ORIGINAL RESEARCH

Multiple Diagnostic Indicators in the Development of Chronic Hepatitis B, Liver Cirrhosis, and Liver Cancer

Chao Yang, BS; Huijuan Geng, BS; Shanshan Zhu, BS; Xiaomeng Zheng, BS; Tiemin Li, MMed; Lin Duan, BS

ABSTRACT

Context • Hepatitis B can develop into cirrhosis, and most liver cancers evolve on the basis of chronic hepatitis and cirrhosis. Many patients are already at an advanced stage when diagnosed. In recent years, clinicians have advocated detection of liver cancer using multiple markers in combination to improve the sensitivity and specificity of testing.

Objective • The study aimed to evaluate the clinical value of using four tumor indicators—urea, alpha L-fucosidase (AFU), carbohydrate antigen 153 (CA153), carbohydrate antigen 125 (CA125), and alpha fetoprotein (AFP) and comparing the use of combined indicators to use of a single indicator for the diagnosis of liver cancer.

Design • The research team performed a prospective study.

Setting • The study took place at Clinical Laboratory, Baoding People's Hospital, Baoding City, Hebei Province, China.

Participants • Participants were 98 patients with chronic hepatitis B, who became the CHB group; 102 patients with liver cirrhosis, who became the cirrhosis group, and 100 patients with liver cancer, who became the liver cancer group. They all had been admitted to the hospital between March 2019 and March 2021.

Outcome Measures • The research team measured the urea, AFU, CA153, CA125, and AFP levels of the three groups, constructed an ROC curve, and analyzed the diagnostic values of the indicators singly and in combination for liver cancer.

Results • For the levels of urea, AFU, CA153, CA125, and AFP, the CHB group's levels were significantly lower than those of the cirrhosis and liver cancer groups (both $P < .001$), and the cirrhosis group's levels were significantly lower than those of the liver cancer group ($P < .001$). In the CHB group, the compensatory group's levels were significantly lower than those of the decompensated group ($P < .05$). In the cirrhosis group, no significant differences existed between the levels of the grade A and grade B groups ($P < .001$), between those of the grade A and grade C groups ($P < .001$), or between those of the grade B and grade C groups ($P < .001$). In the cirrhosis group, the levels of the no ascites group were significantly lower than those of the ascites group ($P < .05$). In the liver cancer group, the levels of the stage I-II group were significantly lower than those of the stage III and stage IV groups (both $P < .05$), and those of the stage III group were significantly lower than those of the stage IV group ($P < .05$). The levels of the <5cm group were significantly lower than those of the ≥5cm group ($P < .001$). The value of using a combination of indicators for diagnosis was significantly higher than that of a single indicator ($P < .001$).

Conclusions • Urea, AFU, CA153, CA125, and AFP all have diagnostic value in the evaluation of chronic hepatitis B-cirrhosis and liver cancer, with the highest efficacy, sensitivity and specificity from a combined test and diagnosis (*Altern Ther Health Med.* 2023;29(3):153-159).

Chao Yang, BS, Physician; **Shanshan Zhu,** BS, Physician; **Xiaomeng Zheng,** BS, Physician; **Tiemin Li,** MMed, Physician; **Lin Duan,** BS, Physician; Clinical Laboratory, Affiliated Hospital of Hebei University, Baoding City, Hebei Province, China. **Huijuan Geng,** BS, Physician, Clinical Laboratory, Baoding People's Hospital, Baoding City, Hebei Province, China.

Corresponding author: Lin Duan, MMed
E-mail: duanlin1030@163.com

Hepatitis B virus (HBV) is the main pathogen causing hepatitis B.[1] Huang et al found that the infection rate for hepatitis B in China is about 65% of the population.[2] Hepatitis can further develop into cirrhosis, and most liver cancers evolve on the basis of chronic hepatitis and cirrhosis.

China is a large country with a significant incidence of liver cancer. The number of patients with liver cancer in China account for about 50% of those worldwide, which seriously impairs public health and safety.[3] Song and Liu found that most liver cancer in China develops on the basis

of chronic hepatitis B and liver cirrhosis.[4] Accurate and effective diagnosis and differentiation of different stages of hepatitis B is the key to preventing tumor progression.

Due to liver cancer's high degree of malignancy, rapid progression, and strong invasiveness, many patients are already at an advanced stage when diagnosed, and no complete radical cure exists for liver cancer at present, leading to a poor prognosis for patients.[5] Increasing the early diagnosis of liver cancer is key to improving its prognosis.

