

Preliminary Study on Clinical Features of Cryptogenic Liver Cancer Based on Clinical Data of 128 Patients with Primary Liver Cancer

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Abstract

Background: To compare the clinical features of viral and cryptogenic liver cancer and to provide evidence of or reference the clinical identification of cryptogenic liver cancer and diagnosis and treatment using Chinese and Western medicine.

Methods: A retrospective analysis of the clinical data (general conditions, laboratory indicators, initial symptoms, and Traditional Chinese medicine (TCM) syndrome types) of 92 cases of viral liver cancer (VLC) and 36 cases of cryptogenic liver cancer (CLC) was performed by using SPSS version 20.0 statistical software.

Results: There were significant differences in triglyceride, γ -glutamyl transpeptidase, and alkaline phosphatase levels, liver fibrosis index (Fibrosis 4 Score, APRI), and initial symptoms ($P < 0.05$) between VLC and CLC. However, there was no statistical difference in TCM syndrome types. Among the 128 patients with primary liver cancer, there was a high proportion of women with cryptogenic liver cancer. Compared to the VLC group, the CLC group was older, had a lower incidence of cirrhosis, and had a higher proportion of surgical resection.

Conclusions: Although the number of research cases was limited, the occurrence of cryptogenic liver cancer was more likely to be associated with abnormal metabolic factors. Cryptogenic liver cancer should be considered in the differential diagnosis when liver fibrosis indicators are detected.

Keywords: Cryptogenic liver cancer; Viral liver cancer; Clinical features; Risk factors; TCM syndrome

Background

Partially idiopathic primary liver cancer with an etiology other than viral hepatitis, excessive drinking, autoimmune liver disease, or hereditary metabolic liver disease is currently known as cryptogenic liver cancer [1]. In this study, a retrospective analysis of primary liver cancer clinical data was performed to compare the similarities and differences between cryptogenic and viral liver cancer with the aim of improving the diagnosis, treatment, and clinical differentiation of cryptogenic liver cancer.

Methodology

General data

A total of 128 patients diagnosed with liver cancer and admitted to our hospital between December

2015 and March 2018 were included. The diagnosis of liver cancer was in accordance with the 2017 Guidelines for the Diagnosis and Treatment of Primary Liver Cancer. The patients were divided into two groups based on the presence or absence of viral infection: a viral liver cancer ($n = 92$; primary liver cancer with confirmed hepatitis B virus [HBV] or hepatitis C virus [HCV] infection) and a cryptogenic liver cancer group ($n = 36$). The study was approved by our hospital's institutional review board, which waived the need for informed consent because of its retrospective nature.

Diagnostic criteria

Diagnostic criteria for cryptogenic liver cancer.

There are currently no unified guidelines or consensus for cryptogenic liver cancer, which is diagnosed by exclusion primarily using the following diagnostic criteria of the 9th National Conference on

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Liver Diseases in Guangzhou in September 2001: (1) No serological or clinical evidence of HBV or HCV infection; (2) alcohol consumption < 40 g/day for men or 20 g/day for women; and (3) no evidence of other causes of chronic liver disease, such as autoimmune hepatitis, drug-induced hepatitis, hemochromatosis, Wilson's disease, Budd-Chiari syndrome, primary biliary cirrhosis, or primary sclerosing cholangitis.

Traditional Chinese medicine syndrome type of liver cancer

This is defined based on the Guiding Principles for Clinical Study of New Chinese Medicines [2] combined with the diagnosis, treatment pathways, and conventions for primary liver cancer in our prevention and treatment center: liver heat blood stasis syndrome, liver and gallbladder damp heat syndrome, liver and spleen deficiency syndrome, spleen deficiency damp obstruction syndrome, liver and kidney yin deficiency syndrome, qi stagnation blood stasis syndrome, and spleen deficiency blood stasis syndrome.

