Original Article

Level and clinical significance of serum CXC chemokine ligand 13 in patients with hepatocellular carcinoma

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Background: CXC chemokine ligand 13 (CXCL13) serves as the ligand for chemokine receptor 5 (CXCR5), The CXCL13/CXCR5 signaling axis plays a crucial role in the pathogenesis and progression of various malignancies. This study aimed to assess the expression and role of serum CXCL13 in patients with hepatocellular carcinoma (HCC) and explore its clinical significance in the diagnosis, treatment, and prognosis evaluation of HCC.

Methods: Serum samples and clinical data were collected from 74 HCC patients, 51 cirrhosis patients, and 53 healthy controls. The expression level of serum CXCL13 was measured using enzyme-linked immunosorbent assay (ELISA). Statistical software was employed to analyze the relationship between CXCL13 levels and clinicopathological features as well as laboratory indicators. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic value of CXCL13 and alpha-fetoprotein (AFP) for HCC.

Results: The level of serum CXCL13 in the HCC group (275.96±145.35 pg/mL) was significantly higher than that in the cirrhosis group (172.11±142.78 pg/mL) and healthy control group (58.83±41.29 pg/mL). The level of CXCL13 in HCC patients with tumor node metastasis (TNM) stage III–IV was significantly higher than that in those with TNM stage I–II, as well as positively correlated with γ-glutamyltransferase (GGT) and model for end-stage liver disease (MELD) values. The area under the ROC curve for CXCL13, AFP, and the combination of CXCL13 with AFP were 0.819, 0.813, and 0.885 respectively. The sensitivity and specificity of the combined CXCL13 with AFP were 88.9% and 77.9% respectively. Moreover, the diagnostic efficacy of combining CXCL13 with AFP was significantly superior to that of using either CXCL13 or AFP alone.

Conclusions: The expression of CXCL13 is upregulated in HCC patients and associated with tumor size, metastasis, GGT, and MELD score. Combining serum CXCL13 with AFP may hold clinical value to the diagnosis of HCC.

Keywords: CXC chemokine ligand 13 (CXCL13); hepatocellular carcinoma (HCC); diagnosis; receiver operating characteristic curve (ROC curve)

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Introduction

Hepatocellular carcinoma (HCC) accounts for approximately 85–90% of primary liver cancer and is currently one of the most prevalent malignant tumors, ranking as the third leading cause of cancer-related mortality in China (1,2). Due to its typically insidious onset, HCC is often diagnosed at advanced stages. Currently, clinical diagnosis relies primarily on alpha-fetoprotein (AFP) combined with liver imaging (3). However, AFP lacks satisfactory sensitivity and specificity (4), and it is not uncommon for patients with benign liver diseases other than liver cancer to experience abnormal increases in AFP levels exceeding the upper limit of normal. The sensitivity and specificity of AFP alone in the diagnosis of HCC are relatively low (5). Therefore, it is crucial to identify serological markers with high sensitivity and specificity for early clinical diagnosis and prognosis evaluation of HCC. CXC chemokine ligand 13 (CXCL13) serves as the ligand for chemokine receptor 5 (CXCR5). The CXCL13/CXCR5 signaling axis not only plays a significant role in inflammatory and allergic responses but also contributes to tumor growth and metastasis (6). The dysregulation of Tfh cells has been linked to solid tumors (7). CXCL13, a chemokine, selectively binds to the receptor CXCR5 and facilitates the migration of B cells and Tfh cells expressing CXCR5 towards lymphoid tissue (8). Numerous studies have investigated the involvement of the CXCL13/CXCR5 signal axis in various tumors, including gastric cancer (9), breast cancer, bowel cancer, lung cancer (10), prostate cancer (11), lymphoma (12), among others. $CD8^+CXCR5^+$ T cells have been identified in T-cell lineage acute lymphoblastic leukemia (13), pancreatic tumors (14), colorectal tumors, as well as adjacent lymph nodes (15). These T cells demonstrate high functionality and their presence is indicative of a favorable prognosis. Previous studies have reported that the CXCL13/CXCR5 signaling axis promotes tumor cell invasion and growth (16,17). Notably, CXCL13 levels are significantly elevated in the serum of HCC patients and may serve as an important early diagnostic and prognostic marker for HCC (6,18,19). Therefore, this study aimed to investigate the relationship between CXCL13 expression and clinicopathological features in HCC patients by measuring serum CXCL13 levels in HCC patients, cirrhosis patients, and healthy controls during the same time period. We present this article in accordance with the STARD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1306/rc).