Multiple Diagnostic Indicators

In recent years, with the progress of molecular biology in cancer research, researchers have found more and more biological indicators for tumor discrimination to provide a basis for treatment.

Although the discovery of such indicators has provided new ideas for the diagnosis of liver cancer, single indicators have problems, such as low sensitivity and low specificity. In recent years, clinicians have advocated detection using multiple markers in combination to improve the sensitivity and specificity of testing.

Disease Indicators

Urea. Urea is a commonly used indicator for evaluating renal function. The normal value of urea is between 2.5 and 7.5mmol/L.[6] Decreased urea isn't of great clinical significance but may occur when the body suffers from malnutrition. An increase in the urea index is of great clinical significance and indicates renal failure.

Patients with liver cancer are prone to hypoproteinemia or ascites due to a protein-synthesis disorder, which is more likely to lead to hepatorenal syndrome. This syndrome can specifically manifest as an increase in the urea index, and different degrees of liver injury can increase urea to different degrees.

Alpha L-fucosidase (AFU). AFU is a lysosomal acid hydrolase widely distributed in the body's tissues and cells. It's involved in the catabolism of glycoproteins and glycolipids containing fucosyl in blood and body fluids and has high activity in the liver, kidneys, and other organs.[6] Clinical studies have pointed out that AFU has diagnostic value for primary liver cancer, but its application is limited due to low sensitivity and specificity.[7]

Carbohydrate antigen 153 (CA153). Researchers first identified serum CA153 in breast cancer. Li et al found that other kinds of tumors, such as ovarian cancer, gastric cancer, and pancreatic cancer, show high expression CA153 in patients' serum, but the specificity and sensitivity of CA153 are insufficient as a single indicator for the diagnosis of liver cancer.[8]

Carbohydrate antigen 125 (CA125). CA125 is a typical tumor marker in epithelial ovarian-cancer tissues. However, Ante et al found that CA125 also exists in ascites in addition to the ovarian epithelium and is rapidly secreted when the peritoneum is subjected to nonspecific stimuli, such as portal hypertension, peritonitis, and cancer metastasis.[9] Yang et al found that CA125 reflects the degree of liver-function damage in patients with liver cirrhosis and can provide a reference for predicting the occurrence of ascites in patients with liver cirrhosis.[10]

Alpha fetoprotein (AFP). Serum AFP is mainly derived from liver-cancer cells and plays a very important role in the diagnosis and study of liver cancer.[11] However, Cheng et al found that a considerable part of AFP is derived from the bile-duct endothelial system and can easily interfere with the diagnosis of liver cancer and lead to misdiagnoses.[12]

Current Study

The current study aimed to evaluate the clinical value of using four tumor indicators—urea, α-L-fucosidase (AFU), carbohydrate antigen 153 (CA153), carbohydrate antigen 125 (CA125), and alpha-fetoprotein (AFP)—and comparing the use of combined indicators to use of a single indicator for the diagnosis of liver cancer.

METHOD

Participants

The research team performed a prospective study, which took place at Clinical Laboratory, Baoding People's Hospital, Baoding City, Hebei Province, China. Potential participants were patients with chronic hepatitis B, who became the CHB group; patients with liver cirrhosis, who became the cirrhosis group; and patients with liver cancer, who became the liver cancer group. They all had been admitted to the hospital between March 2019 and March 2021.

The study included potential participants if they: (1) had met the diagnostic criteria for chronic hepatitis B in the *Guidelines for the Prevention and Treatment of Chronic Hepatitis B, 2019 edition,*[13] or for liver cirrhosis in the *Chinese Medical Association's Guidelines for the Diagnosis and Treatment of Liver Cirrhosis*,[14] or for liver cancer in the *Guidelines for Stratified Screening and Surveillance of Primary Liver Cancer, 2020 edition*[15]; (2) had not received relevant treatment during the 3 months prior to their hospital admission; and (3) had an Eastern Collaborative Oncology Group (ECOG) score of 0-1.[16]

The study excluded potential participants if they: (1) were breastfeeding or pregnant women, (2) had a previous history of bone-marrow or autologous stem-cell transplantation, (3) had other malignant tumors, (4) had a difficult-to-control systemic infection or other major disease, or (5) had an abnormal coagulation function.

The Medical Ethics Committee of the hospital approved the study's protocols. The study was conducted in strict compliance with the Declaration of Helsinki, and all study subjects signed an informed consent form.

Procedures

Venous blood collection. To determine the values for the diagnostic indicators, the research team: (1) collected 5 ml of participants' fasting peripheral venous blood, (2) centrifuged it at 3000 r/min for 10 min, and (3) collected and stored the upper serum at -70°C for testing.