Metabolic syndrome diagnostic criteria

According to the diagnostic criteria for metabolic syndrome established by the Chinese Medical Association Chinese Diabetes Society in 2004, they are as follows: [3] (1) central obesity (body mass index [BMI] $\geq 25 \text{ kg/m}^2$); (2) hypertension $\geq 140/90 \text{ mmHg}$ and/or current diagnosis of hypertension; (3) hyperglycemia (fasting blood glucose) $\geq 6.1 \text{ mmol/L}$ and/or 2-h postprandial blood glucose $\geq 7.8 \text{ mmol/L}$; and (4) hyperlipidemia (triglycerides [TG] $\geq 1.7 \text{ mmol/L}$) and/or fasting high-density apolipoprotein cholesterol ($<0.9 \text{ mmol/L}$ in males, $<1.0 \text{ mmol/L}$ in females).

Inclusion and exclusion criteria

Inclusion criteria are as follows: (1) meeting the diagnostic criteria for primary liver cancer; (2) being 18 years of age or older; (3) having a Karnofsky Performance Status Scale score ≥ 50 points; and (4) having complete four-diagnostic information available.

Exclusion criteria are as follows: (1) inclusion criteria not met; (2) severe heart, brain, or kidney disease, or mental disability; (3) poor compliance, unwillingness or refusal to undergo follow-up; and (4) history of alcoholism (alcohol consumption $\geq 40 \text{ g/day}$ in males or $\geq 20 \text{ g/day}$ in females; $> 80 \text{ g/day}$ for 5 years or 2 weeks consecutively).

Observational indices

General characteristics (age, sex, surgical status, metabolic syndrome, cirrhosis, Child-Pugh classification), relevant laboratory indices such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ -glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), serum albumin (ALB), blood lipids (total cholesterol [CHO], TG), and alpha-fetoprotein (AFP), initial symptoms, and traditional Chinese medicine (TCM) syndrome types.

Statistical analysis

The statistical analysis was performed using SPSS 20.0 statistical software. The level of significance was $\alpha = 0.05$. Continuous data were first tested for normality and variance. Mean $\pm$ standard deviation was used to express normal data, while median and interquartile range were used to express non-normal data. The t-test was used for continuous data conforming to the normal distribution, while the rank-sum test was used for data not conforming to the normal distribution. The χ^2 test was used for count data. The rank-sum test for comparing two samples was used for ordinal data. Logistic regression analysis and Spearman's regression analysis were used for the correlation analysis. The survival function was analyzed using the Kaplan-Meier method.

Results

Clinical characteristics

The patients' general information and cirrhosis background are compared in Table 1. Among the 128 patients with primary liver cancer, there was a high proportion of women with cryptogenic liver cancer. Compared to the viral liver cancer group, the cryptogenic liver cancer group was older, had metabolic syndrome, and had a higher proportion of surgical resection. History of smoking and family history were higher in the viral liver cancer group; the intergroup difference was statistically significant ($P < 0.05$). There was no statistically significant intergroup difference in Child-Pugh classification ($P > 0.05$), but there were statistically significant intergroup differences in metabolic syndrome ($P = 0.012$) and the proportion of patients with cirrhosis ($P < 0.001$).

Laboratory tests

Comparison of liver function between the two groups. There were statistically significant

intergroup differences in GGT ($z = 0.048$) and ALP ($z = 0.009$) but no statistically significant intergroup differences in serum ALT, AST, total bilirubin (TBIL), ALB, and albumin/globulin (A/G). There was a statistically significant intergroup difference in ALP ($P = 0.03$) but no statistically significant intergroup differences in ALT, AST, GGT, ALB, A/G, or cholinesterase (CHE) (Table 2).

Comparison of blood lipids and glucose indices.

There were statistically significant intergroup differences in TG ($P = 0.01$). There were no statistically significant differences in CHO, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), or blood glucose (Table 2) between VLC and CLC.

Comparison of liver fibrosis indices FIB-4 and APRI.

APRI = $[\text{AST (IU/L)} / \text{ULN}] \times 100 / \text{PLT (109/L)}$; and FIB-4 = $[\text{Age (yrs)} \times \text{AST (IU/L)}] / [\text{PLT (109/L)} \times \text{ALT (IU/L)}^{1/2}]$. The serum FIB-4 and APRI values of the cryptogenic liver cancer group were significantly lower than those of the viral liver cancer group ($P = 0.033$ and $P = 0.017$, respectively) (Table 2).