Highlight box

Key findings

- The present study suggests that CXC chemokine ligand 13 (CXCL13) may hold clinical potential as a serological marker for hepatocellular carcinoma (HCC) diagnosis and prognosis evaluation.

What is known and what is new?

- Clinical diagnosis relies primarily on alpha-fetoprotein combined with liver imaging.
- We explored the relationship between CXCL13 expression and clinicopathological features in HCC patients by measuring serum CXCL13 levels in HCC patients, cirrhosis patients, and healthy controls during the same time period.

What is the implication, and what should change now?

- In terms of the fundamental aspects, further investigation is required to elucidate the underlying mechanisms of CXCL13 on HCC. In the clinical domain, exploring whether CXCL13/chemokine receptor 5 can serve as therapeutic targets would provide novel insights for treatment strategies.

Methods

Subjects

It is a prospective study. The observation group consisted of 74 HCC patients admitted to the Department of Infectious Diseases of The Affiliated Hospital of Guizhou Medical University from January 2023 to April 2024 consecutively, including 62 males and 12 females. The mean age was (56.99±11.36) years (range, 29–88 years). Diagnosis of HCC primarily relied on imaging examinations such as enhanced computed tomography (CT), magnetic resonance imaging (MRI), angiography, and/or tumor biopsy. Patients with autoimmune diseases and other tumors were excluded from the study. Additionally, a benign liver disease control group comprised of 51 patients diagnosed with liver cirrhosis through MRI or CT or histopathological biopsy in The Affiliated Hospital of Guizhou Medical University was randomly selected. And the patients in both the HCC and the cirrhosis group with causes unrelated to hepatitis B were excluded. Therefore, the background disease of the patients in this study was hepatitis B virus (HBV)-related liver cirrhosis and HBV-related HCC. Along with a healthy control group consisting of 53 individuals who underwent physical examination at The Affiliated Hospital of Guizhou

Medical University during the same period. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Guizhou Medical University (No. 2021316), and informed consent was obtained from all individual participants.

Detection of serum CXCL13 levels

The serum level of CXCL13 in each group was detected using the enzyme-linked immunosorbent assay (ELISA). The detection kit, purchased from Jiangsu Jingmei Biotechnology Co., LTD. (Yancheng, China), was utilized following the provided instructions. The lowest detectable limit for CXCL13 was 1 pg/mL.

Statistical analysis

The data obtained from this study were subjected to statistical analysis using Graph Pad Prism software, version 9, or IBM SPSS 27 software. Experimental results were presented as mean ± standard deviation (SD). The dose data were analyzed using independent sample *t*-test and one-way analysis of variance (ANOVA). Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic value of CXCL13 and AFP for HCC. Spearman rank correlation analysis was employed for assessing correlations. A significance level of $P<0.05$ was considered statistically significant to evaluate the potency.