The research team purchased the AU5821 automatic biochemical analyzer (Beckman Coulter Company, Brea, California, USA) to measure the urea level and AFU and the Roche E601 electrochemiluminescence analyzer (Roche Diagnostic Products, Shanghai, China) to measure the CA153, CA125, and AFP levels. The instrument was equipped with the original reagents, and the operation was carried out strictly according to the manufacturers' instructions.

Outcome Measures The research team measured the urea, AFU, CA153, CA125, and AFP levels of the three groups, constructed an ROC curve, and analyzed the diagnostic values of the indicators singly and in combination for liver cancer.

Outcome Measures

Diagnostic indicators. AFU is a marker for detecting primary liver cancer, and elevated levels may be caused by acute hepatitis or diseases such as cirrhosis or primary liver cancer.[17] CA125 and CA153 are common clinical tumor markers, and elevated levels of the markers suggest that a tumor lesion may be present somewhere in the body. [18] AFP is used as an aid in the diagnosis of primary liver cancer and other malignancies, elevated levels of AFP can be detected in the serum of 80% of patients with primary liver cancer.[19] Urea is used to respond to kidney function, with higher levels indicating poorer kidney function.[20]

Indicators for the CHB group. The research team divided the CHB group into compensatory group and decompensated group according to the compensatory situation. CHB compensated stage: The patient has some symptoms, but the liver is still able to exercise normal functions. CHB decompensated stage: CHB progresses to cirrhosis, and the remaining functions of the liver itself can no longer undertake the normal functional operation of the body.

Indicators for the cirrhosis group. The research team divided the cirrhosis group: (1) into the grade A, grade B, and grade C groups according to Child-Pugh classification.[21] and (2) into the ascites and the no ascites groups according to ascites status. The different status of the 5 indicators (general condition, ascites, serum bilirubin, serum albumin concentration and prothrombin time) of the patients were divided into three levels, with scores of 1, 2 and 3, respectively, and the scores of the 5 indicators were summed, with the lowest total score being 5 and the highest score being 15. Grade A: 5-6 points, low surgical risk, best prognosis, 1-2 year survival rate of 100% to 85%. Grade B: 7-9 points, moderate surgical risk, 1~2 years survival rate 80%~60%. Grade C: ≥10 points, greater surgical risk, worst prognosis, 1~2 years survival rate 45%~35%.

Indicators for the liver cancer group. The research team divided the liver cancer group: (1) into the stage I-II, stage III, and stage IV groups according to the stages of the participants' liver cancer and (2) into the ≥ 5cm and <5 cm group, according to the participants' tumor diameters. Stage I: single tumor, no vascular invasion, extrahepatic metastasis, and liver function of Child-Pugh grade A or B. Stage II: 2~3 tumor numbers, single tumor maximum diameter >3 cm, no vascular invasion, extrahepatic metastasis. Stage III: with vascular invasion. Stage IV: Child-Pugh grade C.[22]

Statistical Analysis

The research team used the SPSS22.0 software (company, city, state, country) for data analysis. The team: (1) expressed count data as numbers and percentages (%) and performed the χ^2 test to compare the groups, (2) expressed the measurement data with normal distribution as means ± standard deviations (SDs) and performed the *t* test to compare the groups, (3) performed a one-way analysis of variance (ANOVA) with a least standard difference (LSD) test if a variance was uniform and the Dunnett-t test if the variance wasn't uniform, and (4) used the receiver operating characteristic (ROC) curve to analyze the diagnostic value of the combined detection of AFU, CA153, CA125 and AFP for liver cancer: $P < .05$ was considered statistically significant

RESULTS

Participants

The study included and analyzed the data of 98 participants with chronic hepatitis B, 102 with liver cirrhosis, and 100 with liver cancer, for 300 participants in total. The CHB group included 52 males and 46 females, with an average age of 45.23 ± 6.75 years, and a range from 29 to 63 years. The cirrhosis group included 54 males and 48 females, with an average age of 44.98 ± 7.03 years and a range from 27 to 61 years. The liver cancer group included 49 males and 51 females, with an average age of 45.18 ± 6.89) years and a range from 29 to 62 years. No significant differences existed in the demographic data among the three groups at baseline ($P > .05$), Table 1.

