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Original Article

Diagnostic value of serum Golgi protein 73 for HBV-related primary hepatic carcinoma

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Abstract: Background: Alpha-fetoprotein (AFP) levels are routinely used for diagnosis and monitoring of hepatic diseases, but it has a limited value. Golgi protein 73 (GP73) has been suggested as a new marker for hepatic diseases. Objective: To explore the clinical value of serum GP73 in different diseases associated with hepatitis B virus (HBV) infection. Method: Between January 2010 and August 2014, serum samples from 88 patients with chronic hepatitis B (CHB), 78 patients with HBV-related liver cirrhosis (LC), and 194 patients with HBV-related primary hepatic cancer (PHC) were collected. Serum samples from 30 healthy volunteers were used as controls. ELISA and microparticle enzyme immunoassay were used to measure serum GP73 and AFP levels. Receiver operating characteristic (ROC) curves were used to analyze the diagnostic value of serum GP73 and AFP for PHC. Results: For the diagnosis of PHC, GP73 showed a sensitivity of 65.5% and specificity of 66.3%, while AFP levels showed sensitivity of 64.4% and specificity of 76.5%. Serial testing (both tests are positive) could increase the specificity (sensitivity of 45.9% and specificity of 85.5%) while parallel testing (any single positive test result) could increase the sensitivity (sensitivity of 84.0% and specificity of 57.2%). Serum GP73 and AFP levels were significantly different between Child-Pugh grades ($P<0.001$ for GP73 and $P=0.044$ for AFP). Significant differences in serum GP73 and AFP were found between TNM stages (all $P<0.001$). Conclusion: Serum GP73 had limited diagnostic value for HBV-related PHC. The combined use of serum GP73 and AFP levels improved the diagnostic efficacy.

Keywords: Hepatitis B virus, primary hepatic carcinoma, Golgi protein 73, alpha fetoprotein

Introduction

Early diagnosis of hepatic carcinoma is a clinical challenge and has been the focus of many research efforts. Alpha-fetoprotein (AFP) has been used for decades, but its sensitivity and specificity are only of 40-65% and 76-96%, respectively [1-3]. Other tumor markers like gamma-glutamyltransferase (GGT) and alkaline phosphatase (ALP) are sometimes used, but they are only auxiliary diagnostic indices that cannot satisfy the clinical needs [3].

Golgi protein 73 (GP73) is a new promising biomarker for the diagnosis of primary hepatic carcinoma (PHC). GP73 is a 73-kDa transmembrane glycoprotein first discovered by Kladney *et al* [4]. In normal adults, the hepatic concentration of GP73 is very low since GP73 is mainly expressed by the biliary epithelial cells but not by liver cells [5]. However, in patients with hepatic diseases, the hepatic expression of GP73 is significantly upregulated [6, 7]. Therefore, GP73 might provide a solution for the early diagnosis of hepatic diseases. A study by Marrero et al. [8] has shown that GP73 had a 62% sensitivity for the early diagnosis of hepatic carcinoma compared with 25% for AFP. Several reports indicated that GP73 levels have an excellent clinical value for the diagnosis of PHC [8, 9] and that the combined use of GP73 and AFP could even improve the detection rate of PHC [10]. On the other hand, Ozkan et al. [11] suggested that GP73 has a low value for the diagnosis and prognosis of early PHC while AFP was better. However, Ozkan et al. [11] included patients with hepatitis C virus (HCV)-associated PHC and their results are still controversial [12, 13]. In addition, the incidence of HCV-associated PHC is higher in Europe and America than in Asia [14], while hepatitis B virus (HBV)-associated PHC is more frequent in Asia than in