Results

Basic information of patients and healthy controls

The demographic characteristics of the 74 HCC patients, including age, gender distribution, AFP levels, model for end-stage liver disease (MELD) score, Child-Pugh score, complications, and laboratory parameters are presented in *Tables 1*,*2*. The average age of the HCC patients was 57 years old with a majority being male (62 males and 12 females). Among them, AFP levels were <200 ng/mL in 49 cases, between 200–400 ng/mL in 3 cases, and >400 ng/mL in 22 cases. MELD scores indicated low risk in 47 cases, intermediate risk in 15 cases, and high risk in 12 cases. Child-Pugh classification (20) revealed that there were 28 cases of Child-Pugh A classification, 25 cases of Child-Pugh B classification, and 21 cases of Child-Pugh C classification. The most common complication observed was ascites (56.76%). The mean values of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (Tbil) and international normalized ratio (INR) were 50.81 U/L, 87.37 U/L, 50.76 μm/L, and 1.32, respectively.

The expression of CXCL13 in serum among the three groups

The ELISA method was employed to detect serum CXCL13 levels in healthy controls, cirrhosis patients, and HCC patients, as illustrated in *Figure 1*. The results revealed that the expression levels of CXCL13 were 58.83±41.29, 172.11±142.78, and 275.96±145.35 pg/mL for the three groups, respectively. One-way ANOVA analysis demonstrated a significantly higher expression of CXCL13 in the HCC group compared to both the healthy control group and cirrhosis group ($P<0.001$). Additionally, the cirrhosis group exhibited significantly elevated CXCL13 expression compared to the healthy control group ($P<0.001$). These results indicate statistically significant differences among all three groups.

The correlation between the expression level of CXCL13 and clinicopathological features

The clinical characteristics of patients in the HCC group were stratified, and the differences in CXCL13 expression across different levels of clinical characteristics were compared, as presented in *Table 3*. The findings revealed that: the serum CXCL13 level was significantly higher in HCC patients with tumor node metastasis (TNM) stage III–IV compared to those with TNM stage I–II; the serum CXCL13 level was significantly higher in HCC patients with tumor diameter >5 cm than those with tumor diameter ≤5 cm; and the serum CXCL13 level was significantly higher in HCC patients with tumor metastasis (including portal vein, hepatic vein tumor thrombus, and distant metastasis) compared to those without metastasis. All aforementioned differences exhibited statistical significance.

The correlation between CXCL13 expression levels and clinical laboratory parameters

We categorized HCC patients into two groups based on the median of continuous laboratory indicators: the group with values ≤ the median and the group with values > the median. The expression levels of CXCL13 were compared between these two groups, as presented in *Table 4*. The results revealed a significantly higher level of CXCL13 expression

Table 1 Characteristics of the patients and the HCs

Characteristics	HCC (n=74)	Cirrhosis (n=51)	HCs (n=53)
Age (years)	56.99±11.36	55.55±11.98	42.25±15.53
Sex			
Male	62 (83.78)	36 (70.59)	18 (33.96)
Female	12 (16.22)	15 (29.41)	35 (66.04)
Serum AFP (ng/mL)			
Total	4,935.63±14,301.49	11.27±27.01	4.41±1.27
<200	49 (66.22)	51 (100.00)	53 (100.00)
200–400	3 (4.05)	0 (0.00)	0 (0.00)
>400	22 (29.73)	0 (0.00)	0 (0.00)
MELD			
≤14	47 (63.51)	34 (66.67)	–
15–18	15 (20.27)	8 (15.69)	–
>18	12 (16.22%)	9 (17.65)	–
Child-Pugh classification			
A	28 (37.84)	11 (21.57)	–
B	25 (33.78)	22 (43.14)	–
C	21 (28.38)	18 (35.29)	–
Portal vein diameter (mm)	14.66±3.71	15.92±4.39	–
Ascites	42 (56.76)	38 (74.51)	–
Spontaneous bacterial peritonitis	12 (16.22)	9 (17.65)	–
Hepatic encephalopathy	4 (5.41)	3 (5.88)	–
Esophageal gastric-fundus variceal	51 (68.92)	39 (76.47)	–
Rupture and bleeding of liver cancer	3 (4.05)	–	–

Data are presented as n (%) or mean ± standard deviation. HCs, healthy controls; HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein; MELD, model for end-stage liver disease.

in HCC patients with AFP > the median compared to those with AFP ≤ the median. Similarly, there was a significant elevation in CXCL13 expression among HCC patients with γ-glutamyltransferase (GGT) > the median when compared to those with GGT ≤ the median.