Diagnostic Indicators by Group

For the levels of AFU (both $P < .001$), CA153 (both $P < .001$), CA125 (both $P < .001$), AFP (both $P < .001$), and urea (both $P < .001$), Table 2 shows that the CHB group's

Table 1. Comparison of baseline information between CHB group, cirrhosis group and liver cancer group (N = 300)

	CHB Group n = 98 Mean ± SD	Cirrhosis Group n = 102 Mean ± SD	Liver Cancer Group n = 100 Mean ± SD	Comparisons Between Groups					
				CHB Group & Cirrhosis Group		CHB Group & Liver Cancer Group		Cirrhosis Group & Liver Cancer Group	
				F	*P* value	*F*	*P* value	*F*	*P* value
Age	45.23±6.75	44.98±7.03	45.18±6.89	0.256	.798	0.052	.959	0.204	.838
Gender Male/Female	52/46	54/48	49/51	0.000	.986	0.327	.568	0.314	.575

Table 2. Comparison of Urea, AFU, CA153, CA125, and AFP Levels Among the Three Groups (N = 300)

Indicator	CHB Group n = 98 Mean ± SD	Cirrhosis Group n = 102 Mean ± SD	Liver Cancer Group n = 100 Mean ± SD	Comparisons Between Groups					
				CHB Group & Cirrhosis Group		CHB Group & Liver Cancer Group		Cirrhosis Group & Liver Cancer Group	
				F	*P* value	*F*	*P* value	*F*	*P* value
AFU, ng/ml	4.18 ± 1.28	7.46 ± 1.40	10.79 ± 3.22	17.270	<.001[a]	18.910	<.001[a]	9.563	<.001[a]
CA153, mIu/L	54.02 ± 10.22	220.63 ± 23.87	252.12 ± 23.45	63.710	<.001[a]	76.780	<.001[a]	9.456	<.001[a]
CA125, mIu/L	40.58 ± 10.80	241.86 ± 27.07	245.03 ± 23.46	68.550	<.001[a]	78.500	<.001[a]	0.889	.375
AFP, μg/L	79.91 ± 10.61	100.98 ± 21.80	136.81 ± 27.25	8.635	<.001[a]	19.290	<.001[a]	10.330	<.001[a]
Urea, mmol/L	6.85 ± 0.32	8.51 ± 0.87	9.54 ± 1.01	17.770	<.001[a]	25.160	<.001[a]	7.771	<.001[a]

[a]*P* < .05, indicating that the CHB group's levels of urea, AFU, CA153, CA125, and AFP were significantly lower than those of the cirrhosis and liver cancer groups and that the cirrhosis group's levels were significantly lower than those of the liver cancer group

Abbreviations: AFP, alpha fetoprotein; AFU, alpha L-fucosidase; CA125, carbohydrate antigen 125; CA153, carbohydrate antigen 153.

Table 3. Comparison of Urea, AFU, CA153, CA125, and AFP Levels in the Compensatory and Decompensation Groups of the Chronic Hepatitis B Group (n = 98)

Group	n	AFU ng/ml Mean ± SD	*t*	*P* value	CA153 mIu/L Mean ± SD	*t*	*P* value	CA125 mIu/L Mean ± SD	*t*	*P* value
Compensatory	56	3.89 ± 1.19	-2.472	.015[a]	50.68 ± 10.00	-3.664	<.001[a]	36.02 ± 9.87	-4.956	<.001[a]
Decompensated	42	4.51 ± 1.30			57.79 ± 9.20			45.74 ± 9.48		
Group	n	AFP μg/L Mean ± SD	*t*	*P* value	Urea mmol/L Mean ± SD	*t*	*P* value			
Compensatory	56	74.28 ± 9.24	-6.728	<.001[a]	5.64 ± 0.65	-7.863	<.001[a]			
Decompensated	42	86.26 ± 8.26			6.97 ± 1.02					

[a]*P* < .05, indicating that the levels of AFU, CA153, CA125, AFP, and urea in the compensatory group were significantly lower than those in the decompensated group

Abbreviations: AFP, alpha fetoprotein; AFU, alpha L-fucosidase; CA125, carbohydrate antigen 125; CA153, carbohydrate antigen 153.

levels were significantly lower than those of the cirrhosis and liver cancer groups, and the cirrhosis group's levels of AFU ($P < .001$), CA153 ($P < .001$), AFP ($P < .001$), and urea ($P < .001$) were significantly lower than those of the liver cancer group. There was no difference in CA125 between the cirrhotic group and the hepatocellular carcinoma group ($P > .05$).

Indicators for the CHB Group

Table 3 shows that the levels of AFU (p=0.015), CA153 ($P < .001$), CA125 ($P < .001$), AFP ($P < .001$), and urea ($P < .001$), in the compensatory group were significantly lower than those in the decompensated group.