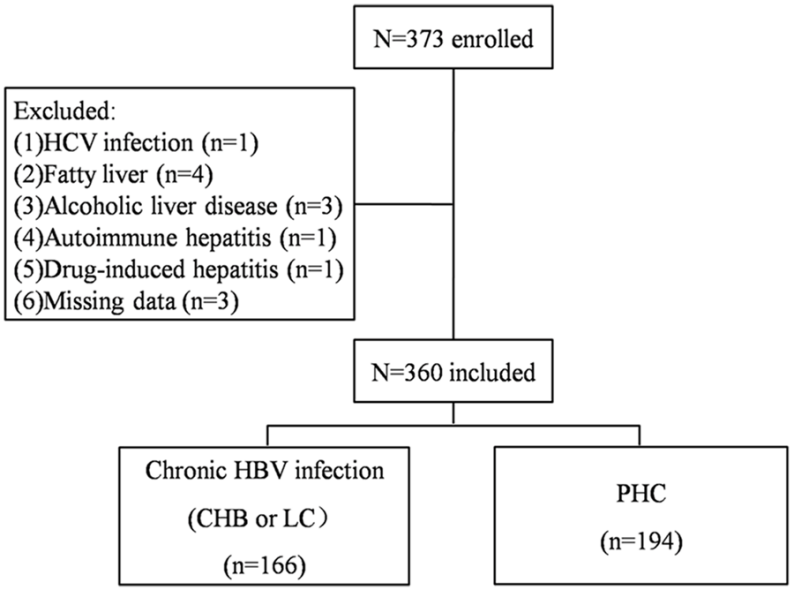

Figure 1. Patients' flowchart.

Europe and America [15]. Therefore, there is no conclusion on the diagnostic value of GP73, in particular for the early diagnosis of HBV-associated PHC. Furthermore, most of these previous studies used semi-quantitative methods for the measurement of GP73.

In 2009, a Chinese team invented a double-antibody sandwich ELISA to detect the serum GP73 levels [6]. However, their study revealed that serum GP73 levels were significantly different between patients with and without hepatic diseases, while increases of serum GP73 levels in patients with PHC were not significantly different from those of patients with other hepatic diseases.

Therefore, the issue of early diagnosis of PHC is still unresolved. Consequently, the present study aimed to investigate the diagnostic value of GP73 for PHC in patients with chronic HBV infection.

Patients and methods

Study design

This was a cross-sectional study that was carried out between January 2010 and August 2014 at the Ningbo No. 2 Hospital (Zhejiang, China). This study was approved by the Ethical Committee of the Ningbo No. 2 Hospital. All patients signed the informed consent.

Patients

Patients had to have received a confirmed diagnosis of chronic hepatitis B (CHB), HBV-related liver cirrhosis (LC), or HBV-related PHC. The diagnoses of CHB and related complications were made according to the current guidelines for HBV infection management [16]. Exclusion criteria were: 1) coinfection with hepatitis A, C, D or E; 2) infection with cytomegalovirus, human herpes virus or human immunodeficiency virus; 3) autoimmune hepatitis, fatty liver or alcoholic liver disease; 4) drug-induced hepatitis; or 5) missing data.

PHC was diagnosed according to internationally recognized standards [17]. The lesion had to be confirmed by pathological examination. The specific clinical diagnostic criteria were: 1) AFP >400 ng/mL after exclusion of active hepatic diseases, pregnancy, embryonic germline tumors, and metastatic liver cancer in the presence of palpable hepatic mass or imaging-confirmed space-occupying lesions with characteristics of hepatic carcinoma; or 2) AFP <400 ng/mL in the presence of a space-occupying lesion with characteristics of hepatic carcinoma confirmed by two imaging results (B-type ultrasound, CT, MRI, etc.) or two positive markers of hepatic carcinoma (AFP heterogeneity, or abnormal prothrombin, GGT isoenzyme II, and α-L-fucosidase) and one imaging-confirmed space-occupying lesions with characteristics of hepatic carcinoma, or clinical manifestation of hepatic carcinoma and affirmative extrahepatic metastatic lesions (including visible bloody ascites or cancer cells found in the ascites), with exclusion of metastatic cancer of liver. TNM staging and Child-Pugh scoring were applied to all patients with PHC [18, 19].

Laboratory testing

Morning fasting venous blood (5 mL) was collected from all subjects. Serum was immediately isolated and stored at -80°C. An Abbott AxSYM Immunoassay System (Abbott Laboratories, Abbott Park, IL, USA) with original kits