Correlation analysis between CXCL13 expression level and prognostic indicators

The correlation analysis between the aforementioned clinical and liver function prognostic indicators and CXCL13 expression revealed a positive correlation with MELD score (r=0.24739, P=0.04) and GGT level (r=0.26017, P=0.03), as depicted in *Figure 2*.

ROC curve evaluation

In order to assess and compare the diagnostic efficacy of CXCL13 and AFP in patients with HCC, we divided the 125 patients collected in this study into two groups: HCC group and non-HCC group. They plotted ROC curves for AFP, CXCL13, and the combination of CXCL13 with AFP, comparing them between the two groups. The larger the area under the curve, the higher the diagnostic accuracy, as depicted in *Figure 3*. The area under the curve for CXCL13 was found to be 0.819, with a cut-off value of 204.69 pg/mL, sensitivity of 70.8%, and specificity of 82.7%. Similarly, for AFP it was observed that its area under the curve was 0.813, with a cut-off value of 7.71 ng/mL, sensitivity of 75.0%, and specificity of 82.3%. Logistic binary regression

Table 2 Clinical laboratory parameters in the patients and HCs

Parameter	HCC (n=74)	Cirrhosis (n=51)	HCs (n=53)
Hematology			
WBC (10^9/L)	6.14±5.53	6.71±5.13	6.49±1.99
Hb (g/L)	113.91±31.69	99.24±32.51	143.70±5.17
PLT (10^9/L)	126.47±96.2	110.29±109.54	237.38±57.58
Biochemistry			
ALT (U/L)	50.81±57.26	63.33±114.88	21.35±12.69
AST (U/L)	87.37±103.19	87.72±150.62	20.87±6.71
GGT (U/L)	199.96±273.29	132.6±213.23	20.68±10.84
ALP (U/L)	196.96±172.77	146.9±119.12	60.96±17.47
Albumin (g/L)	33.54±6.41	32.65±7.83	43.95±3.09
Tbil (μm/L)	50.76±69.36	97.17±163.49	9.77±5.41
CHE (U/L)	4,152.58±2,278.03	3,090.85±2,129.16	8,052.36±1,095.84
Creatinine (μm/L)	91.62±93.22	93.65±55.14	67.60±19.70
PT (s)	15.37±3.49	17.02±5.45	–
INR	1.32±0.35	1.51±0.54	–
PTA (%)	69.88±20.91	59.54±23.48	–

Data are presented as mean ± standard deviation. HCs, healthy controls; HCC, hepatocellular carcinoma; WBC, white blood cell; Hb, hemoglobin; PLT, platelets; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; ALP, alkaline phosphatase; Tbil, total bilirubin; CHE, cholinesterase; PT, prothrombin time; INR, international normalized ratio; PTA, prothrombin activity.

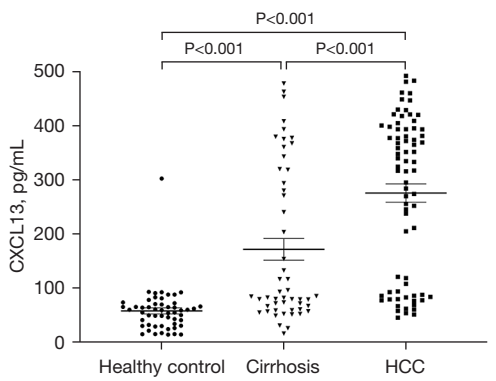

Figure 1 The serum concentration of CXCL13 was found to be significantly higher in patients with HCC (n=74) compared to those with cirrhosis (n=51) or healthy individuals (n=53). The expression levels of serum CXCL13 were analyzed in HCC, cirrhosis, and healthy controls. Statistical comparisons between the groups were performed using one-way analysis of variance. CXCL13, CXC chemokine ligand 13; HCC, hepatocellular carcinoma.