Indicators for the Cirrhosis Group

Table 4 shows that no significant differences existed in the levels of AFU, CA153, CA125, AFP, or urea among the grade A, grade B, and grade C groups ($P > .05$).

Table 5 shows that the levels of AFU, CA153, CA125, AFP, and urea of the no ascites group were significantly lower than those of the ascites group (all $P < .001$).

Indicators for the Liver Cancer Group

Table 6 shows that the levels of AFU (both $P < .001$), CA153 (both $P < .05$), CA125 (both $P < .05$), AFP (both $P < .001$), and urea (both $P < .05$) of the stage I-II group were significantly lower than those of the stage III and stage IV groups, and those of the stage III group were significantly lower than those of the stage IV group ($P < .05$).

Table 7 shows that the levels of AFU ($P < .001$), CA153 ($P < .001$), CA125 ($P < .001$), AFP ($P < .001$), and urea ($P < .001$) of the <5cm group were significantly lower than those of the ≥5cm group ($P < .05$).

Table 4. Comparison of Urea, AFU, CA153, CA125, and AFP Levels in Class A, B, and C Groups of the Cirrhosis Group (n = 102)

Indicator	Class A Group n = 31 Mean ± SD	Class B Group n = 39 Mean ± SD	Class C Group n = 32 Mean ± SD	Comparisons Between Groups					
				Class A Group & Class B Group		Class A Group & Class C Group		Class B Group & Class C Group	
				F	*P* value	*F*	*P* value	*F*	*P* value
AFU, ng/ml	7.23 ± 1.36	7.49 ± 1.45	7.65 ± 1.39	0.766	.447	1.212	.230	0.471	.639
CA153, mIu/L	217.12 ± 24.23	220.35 ± 23.56	224.36 ± 24.12	0.563	.576	1.188	.239	0.706	.483
CA125, mIu/L	238.25 ± 30.04	241.02 ± 28.25	246.39 ± 22.36	0.396	.693	1.223	.226	0.874	.385
AFP, μg/L	98.23 ± 22.36	101.31 ± 22.01	103.24 ± 21.38	0.578	.566	0.909	.367	0.372	.711
Urea, mmol/L	8.54 ± 0.97	8.51 ± 0.99	8.63 ± 1.06	0.127	.899	0.351	.727	0.492	.624

Abbreviations: AFP, alpha fetoprotein; AFU, alpha L-fucosidase; CA125, carbohydrate antigen 125; CA153, carbohydrate antigen 153.

Table 5. Comparison of Urea, AFU, CA153, CA125, and AFP Levels in the No Ascites and Ascites Groups of the Cirrhosis Group

Group	n	AFU ng/ml Mean ± SD	*t*	*P* value	CA153 mIu/L Mean ± SD	*t*	*P* value	CA125 mIu/L Mean ± SD	*t*	*P* value
No ascites	58	6.65 ± 0.99	-9.058	<.001[a]	210.89 ± 17.49	-5.331	<.001[a]	228.87 ± 19.03	-6.656	<.001[a]
Ascites	44	8.54 ± 1.11			233.46 ± 25.24			258.99 ± 26.69		

Group	n	AFP μg/L Mean ± SD	*t*	*P* value	Urea mmol/L Mean ± SD	*t*	*P* value
No ascites	58	91.12 ± 18.55	-6.116	<.001[a]	7.84 ± 0.83	-4.659	<.001
Ascites	44	113.97 ± 18.86			8.73 ± 1.10		

[a]*P* < .05, indicating that the levels of AFU, CA153, CA125, AFP, and urea of the no ascites group were significantly lower than those of the ascites group

Abbreviations: AFP, alpha fetoprotein; AFU, alpha L-fucosidase; CA125, carbohydrate antigen 125; CA153, carbohydrate antigen 153.

Table 6. Comparison of Urea, AFU, CA153, CA125, and AFP Levels in the Stage I-II, Stage III, and Stage IV Groups of the Liver Cancer Group

Indicator	Stage I-II Group n = 39 Mean ± SD	Stage III Group n = 36 Mean ± SD	Stage IV Group n = 25 Mean ± SD	Comparisons Between Groups					
				Stage I-II Group & Stage III Group		Stage I-II Group & Stage IV Group		Stage III Group & Stage IV Group	
				F	*P* value	*F*	*P* value	*F*	*P* value
AFU, ng/ml	8.26 ± 1.39	10.36 ± 1.95	15.35 ± 1.34	5.402	<.001	20.190	<.001	11.090	<.001
CA153, mIu/L	228.12 ± 20.36	239.56 ± 21.32	258.36 ± 19.18	2.377	.020	5.927	<.001	3.526	<.001
CA125, mIu/L	229.57 ± 18.25	248.35 ± 19.24	264.39 ± 20.17	4.338	<.001	7.147	<.001	3.140	.003
AFP, μg/L	115.36 ± 19.57	142.32 ± 20.32	162.32 ± 19.57	5.852	<.001	9.366	<.001	3.838	<.001
Urea, mmol/L	8.56 ± 0.99	9.37 ± 1.02	10.16 ± 1.05	3.489	<.001	6.161	<.001	2.940	.005