Table 1. Characteristics of the patients

	HBV and HBV-LC	PHC	P
	N=166	N=194	
Sex (male, %)	125, 75.3%	162, 83.5%	0.054
Age	46.3±13.9	55.9±11.0	<0.001
BMI (kg/m^2)	23.3±2.7	21.9±2.6	<0.001
Comorbidities (n, %)	15, 9.0%	43, 22.2%	<0.001
Diabetes (n)	7	12	
Hypertension (n)	7	30	
Coronary heart disease (n)	1	1	
Child-Pugh			0.045
A (n, %)	98, 59.0%	89, 45.9%	
B (n, %)	46, 27.7%	70, 36.1%	
C (n, %)	22, 13.3%	35, 18.0%	
HBeAg positive (n, %)	83, 50.0%	51, 26.3%	<0.001
HBV DNA >2 log (n, %)	120, 72.3%	116, 59.8%	0.013
Prothrombin time (s)	14.45 (13.20-16.88)	13.05 (11.70-15.08)	<0.001
Total bilirubin (mmol/L)	26.75 (15.83-48.70)	21.55 (14.90-44.03)	0.195
TP	66.60 (61.45-72.33)	66.55 (60.90-71.93)	0.471
ALB	35.60 (29.50-40.48)	32.40 (28.45-36.70)	0.001
ALT	47.50 (27.00-135.00)	41.00 (27.00-63.75)	0.055
AST	59.50 (36.25-103.00)	58.00 (40.25-100.75)	0.477
AST/ALT	1.08 (0.68-1.56)	1.48 (1.11-1.99)	<0.001
ALP	102.50 (80.25-142.00)	117.00 (86.00-197.50)	<0.001
GGT	73.50 (36.25-132.00)	105.50 (54.00-194.75)	<0.001
AFP	9.73 (4.34-42.38)	112.43 (13.82-1916.85)	<0.001
GP73	123.25 (87.22-172.75)	179.33 (111.52-249.36)	<0.001

HBV: hepatitis B virus; LC: liver cirrhosis; PHC: primary hepatic cancer; BMI: body mass index; TP: total protein; ALB: albumin; ALT: alanine transaminase; AST: aspartate transaminase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transpeptidase; AFP: alpha-fetoprotein; GP73: Golgi protein 73.

was used to perform the microparticle enzyme immunoassay for the measurement of AFP. An Olympus AU 2700 automatic biochemical analyzer with original kits (Olympus, Tokyo, Japan) was used to measure serum total protein (TP), albumin (ALB), aspartate transaminase (AST), alanine aminotransferase (ALT), AST/ALT, ALP, GGT and total bilirubin (TB).

Measurement of GP73

The quantitative GP73 enzyme-linked immune sorbent assay (ELISA) 96T detection kit (Hotgen Biotech, Beijing, China, lot No.: 20140502) and the Anthos PHOMO microplate reader (Anthos Labtec Instruments, Austria) were used. This kit uses the double-antibody sandwich ELISA method to quantify the GP73 concentrations from serum or plasma samples. The microplate is pre-coated with the monoclonal antibody against GP73, which binds the GP73 of the samples; the complex is then detected using HRP-conjugated GP73-polyclonal antibody and 3,3',5,5'-tetramethylbenzidine as HRP substrate. The optical density (OD) value is measured by the microplate reader and a standard curve is created to calculate the GP73 concentration in the samples.

Statistical analysis

All data were analyzed using SPSS 16.0 (IBM, Armonk, NY, USA). The distribution of serum GP73, AFP, ALT, AST, AST/ALT, ALP, GGT, TP, ALB, and PT were skewed. Therefore, they are expressed as medians (quartiles) and were analyzed using the Mann Whitney U test (for pairwise comparisons), and the Kruskal-Wallis H test and Nemenyi test (for comparisons of multiple groups). Age and BMI were normally distributed. They are expressed as means ± standard deviation and were analyzed using