analysis along with SPSS statistical software's ROC curve were employed to determine the diagnostic efficacy when combining CXCL13 with AFP; resulting in an area under the curve value of 0.885 along with a sensitivity rate of 88.9% and specificity rate of 77.9%. A *Z*-test was conducted to compare these areas under curves for CXCL13 alone versus AFP alone as well as for their combination (CXCL13 combined with AFP). The results indicated no significant difference in diagnostic efficacy between CXCL13 and AFP (P=0.88), while demonstrating that combining CXCL13 with AFP yielded significantly better diagnostic efficacy compared to using only CXCL13 (P=0.001) or only AFP (P=0.02).

Discussion

Tumor growth, differentiation, and metastasis are not only influenced by the genetic factors and biochemical characteristics of the tumor itself but also closely associated with the immune microenvironment of the tumor.

Table 3 The correlation between the expression level of CXCL13 and clinicopathological features

Parameters	N	CXCL13 (pg/mL)	P
Age (years)			0.22
≤65	54	288.54±142.53	
>65	20	241.99±151.13	
Sex			0.24
Male	62	284.71±145.25	
Female	12	230.78±143.41	
Tumor stage			0.001
I–II	31	213.50±155.92	
III–IV	43	321.00±120.02	
Tumor size (cm)			0.005
≤5	35	227.10±149.20	
>5	39	319.80±128.44	
No. of tumors			0.25
Single	26	252.20±164.39	
Multiple	48	292.20±130.31	
Metastasis			0.02
Presence	28	324.50±120.37	
Absence	46	246.40±152.40	
MELD			0.17
≤14	47	269.04±144.67	
15–18	15	242.42±153.17	
>18	12	344.99±126.09	
Child-Pugh classification			0.86
A	28	270.86±137.68	
B	25	289.14±151.51	
C	21	267.80±155.32	
Cirrhosis			0.43
Presence	62	270.00±146.43	
Absence	12	306.50±141.74	
Ascites			0.62
Presence	42	268.60±155.49	
Absence	32	285.60±132.69	
Esophageal gastric-fundus variceal			0.50
Presence	51	268.20±148.97	
Absence	23	293.10±145.35	

Data are presented as number or mean ± standard deviation. CXCL13, CXC chemokine ligand 13; MELD, model for end-stage liver disease.

Table 4 The correlation between CXCL13 expression levels and clinical laboratory parameters

Parameter	CXCL13 (pg/mL)	P
Serum AFP (ng/ml)		0.01
≤ medium	234.80±148.12	
> medium	317.10±131.99	
WBC (10^9/L)		0.82
≤ medium	272.20±142.19	
> medium	279.80±150.32	
Hb (g/L)		0.73
≤ medium	281.80±151.40	
> medium	270.10±140.89	
PLT (10^9/L)		0.29
≤ medium	258.10±150.13	
> medium	293.80±140.16	
ALT (U/L)		0.11
≤ medium	248.90±136.45	
> medium	303.06±150.72	
AST (U/L)		0.19
≤ medium	253.50±135.73	
> medium	298.39±152.92	
GGT (U/L)		0.041
≤ medium	241.15±144.85	
> medium	310.78±143.23	
ALP (U/L)		0.78
≤ medium	280.66±131.97	
> medium	271.27±159.32	
Albumin (g/L)		0.58
≤ medium	285.35±151.62	
> medium	266.58±140.26	
Tbil (μm/L)		0.67
≤ medium	268.73±142.38	
> medium	283.20±149.87	
Cholinesterase (U/L)		0.74
≤ medium	281.58±157.83	
> medium	270.34±133.67	

Table 4 *(continued)*

Table 4 *(continued)*

Parameter	CXCL13 (pg/mL)	P
Creatinine (μm/L)		0.47
≤ medium	288.20±145.71	
> medium	263.75±145.96	
INR		0.56
≤ medium	265.96±141.18	
> medium	285.96±150.69	

Data are presented as mean ± standard deviation. CXCL13, CXC chemokine ligand 13; AFP, alpha-fetoprotein; WBC, white blood cell; Hb, hemoglobin; PLT, platelets; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; ALP, alkaline phosphatase; Tbil, total bilirubin; INR, international normalized ratio.