[a]*P* < .05, indicating that the levels of AFU, CA153, CA125, AFP, and urea of the stage I-II group were significantly lower than those of the stage III and stage IV groups, and those of the stage III group were significantly lower than those of the stage IV group

Abbreviations: AFP, alpha fetoprotein; AFU, alpha L-fucosidase; CA125, carbohydrate antigen 125; CA153, carbohydrate antigen 153.

Table 7. Comparison of Urea, AFU, CA153, CA125, and AFP Levels in the Tumor diameter <5cm group and ≥5cm Groups of the Liver Cancer Group

Group	n	AFU ng/ml Mean ± SD	*t*	*P* value	CA153 mIu/L Mean ± SD	*t*	*P* value	CA125 mIu/L Mean ± SD	*t*	*P* value
Tumor diameter <5cm group	58	8.96 ± 1.83	-8.935	<.001[a]	231.76 ± 21.01	-4.385	<.001[a]	236.09 ± 20.52	-4.996	<.001[a]
Tumor diameter ≥5cm group	42	13.31 ± 3.02			250.90 ± 22.27			257.39 ± 21.76		

Group	n	AFP μg/L Mean ± SD	*t*	*P* value	Urea mmol/L Mean ± SD	*t*	*P* value
Tumor diameter <5cm group	58	124.50 ± 23.42	-6.239	<.001[a]	8.63 ± 1.01	-6.052	<.001[a]
Tumor diameter ≥5cm group	42	153.79 ± 22.81			10.06 ± 1.11		

[a]$P < .05$, indicating that the levels of AFU, CA153, CA125, AFP, and urea of the <5cm group were significantly lower than those of the ≥5cm group

Abbreviations: AFP, alpha fetoprotein; AFU, alpha L-fucosidase; CA125, carbohydrate antigen 125; CA153, carbohydrate antigen 153.

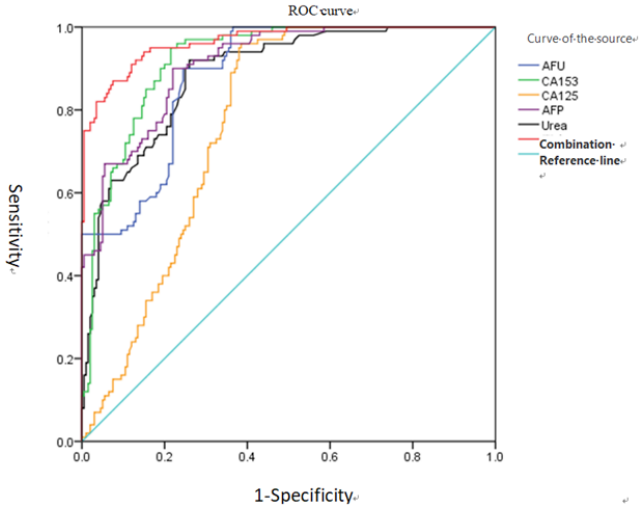
Table 8. Diagnostic Value of Urea, AFU, CA153, CA125, AFP and their Combination for Liver Cancer

Index	AUC Value	The Best Cutoff Value	The Most Approximate Index	Sensitivity	Specificity	P Value	95% CI
AFU	0.907	7.79 ng/ml	0.635	0.830	0.715	<.001[a]	0.873-0.942
CA153	0.861	211.58 mIu/L	0.615	0.910	0.715	<.001[a]	0.821-902
CA125	0.761	224.22 mIu/L	0.405	0.790	0.615	<.001[a]	0.709-0.813
AFP	0.845	142.635 μg/L	0.590	0.800	0.790	<.001[a]	0.801-0.890
Urea	0.887	8.455 mmol/L	0.660	0.920	0.740	<.001[a]	0.850-0.924
Combination	0.965		0.795	0.870	0.925	<.001[a]	0.946-0.984

[a]$P < .05$, indicating that the value of using a combination of indicators for diagnosis was significantly higher than that of a single indicator

Abbreviations: AFP, alpha fetoprotein; AFU, alpha L-fucosidase; CA125, carbohydrate antigen 125; CA153, carbohydrate antigen 153.