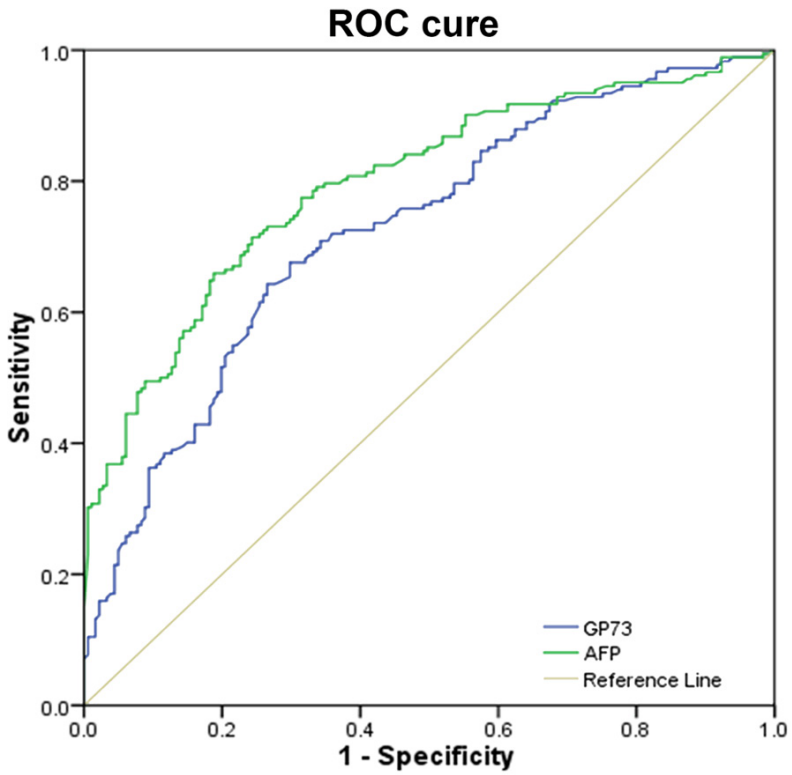

Figure 2. ROC curve of the efficiency of serum GP73 and AFP in diagnosing PHC from the whole study population.

the Student's t test. Categorical data are expressed as frequencies. The receiver operating characteristic (ROC) curve was plotted and the area under the curve (AUC) was used to assess the diagnostic values of serum GP73 and AFP for PHC. The Z test for normality was used for the comparison of AUC. Two-sided *P*-values <0.05 indicated statistical significance.

Results

Enrollment

Figure 1 presents the patients' flowchart. A total of 373 patients with HBV infections were enrolled. One patient with HCV infection, four with fatty liver, three with alcoholic liver, one with autoimmune hepatitis, one drug-induced hepatitis, and three with missing data were excluded. Therefore, 360 patients were enrolled. Among these 360 patients, 88 had CHB (72 men and 16 women, mean age of 38.7±11.6 years old; 68, 19, and 1 were Child-Pugh grade A, B, and C, respectively), 78 had HBV-related LC (53 men and 23 women, mean age of 55.1±10.9 years old; 30, 27, and 21 were Child-Pugh grade A, B and, C, respectively), and 194 had HBV-related PHC (162 men and 32 women, mean age of 55.9±11.0 years old; 89, 70, and 35 were Child-Pugh grade A, B, and C, respectively; 34, 47, 91, and 22 were stage I, II, III, and IV, respectively; early hepatic carcinoma included TNM stages I and II). **Table 1** presents the characteristics of the patients.

ROC curve analysis of the diagnostic efficiency of GP73 and AFP

Results from the ROC curve analysis for the whole population (normal volunteers and those with HBV-related diseases) indicated a slightly poorer diagnostic efficiency for PHC with serum GP73 levels compared with serum AFP levels (Z=2.177, *P*=0.029) (**Figure 2**).

Diagnostic value of serum GP73 and AFP levels for PHC

Based on the ROC curve analysis, the cutoff values for AFP [43.26 ng/mL, AUC (95% CI) 0.776 (0.731-0.816), *P*<0.001] and GP73 [145 ng/mL, AUC (95% CI) 0.713 (0.666-0.758), *P*<0.001] showed that some PHC patients with normal AFP levels had elevated GP73 level, indicating that these two indices were to some extend complementary. Therefore, we further investigated the combination of the two markers, and found that serial testing (both rests are positive) could increase the specificity while parallel testing (any single positive test result) could increase the sensitivity (**Table 2**).

Comparison of serum GP73 levels in PHC with various disease degrees (Child-Pugh A, B, and C)

Serum GP73 and AFP levels were significantly different between Child-Pugh grades (*P*<0.001 for GP73 and P=0.044 for AFP). Serum GP73 levels were significantly increased with the Child-Pugh grade (all *P*<0.05) while the differ-

Table 2. Diagnostic values of GP73 and AFP for PHC in patients with CHB

	Sensitivity	Specificity	PPV	NPV
AFP	64.4% (125/194)	76.5% (127/166)	76.2% (125/164)	64.8% (127/196)
GP73	65.5% (127/194)	66.3% (110/166)	69.4% (127/183)	62.2% (110/177)
AFP+GP73	45.9% (89/194)	85.5% (142/166)	78.2% (89/113)	57.5% (142/247)
AFP or GP73	84.0% (163/194)	57.2% (95/166)	69.7% (163/234)	75.4% (95/126)

PPV: positive predictive value; NPV: negative predictive value; AFP: alpha-fetoprotein; GP73: Golgi protein 73.