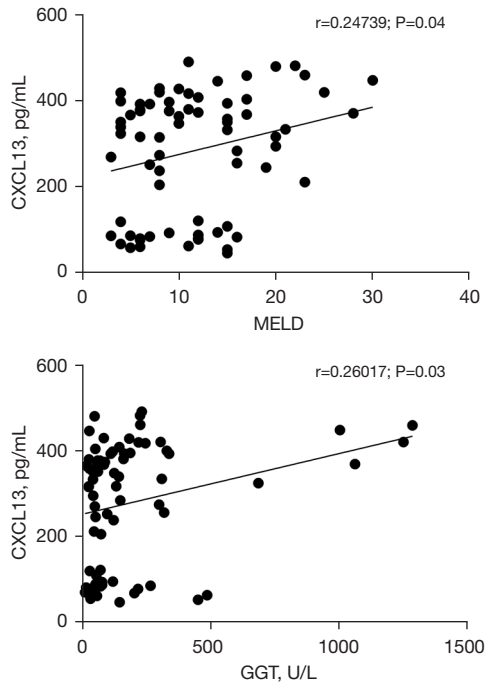

Figure 2 Correlation between serum CXCL13 levels and prognostic indicators of patients with HCC. CXCL13, CXC chemokine ligand 13; MELD, model for end-stage liver disease; GGT, γ-glutamyltransferase; HCC, hepatocellular carcinoma.

Chemokines are a family of chemotactic cytokines or ligands that selectively attract and activate different cell types (21-23). The interaction between chemokine ligands and receptors involves significant signaling plasticity and complexity, which is crucial for fine-tuning the chemical

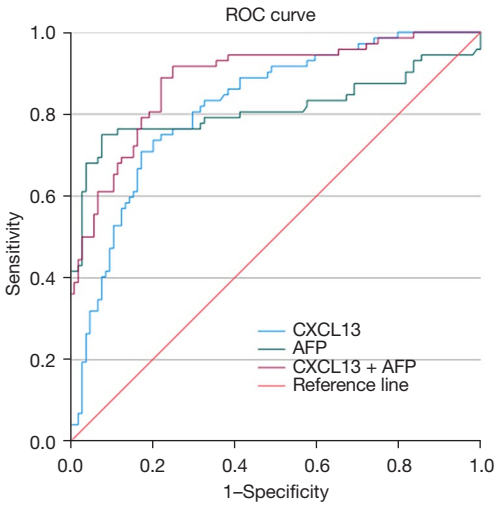

Figure 3 ROC curves of the HCC group compared with the non-HCC group. ROC, receiver operating characteristic; CXCL13, CXC chemokine ligand 13; AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma.

attraction of specific leukocyte subsets (23). However, disruption in chemokine signaling events can have multiple effects on determining the course of tumor initiation and progression (24). Elevated expression levels of various chemokine ligands and receptors have been reported in numerous tumors (25-31); indicating that aberrant activation of potential signaling effectors can impact key processes in most cancers (23,32-34). There have been several studies on the CXCL13/CXCR5 signaling axis in different tumors (35-37), and CXCL13-mediated recruitment of $CXCR5^{+}CD8^{+}$ T cells in the liver contributes to viral control during chronic HBV infection (38). However, there is limited research on the role played by the CXCL13/CXCR5 signaling axis in liver cancer. HCC is closely associated with chronic HBV infection. Therefore, this study aims to analyze serum expression levels of CXCL13 among HCC patients, cirrhosis patients, and healthy controls to preliminarily explore the relationship between CXCL13 and occurrence, development as well as clinical prognosis of HCC.