Figure 1. ROC Curve



Diagnostic Value of Indicators

Table 8 and Figure 1 show the AUC values of AFU, CA153, CA125, AFP, and urea for the diagnosis of liver cancer were 0.907, 0.861, 0.761, 0.848, and 0.887, respectively. The sensitivity of urea at 0.920 and the specificity of AFP at 0.790 were significantly higher than those of the other indicators singly. The AUC value was 0.965, the sensitivity was 0.870, and the specificity was 0.925 for the combined use of all indicators. The value of using a combination of indicators for diagnosis was significantly higher than that of a single indicator ($P < .001$).

DISCUSSION

The current study found that the urea level of the liver cancer group was significantly higher than those of the other two groups. In the liver cancer group, the stage IV group's urea level was significantly higher than those of the stage III and I-II groups, and the urea level of the tumor diameter ≥5 cm group was higher than that of the <5 cm group, which indicates that urea has a good diagnostic effect for liver cancer.

The current study found that the AFU level of the liver cancer group was significantly higher than those of liver cirrhosis and hepatitis group. Also the AFU level of the stage IV group was significantly higher than that of the stage III and I-II groups, and the AFU level of the ≥5cm group was significantly higher than that of the <5cm group, indicating that AFU had a good discriminative effect on the development of liver cancer. At the same time, it can provide the basis for a pathological diagnosis of liver cancer.

The current study showed that the expression of liver cancer in the serum of the liver cancer group significantly increased, suggesting that CA153 has a certain diagnostic role for liver cancer.

The current study found that the serum CA153 level of the stage IV group of the liver cancer group was significantly higher than that of the stage I-II and III groups. In the CHB group, the level of serum CA153 in the decompensated group was significantly higher than that in the compensated group, suggesting that the concentration of CA125 gradually increased with the progression of CHB disease.

Meanwhile, in the cirrhosis group, the level of CA125 in the ascites group was significantly higher than that in the no ascites group, indicating that CA125 can an indicator to reflect the degree of liver-function damage in patients with liver cirrhosis and can provide a reference for predicting the occurrence of ascites in patients with liver cirrhosis, as Yang et al previously found.[10]

The current study showed that the expression level of AFP increased with the progression of the disease, but the expression of AFP was highest in the liver cancer group. Meanwhile, AFP level is affected by the tumor size in patients with liver cancer, which also confirms that AFP is related to liver-cancer cells. Therefore, the specificity of detection using AFP as a single indicator in the diagnosis of HBV-related liver cancer in the current study was the highest of the indicators, at 0.790.

The current study found that the AUC value of diagnosis using a combination of urea, AFU, CA153, CA125, and AFP as indicators was 0.965; the sensitivity was 0.870; and the specificity was 0.925, which were all greater than those of any single indicator, indicating that the combination of the five indicators had the highest diagnostic efficiency and could effectively improve the accuracy of liver-cancer diagnosis.

The current study had some shortcomings, such as a small sample size and its status as a retrospective study, which may have had a certain impact on the results, and the findings need to be verified by future prospective studies with high quality and large samples.

CONCLUSIONS

Urea, AFU, CA153, CA125, and AFP all have diagnostic value in the evaluation of chronic hepatitis B-cirrhosis and liver cancer, with the highest efficacy, sensitivity and specificity from a combined test and diagnosis.