Table 3. Comparison of GP73 and AFP levels according to Child-Pugh stages and TNM staging

	Child-Pugh grade				
	A (n=88)	B (n=71)	C (n=35)	P	
GP73 (ng/mL)	139.8 (97.50-191.50)	192.5 (138.10-246.00)	260 (211.00-323.50)	<0.001	
AFP (ng/mL)	79.55 (9.33-513.01)	140.23 (29.60-1269.00)	907.58 (24.28-14670.00)	0.044	
TMN stage	I (n=34)	II (n=47)	III (n=91)	IV (n=22)	P
GP73 (ng/mL)	158 (84.00-245.02)	146 (97.00-191.20)	192 (138.67-254.00)	215.24 (159.50-282.03)	0.001
AFP (ng/mL)	46.09 (8.38-154.40)	31.06 (7.00-228.28)	260.5 (32.40-1000.00)	454.55 (44.65-6431.00)	<0.001

ence in AFP levels was only significant between Child-Pugh grades A and C (P<0.05) (**Table 3**).

Comparison of serum GP73 levels in patients with different TNM stages

Significant differences in serum GP73 and AFP were found between the TNM stages (all P<0.001). Serum GP73 and AFP levels were increased with TNM stages, with significantly higher levels of serum GP73 and AFP found in patients with stages III and IV compared with stages I and II (all P<0.05) (**Table 3**).

Discussion

The aim of the present study was to explore the clinical value of serum GP73 in different diseases associated with HBV infection. Results showed that for the diagnosis of PHC, GP73 showed a sensitivity of 65.5% and specificity of 66.3%, while AFP levels showed sensitivity of 64.4% and specificity of 76.5%. Serial testing (both rests are positive) could increase the specificity (sensitivity of 45.9% and specificity of 85.5%) while parallel testing (any single positive test result) could increase the sensitivity (sensitivity of 84.0% and specificity of 57.2%). Serum GP73 and AFP levels were significantly different between Child-Pugh grades. Significant differences in serum GP73 and AFP were found between TNM stages.

The results of the present study suggest that serum GP73 had a limited value for the diagnosis of HBV-related PHC and therefore could not replace AFP for the diagnosis of PHC, which is consistent with some previous studies [2, 20]. However, some other studies reported that GP73 had a better diagnostic value than AFP [8, 12, 21, 22]. These differences might be due to the populations being studied including the causes of liver cancer, ethnicity, level of income, etc.

Previous studies revealed that the combined use of serum GP73 and AFP could increase the diagnostic efficiency for PHC [20]. Therefore, we analyzed the complementarity between the two tests, and found that they were actually complementary to one another since some patients with PHC had normal AFP levels but elevated GP73 levels. Therefore, we further investigated the combined diagnosis targeting the differentiation from PHC from HBV-related LC, and found that serial testing (the two tests are positive) could increase the specificity while parallel testing (only one positive test) could increase the sensitivity. As a result, it might be possible to use the two tests to diagnose PHC.

Our results showed that serum GP73 increased with disease severity of CHB, LC, and PHC, indicating that serum GP73, to some extent, reflect liver damage. Indeed, Marrero et al. [8] showed that GP73 were higher in patients with early PHC compared with cirrhosis without cancer. Hu et al. [22] showed that GP73 had a good capability to differentiate cirrhosis from stage I and II PHC. Wang et al. [21] showed that GP73

were lower in patients with cholangiocarcinoma compared with patients with HBV-induced PHC.

In addition, the present study revealed that serum GP73 and AFP levels were increased with TNM stages, and significantly higher levels of serum GP73 and AFP were found in patients with stage III and IV cancer compared with stages 1 and 2. These results are consistent with previous studies [23, 24], but it is still controversial [6, 11].

The present study is not without limitations. Indeed, the sample size was relatively small. In addition, only two serum markers were examined. A more comprehensive panel of markers could reveal even better combinations for the diagnosis of PHC. Indeed, a previous study revealed that serum GP73 combined with serum desgamma carboxy prothrombin (DCP) provided a good diagnostic yield [25]. Additional studies are necessary to address these issues, and large-scale diagnostic studies are necessary to determine the best cut points.

Conclusion

Serum GP73 had limited diagnostic value for HBV-related PHC. The combined use of serum GP73 and AFP levels improved the diagnostic efficacy.

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Disclosure of conflict of interest

None.

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