The present study revealed a significant upregulation of CXCL13 expression in patients with HCC compared to both healthy controls and cirrhosis. Additionally, the expression of CXCL13 was significantly higher in cirrhosis patients than in healthy controls. These results suggest that CXCL13 is highly expressed in HCC and plays a crucial role in tumor occurrence and development through the

recruitment of Tfh, B cells and $CXCR5^{+}CD8^{+}$ T cells by CXCL13 within the tumor microenvironment to exert an anti-tumor effect. Liver cirrhosis is characterized by chronic liver inflammation and repeated repair processes. The main pathogenesis involves persistent inflammation, leading to infiltration of numerous inflammatory cells into the liver during fibrosis and cirrhosis (39). In this study, we observed a significantly elevated level of serum CXCL13 in patients with cirrhosis compared to healthy individuals, which may be attributed to the local inflammatory state within the liver among these patients.

In addition, the results of this study revealed a significant correlation between serum CXCL13 expression and TNM stage, tumor size, and tumor metastasis in patients with HCC. These results suggest that CXCL13 may play a crucial role in the invasion and metastasis of HCC cells, indicating its potential as a serological marker for diagnosing and evaluating HCC metastasis.

The liver reserve function of patients with HCC is generally impaired, and the majority of HCC patients also suffer from cirrhosis. Among them, those with decompensated cirrhosis are particularly susceptible to liver failure. Adequate liver reserve function is crucial for the treatment of HCC, including hepatectomy, transarterial chemoembolization (TACE), and targeted immunotherapy, as it serves as an important prognostic factor. Therefore, we conducted a correlation analysis between laboratory indicators of liver function and composite scores with CXCL13 levels. Our findings revealed a positive correlation between MELD score and GGT level with CXCL13 expression in HCC patients. Thus, CXCL13 may serve as a serological marker for evaluating the prognosis of HCC patients.

In order to further investigate the diagnostic efficacy of CXCL13 for HCC patients, a total of 125 patients were enrolled in this study and divided into two groups: the HCC group and the non-HCC group. ROC curves were constructed for AFP, CXCL13, and the combination of CXCL13 with AFP, which were then compared between the two groups. The results revealed that there was no significant difference in diagnostic efficacy between CXCL13 and AFP alone. However, when AFP being combined with CXCL13 the ROC curves exhibited significantly improved diagnostic efficacy compared to either marker alone. This suggests that combining CXCL13 with AFP can enhance both sensitivity and efficacy in diagnosing HCC.

Previous study had only drawn ROC curves for CXCL13 using healthy individuals as controls for the HCC group (19). However, clinically distinguishing HCC from liver cirrhosis or regenerative nodules is more common. Therefore, this study included 51 patients with liver cirrhosis (including a small number of patients with liver regenerative nodules) as well as healthy individuals to form the non-HCC group. Consequently, this study obtained a more accurate diagnostic cut-off value for CXCL13. Furthermore, our findings confirmed that serum levels of CXCL13 in HCC patients were significantly higher than those in both liver cirrhosis patients and healthy controls. Nevertheless, the proportion of patients with advanced HCC was higher compared to those with early HCC in our study, which is attributed to the fact that a majority of HCC patients are diagnosed at an advanced stage, thereby rendering the sample of HCC patients less representative. And the effect and mechanism of CXCL13 on HCC remain unclear and need further exploration.

Conclusions

The expression of CXCL13 is significantly upregulated in the serum of patients with HCC, and its levels are associated with tumor TNM stage, size, metastasis, as well as GGT and MELD score. The findings suggest that CXCL13 may hold clinical potential as a serological marker for HCC diagnosis and prognosis evaluation, while also serving as a promising therapeutic target for further exploration and investigation.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Guizhou Medical University (No. 2021316), and informed consent was obtained from all individual participants.

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