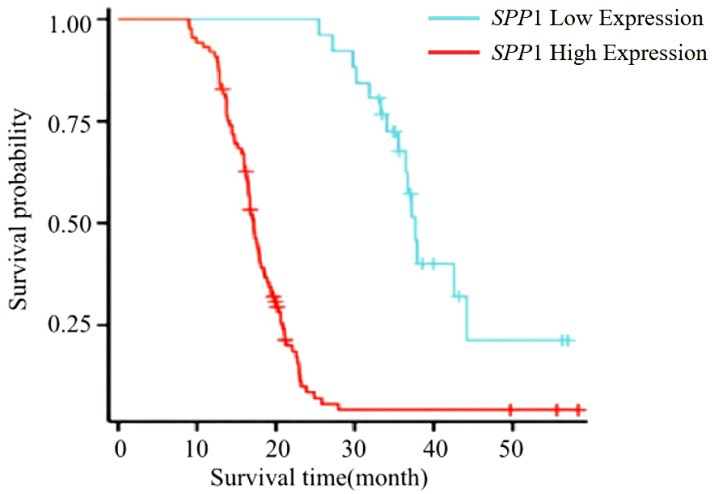

Figure 4. Kaplan-Meier analysis of the relationship between *SPP1* expression levels and survival prognosis

4. Discussion

Liver cancer ranks as the sixth most commonly diagnosed cancer and the fourth leading cause of cancer-related deaths globally. According to relevant statistics [7], the incidence rate of liver cancer is highest in East Asia, accounting for 35.5% of the global cases. The pathogenesis of liver cancer is complex and multifactorial. Chronic hepatitis B virus, hepatitis C virus, aflatoxin-contaminated food, excessive alcohol consumption, smoking, and type 2 diabetes are significant risk factors associated with liver cancer development [8]. Modern medical research has demonstrated that the liver possesses a low level of pain sensation, and even when liver disease occurs, the body often fails to detect it through pain feedback mechanisms [9]. As a result, the clinical manifestations of liver disease are relatively subtle. Consequently, many patients with liver cancer are diagnosed only in the advanced stages, leading to a poor prognosis. Therefore, early identification of diagnostic and prognostic markers for liver cancer is essential for improving diagnostic accuracy, enhancing treatment efficacy, improving patient outcomes, and reducing mortality rates.

SPP1, a crucial extracellular matrix component, is secreted by various cell types, including tumor cells, immune cells, fibroblasts, osteoclasts, smooth muscle cells, lymphocytes, and epithelial cells [10]. Studies have revealed that the upregulation of *SPP1* in tumor tissues and plasma correlates with poor prognosis in patients with various cancers [11]. The findings of this study indicated that the expression level of *SPP1* is significantly elevated in advanced liver cancer tissues. Furthermore, *SPP1* expression is closely associated with tumor size, Child-Pugh grading, lymph node metastasis, BCLC staging, and patient survival prognosis. Analyzing the expression level of *SPP1* may, therefore, hold significant value in evaluating disease progression and predicting patient survival outcomes.

Additionally, the study identified tumor size, Child-Pugh grading, lymph node metastasis, BCLC staging, and high *SPP1* expression as independent risk factors affecting survival in patients with advanced liver cancer. Advanced liver cancer often entails large tumor size or metastasis, which increases treatment complexity and mortality risk. Specifically, larger liver tumors exhibit higher growth rates, greater invasiveness, and stronger metastatic potential. These larger tumors are more prone to invading adjacent blood vessels and tissues, leading to complications such as liver dysfunction, portal hypertension, and ascites, ultimately increasing the risk of mortality [12]. The Child-Pugh scoring system remains a critical tool for evaluating liver function. Higher Child-Pugh grades indicate progressively severe liver dysfunction and diminishing therapeutic effectiveness [13]. Furthermore, lymphangiogenesis and lymph node metastasis serve as crucial prognostic indicators for malignant hepatobiliary tumors and are closely linked to poorer outcomes. The liver produces approximately 25% to 50% of the body's lymphatic fluid and contains an extensive lymphatic network. The lymphatic system plays an integral role in immune and inflammatory responses [14].

Luan *et al.* [15] reported a negative correlation between *SPP1* expression and overall survival in patients with lung adenocarcinoma, noting its association with clinical stage, lymph node metastasis, and survival status. Their findings suggest that *SPP1* could serve as a valuable molecular marker for the diagnosis, treatment, and prognosis evaluation of lung adenocarcinoma. Similarly, the Kaplan-Meier survival curve analysis in this study demonstrated that patients with low *SPP1* expression exhibited longer survival periods. This finding underscores the significant correlation between elevated blood *SPP1* expression and poorer prognosis in patients with advanced liver cancer following hepatic artery interventional chemotherapy embolization. Thus, *SPP1* may be a valuable biomarker for predicting prognosis.

This study, however, has certain limitations. The research duration was relatively short, and the sample size

was comparatively small. Additionally, the mechanism through which *SPP1* influences survival prognosis in patients with liver cancer remains unclear. Future research should focus on elucidating the underlying mechanisms and exploring the development of *SPP1*-targeted therapies for liver cancer treatment.

5. Conclusion

SPP1 is significantly upregulated in advanced liver cancer tissues and holds potential value in predicting the survival outcomes of patients with advanced liver cancer undergoing hepatic artery chemoembolization treatment. *SPP1* is anticipated to serve as a potential prognostic indicator for evaluating the outcomes of interventional treatments. Furthermore, it can be utilized in conjunction with clinical indicators, including tumor size, Child-Pugh grading, lymph node metastasis, and BCLC staging, to predict or assess the postoperative survival of patients with liver cancer.

Funding

(1) Medical Research Project of Xi'an Science and Technology Bureau "Molecular Mechanism of miR-1305 Competitive Endogenous circRNA in the Development of Liver Cancer" (Project No. 22YXYJ0134)

(2) General Project of Key Research and Development Program of Shaanxi Provincial Department of Science and Technology "Mechanism Study on the Inhibition of Liver Cancer Invasion and Metastasis by Downregulating METTL3 and Reducing the m6A Modification Level of MMP3 with Honokiol" (Project No. 2023-YBSF-631)

Disclosure statement

The authors declare no conflict of interest.

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