Comparison of tumor markers.

When the AFP positivity rate in the cryptogenic liver cancer group (44.4%) was lower than that of the viral liver cancer group (65.3%), the difference was significant ($P = 0.031$) (Table 3). When the AFP positivity rate in the cryptogenic liver cancer group (19.4%) was lower than that of the viral liver cancer group (40.2%), the difference was statistically significant ($P = 0.026$). There was no statistically significant intergroup difference in carcinoembryonic antigen (CEA) positivity rate ($P = 0.222$).

Comparison of initial symptoms. The top three initial symptoms in the cryptogenic liver cancer group were flank and abdominal pain, jaundice, and asymptomatic (accidental findings by routine health examination). The top three initial symptoms in the viral liver cancer group were asymptomatic (accidental findings by routine health examination), flank and abdominal pain, and abdominal distension. The difference in initial symptoms between the two groups was statistically significant ($P = 0.018$) (Table 4).

Comparison of TCM syndrome types. There are seven TCM syndrome types: liver heat blood stasis syndrome, liver and spleen deficiency syndrome,

Table 1. Comparison of baseline characteristics

		Cryptogenic liver cancer group	Viral liver cancer group	<i>P</i>
Sex	Male	22 (61.1%)	75 (81.5%)	*0.015
	Female	14 (38.9%)	17 (18.5%)	
Age (years)	-	67.61 ± 9.810	61.88 ± 8.773	**0.002
	A	16 (44.4%)	33 (35.9%)	
Child-Pugh score	B	16 (44.4%)	47 (55.1%)	0.400
	C	4 (11.2%)	12 (13.0%)	
Surgery	No	23 (63.9%)	75 (81.5%)	*0.034
	Yes	13 (36.1%)	17 (18.5%)	
History of smoking	No	24 (66.7%)	39 (42.4%)	*0.014
	Yes	12 (33.3%)	53 (57.6%)	
Family history	No	29 (80.6%)	50 (54.3%)	**0.006
	Yes	7 (19.4%)	42 (45.7%)	
Metabolic syndrome	No	25 (69.4%)	81 (88.0%)	*0.012
	Yes	11 (30.6%)	11 (12.0%)	
Cirrhosis	No	20 (55.6%)	16 (17.4%)	**<0.001
	Yes	16 (44.4%)	76 (82.6%)	

Table 2. Comparison of liver function, metabolic, and liver fibrosis indices

		Cryptogenic liver cancer	Viral liver cancer	P
Liver function	GGT ¹	188.90 (74.50, 448.93)	119.40 (51.35, 270.33)	*0.048
	ALP	213.90 (112.03, 423.18)	135.250 (87.18, 244.00)	**0.009
Liver lipid profile	CHO	4.34 (3.23, 5.94)	3.91 (3.44, 5.15)	0.488
	TG	1.12 (0.87, 1.72)	0.88 (0.65, 1.30)	*0.010
	HDL-C	0.79 (0.66, 1.15)	0.90 (0.66, 1.16)	0.454
	LDL-C	2.54 (1.98, 3.91)	2.57 (2.01, 3.24)	0.756
Blood glucose	GLU	5.25 (4.71, 6.31)	5.09 (4.50, 5.98)	0.505
Liver fibrosis indices	FIB-4	3.242 (2.041, 4.739)	4.22 (2.591, 7.127)	*0.033
	APRI	1.139 (0.499, 1.481)	1.199 (0.618, 2.172)	*0.017

¹GGT:γ-glutamyl transpeptidase; ALP: alkaline phosphatase; CHO: cholesterol; TG: triglyceride; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; GLU: blood glucose; liver fibrosis index: Fibrosis 4 Score, APRI.