REFERENCES

1. Bian DD, Zheng SJ. Role of serum HBV RNA quantification in guiding the course of antiviral therapy for chronic hepatitis B. *Journal of Clinical Hepatobiliary Disease.* 2020;36(8):4.
2. Huang Y, Wang W, Zhang CH, et al. Investigation on hepatitis B infection and related knowledge and behavior among HBSAG positive families in Guangzhou. *China Vaccines and Immunization.* 2021;27(2):4.
3. Ma HY, Ao YK, Liu WB, Cao GW. [A bibliometric analysis on cohort study of liver cancer in China]. *Zhonghua Liu Xing Bing Xue Za Zhi.* 2020;41(1):115-119.
4. Song TQ, Liu YY. Primary hepatocellular carcinoma conversion therapy and maintenance treatment strategy. *Chinese Journal of Practical Surgery.* 2021;41(3):4.
5. Guo C, Zou X, Hong Z, et al. Preoperative transarterial chemoembolization for barcelona clinic liver cancer stage A/B hepatocellular carcinoma beyond the milan criteria: a propensity score matching analysis. *HPB (Oxford).* 2021;23(9):1427-1438. doi:10.1016/j.hpb.2021.02.006
6. Guo ZP, Yin F. Application value of alpha-fetoprotein, leucine aminopeptidase and α-L-fucosidase expression in diagnosis of primary hepatocellular carcinoma alone and in combination. *Chin J General Clinic.* 2020;36(2):5.
7. Liu D, Luo Y, Chen L, et al. Diagnostic value of 5 serum biomarkers for hepatocellular carcinoma with different epidemiological backgrounds: A large-scale, retrospective study. *Cancer Biol Med.* 2021;18(1):256-270. doi:10.20892/j.issn.2095-3941.2020.0207
8. Li Y, Wang F, He XD. The value of CA153 combined with CA199 in the differential diagnosis of benign and malignant abdominal effusion. *Journal of Practical Cancer.* 2020;35(1):66-68.
9. Vuković A, Kuna K, Lončar Brzak B, et al. The role of salivary and serum ca125 and routine blood tests in patients with ovarian malignancies. *Acta Clin Croat.* 2021;60(1):55-62. doi:10.20471/acc.2021.60.01.08
10. Yang Y, Hu YM, Han J, et al. Effects of sorafenib on liver function and serum levels of AFP, CEA, CA125, CA19-9 in elderly patients with primary liver cancer. *Zhongguo Laonianxue Zazhi.* 2020;40(13):4.
11. Qin S, Tang SH, Wang XH, et al. The value of serum alpha-fetoprotein in the prognosis assessment of hepatitis B-related acute-on-chronic liver failure treated with artificial liver. *Chinese Journal of Liver Disease.* 2020;28(1):4.
12. Cheng SP, Li M, Tan SY. Diagnostic value of serum AFP, PIVKA-II, GGT, GGT/ALT in early primary hepatocellular carcinoma. *Shandong Medicine.* 2021;61(1):5.
13. Lu HY, Xu XY. Interpretation of the guidelines for prevention and treatment of chronic hepatitis B (2019 edition). *Journal of Clinical Internal Medicine.* 2020;37(8):3.
14. Hepatology Society of Chinese Medical Association. *Zhonghua Gan Zang Bing Za Zhi.* 2019;27(11):20. in Chinese.
15. Hepatobiliary and Pancreatic Disease Prevention and Control Committee of Chinese Preventive Medicine Association, Hepatology Committee of Chinese Research Hospital Association, Hepatology Society of Chinese Medical Association, et al. Guidelines for stratified screening and surveillance of primary liver cancer (2020 edition). *Clin Hepatobiliary Diseases.* 2021;37(2):10.
16. McPhail S, Swann R, Johnson SA, et al; ICBP Module 9 Emergency Presentations Working Group. Risk factors and prognostic implications of diagnosis of cancer within 30 days after an emergency hospital admission (emergency presentation): an International Cancer Benchmarking Partnership (ICBP) population-based study. *Lancet Oncol.* 2022;23(5):587-600. doi:10.1016/S1470-2045(22)00127-9
17. Fan N, Li P, Zhou Y, et al. Demystifying Lysosomal α-l-Fucosidase in Liver Cancer-Bearing Mice by Specific Two-Photon Fluorescence Imaging. *ACS Sens.* 2022;7(1):71-81. doi:10.1021/acssensors.1c01630
18. Li G, Zhang H, Zhang L, et al. Serum Markers CA125, CA153, and CEA along with Inflammatory Cytokines in the Early Detection of Lung Cancer in High-Risk Populations. *BioMed Res Int.* 2022;2022:1394042. doi:10.1155/2022/1394042
19. Wang X, Wang Q. Alpha-Fetoprotein and Hepatocellular Carcinoma Immunity. *Can J Gastroenterol Hepatol.* 2018;2018:9049252. doi:10.1155/2018/9049252
20. Weiner ID, Mitch WE, Sands JM. Urea and Ammonia Metabolism and the Control of Renal Nitrogen Excretion. *Clin J Am Soc Nephrol.* 2015;10(8):1444-1458. doi:10.2215/CJN.10311013
21. Peng Y, Qi X, Guo X. Child-Pugh Versus MELD Score for the Assessment of Prognosis in Liver Cirrhosis: A Systematic Review and Meta-Analysis of Observational Studies. *Medicine (Baltimore).* 2016;95(8):e2877. doi:10.1097/MD.0000000000002877
22. Piñero F, Dirchwolf M, Pessôa MG. Biomarkers in Hepatocellular Carcinoma: Diagnosis, Prognosis and Treatment Response Assessment. *Cells.* 2020;9(6):1370. doi:10.3390/cells9061370