Table 3. Comparison of AFP and CEA positivity rates

Tumor marker	Status	Cryptogenic liver cancer	Viral liver cancer	P
AFP (>20 ng/mL)	Positive	16 (44.4%)	60 (65.3%)	*0.031
AFP (>400 ng/mL)	Positive	7 (19.4%)	37 (40.2%)	*0.026
CEA (>5 ng/mL)	Positive	12 (33.3%)	21 (22.8%)	0.222

Table 4. Comparison of initial symptoms

		Cryptogenic liver cancer group		Viral liver cancer group	
		n	%	n	%
Initial symptom	None (found on physical examination)	4	11.1	27	29.3
	Fatigue	2	5.6	3	3.3
	Flank/abdominal pain	12	33.3	22	23.9
	Abdominal distension	3	8.3	16	17.4
	Jaundice	7	19.4	3	3.3
	Emaciation	2	5.5	3	3.3
	Poor appetite, vomiting	1	2.8	7	7.6
	Fever	2	5.6	6	6.4
	Diarrhea	0	0	2	2.2
	Hiccup	2	5.6	0	0
	Dyspnea	1	2.8	0	0
	Edema	0	0	1	1.1
	Shoulder/back pain	0	0	1	1.1
	Low back pain	0	0	1	1.1
	Total	36	100	92	100

Table 5. Comparison of different TCM syndrome types

		Number		<i>P</i>
		Cryptogenic liver cancer group	Viral liver cancer group	
TCM syndrome	Liver heat blood stasis syndrome	5	11	0.766
	Liver and spleen deficiency syndrome	6	15	0.960
	Liver and gallbladder damp heat syndrome	8	18	0.737
	Spleen deficiency damp obstruction syndrome	5	10	0.633
	Liver and kidney <i>yin</i> deficiency syndrome	5	22	0.211
	Qi stagnation blood stasis syndrome	7	11	0.273
	Spleen deficiency blood stasis syndrome	0	5	0.154

liver and gallbladder damp heat syndrome, spleen deficiency damp obstruction syndrome, liver and kidney *yin* deficiency syndrome, *qi* stagnation blood stasis syndrome, and spleen deficiency blood stasis syndrome. The differences between the two groups were not statistically significant ($P = 0.597$) (Table 5).

Discussion

To date, HBV, HCV, and alcohol have been recognized as three of the major causes of primary liver cancer. The etiology of cryptogenic liver cancer remains unknown, and it is currently believed that nonalcoholic fatty liver disease (NAFLD), including nonalcoholic steatohepatitis (NASH), is a potential causative factor [4]. With the normal application of drugs against HBV and HCV infection, primary liver cancer caused by viral infection can be gradually controlled, the spectrum of NAFLD is continuously extended, and NAFLD is closely associated with the metabolic syndrome, especially obesity, type 2 diabetes, and dyslipidemia [5].

The present study showed statistically significant differences in age, sex, metabolic syndrome, and blood lipids (TG) between the two groups of patients ($P < 0.05$). Cryptogenic liver cancer patients had later mean age at onset, which is consistent with a study by Chen et al. [6]; this may be due to long-term repeated low-intensity effects of certain pathogenic factors leading to the delayed onset of liver cancer. Studies have found that the mean age of

patients with cryptogenic cirrhosis (CC) is 8 years later than that of patients with HCV-related cirrhosis and the age at which CC progresses to liver cancer in CC patients is about 3 years later than that in those with HCV-related cirrhosis, which demonstrates that the development of NAFLD is a long and slow process. We found that the proportion of patients in the cryptogenic liver cancer group complicated with metabolic syndrome (30.6%) was significantly higher than that in the viral liver cancer group (12.0%), as was the TG level, indicating that NAFLD may be an important cause of the development of cryptogenic liver cancer. In the present study, the proportion of women was higher in the cryptogenic liver cancer group than in the viral liver cancer group, which may be related to the relatively high incidence of obesity among middle-aged and elderly women.

A study [7] reported that diabetes is strongly correlated with the development of NAFLD. Insulin resistance and hyperinsulinemia play an important role in the pathogenesis of NAFLD-related liver cancer. However, the case data in the present study did not indicate a difference in blood glucose between cryptogenic liver cancer and viral liver cancer patients. Of course, one reason is the limited number of cases, but disordered glucose metabolism in the course of liver cancer cannot be ruled out since it may mask the relationship with the difference in blood glucose levels between the two groups.

The present study also found that among the liver function indices, GGT and ALP were worse in the cryptogenic liver cancer group than in the viral

liver cancer group. In a study of 2,645 patients with primary liver cancer (HCC), Hsu et al. [8] indicated that liver and kidney function were worse in patients with cryptogenic liver cancer than in those with liver cancer due to other causes. The reason may be that cryptogenic liver cancer is hidden and difficult to identify in the early stages.

In the present study, when the threshold of AFP was defined as 400 ng/mL, the positive detection rate of cryptogenic liver cancer was 19.4%, significantly lower than that of viral liver cancer (40.2%). These results are consistent with those of Reddy et al. and Hsu et al. [8-10]; that is, the proportion of patients with elevated AFP in the cryptogenic liver cancer group was smaller than that among patients with other types of liver cancer. Notably, when the threshold of AFP was defined as 20 ng/mL, the positive detection rate of the cryptogenic liver cancer group increased (44.4%). Although this value was lower than that of the viral liver cancer group (65.3%), the difference was statistically significant ($P < 0.05$), indicating that AFP (alone or combined with CEA) is less sensitive for diagnosing cryptogenic liver cancer.

Liver fibrosis and cirrhosis account for 80% of all patients with primary liver cancer in China. Of the 128 patients with primary liver cancer included in the present study, 92 were complicated by cirrhosis, accounting for 72% of the total, which is consistent with previous reports. However, the incidence of CC and liver fibrosis indices (FIB-4, APRI) were significantly lower than in the viral liver cancer group. Previous retrospective studies showed that the proportion of patients with virus-related cirrhosis is 71.1% and the proportion with cryptogenic cirrhosis is 6.9%, although related studies support the disease progression of NAFLD-NASH-CC-HCC [11]. However, a study by Chagas et al. [12] showed that NAFLD can directly progress to HCC without development of cirrhosis in some patients. Measuring the new indices APRI and FIB-4 has become routine in China [13], and it is starting to become widely used in clinical practice. However, whether measurement of liver fibrosis indices has clinical significance for etiological analysis and early identification of cryptogenic liver cancer must be confirmed in further studies.

The present study showed that the main initial symptom of cryptogenic liver cancer in patients is flank/abdominal pain and jaundice, and the proportion of patients who undergo surgical treatment was higher in this group than in the viral liver cancer group ($P < 0.05$). The frequency of disease identification during physical examination

was higher in the viral liver cancer group than in the cryptogenic liver cancer group, but the proportion of patients who underwent surgical treatment was relatively low. This may be because despite viral liver cancer being discovered earlier, the conditions of more such patients are complicated by cirrhosis and they have poor baseline liver functions, reducing the opportunity for surgical treatment. Siriwardana et al. [8] found that patients with cryptogenic liver cancer have more single tumors, which may be the reason for the greater opportunities for surgical treatment. The present study also showed that although the prognosis of the cryptogenic and viral liver cancer groups was generally similar, patients in the latter group were often in the middle and late stages at the time of diagnosis and prognosis was poor due to limited treatment options.

There are no names for cryptogenic liver cancer in the annals of TCM, and the literature contains no records comparing the TCM syndrome types of cryptogenic liver cancer with those of viral liver cancer. At the time of consultation, we confirmed the diagnosis of patients based on flank pain, hepatocarcinoma, abdominal mass, and jaundice in the TCM lexicon and found that TCM syndrome type tends to include liver and gallbladder damp heat syndrome, qi stagnation blood stasis syndrome, and liver stagnation and spleen deficiency syndrome. Further studies require the accumulation of more case studies to develop a relatively uniform type of TCM syndrome and refine the evaluation system for TCM syndrome differentiation, which will be an important step toward more effective and beneficial comprehensive treatment of liver cancer using TCM.

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Citation: Zhao YH, Chen MY, Yang RX, Lv Q. Preliminary Study on Clinical Features of Cryptogenic Liver Cancer Based on Clinical Data of 128 Patients with Primary Liver Cancer. *Gastroenterology & Hepatology Research*, 2019, 1 (1): 11-17.

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