

Increased Serum Pentraxin 3 Levels are Associated with Poor Prognosis of Hepatitis B Virus-Related Hepatocellular Carcinoma

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Background: Hepatocellular carcinoma (HCC) is a major cause of liver-related mortality. Serum pentraxin 3 (PTX3) has been revealed to be associated with the development of hepatitis B virus (HBV)-related HCC. This study evaluated whether serum PTX3 is related to the survival of HBV-related HCC patients.

Methods: One hundred and seven patients with HBV-related HCC were included. Baseline serum PTX3 levels were quantified using quantitative immunoassay. The HCC patients were followed-up for a median of 24 months and divided into high serum PTX3 level and low PTX3 level groups according to the baseline serum PTX3 levels. The overall survivals of the HBV-related HCC patients according to the serum PTX3 levels were compared. Factors potentially influencing the prognosis of the patients with HBV-related HCC were analyzed.

Results: HCC patients with high serum PTX3 levels [PTX3 > 9.25ng/mL (n=85)] had a shorter overall survival time than HCC patients with low serum PTX3 levels [PTX3 ≤ 9.25ng/mL (n=22)] ($P = 0.049$). HCC patients with serum PTX3 levels between >9.25ng/mL and ≤9.25ng/mL had significant difference in HCC histology grade. Multivariate analysis showed that PTX3 level was an independent risk factor related to the overall survival of HCC patients (hazard ratio: 1.058, 95% confidence interval: 1.031–1.085, $P < 0.001$).

Conclusion: These results support the involvement of PTX3 in the disease progression of HCC and suggest the potential of using serum PTX3 levels as a biomarker for the prognostic prediction of HBV-related HCC patients.

Keywords: hepatocellular carcinoma, pentraxin 3, chronic HBV infection, survival, prognosis

Introduction

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths worldwide.¹ Hepatitis B virus (HBV) is one of the major causative agents associated with HCC development worldwide^{2–4} and the most common causative agent of HCC in China⁵. The lack of biomarkers for the early detection and approaches for the cure significantly affects the prognosis of HCC.^{6,7} Among the various serum markers, alpha-fetoprotein (AFP) has been the mostly used biomarker for HCC detection and prognosis.⁸ However, the sensitivity and specificity of AFP for the detection and prognosis of HCC, especially for AFP negative HCC, remain unsatisfactory.^{8–10} Therefore, to improve the management of HCC patients, the identification of new biomarkers remains an urgent need.

Pentraxin 3 (PTX3), also known as tumor necrosis factor-stimulated gene 14 (TSG-14), is a long pentraxin of the pentraxin superfamily.^{11,12} It is a typical acute-phase protein

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produced by a variety of cells, such as leukocytes, dendritic cells, and endothelial cells, in response to local inflammation.^{13–15} PTX3 plays a critical homeostatic role in linking innate immunity, tissue repair, inflammation, and cancer.^{16,17} Furthermore, PTX3 is involved in the regulation of the biological behaviors such as proliferation, angiogenesis and metastasis associated with malignancies.¹⁷ In terms of HCC, studies have showed that PTX3 could enhance HCC progression.¹⁸ Elevated PTX3 expression in tumor tissues is associated with poor prognosis in HCC patients.¹⁸ Serum PTX3 is a risk factor for HCC development in chronic hepatitis C virus (HCV) infection.¹⁹ In HBV infection, serum PTX3 level is associated with the development of HCC and has a diagnostic value for HCC including AFP negative HCC.²⁰

However, whether serum PTX3 levels are related to the prognosis of HBV-related HCC patients remains unknown. This study, therefore, investigated the association of serum PTX3 levels with the overall survival of patients with HBV-related HCC.

Methods

Patients

Patients with HBV-related HCC were recruited from the First Affiliated Hospital of Xi'an Jiaotong University. HBV-related HCC was diagnosed based on the evidence of chronic HBV infection and the characteristics of ultrasound, computed tomography and/or magnetic resonance and/or histopathology.²¹ HCC stage was defined based the Barcelona Clinic Liver Cancer (BCLC) staging system.²² Patients aged less than 18 years were excluded. Patients with liver diseases related to other etiologies including nonalcoholic fatty liver disease, alcoholic liver disease, and drug-induced liver injury were excluded. Patients with autoimmune diseases such as autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis and systemic lupus erythematosus, and severe disorders of other systems were also excluded. The patients were followed-up at 1- to 3-month intervals according to the disease condition.

This study conformed with the Declaration of Helsinki. The study approval was obtained from the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (2013–086). Each patient gave informed consent.

Determination of Laboratory Parameters and Serum PTX3 Levels

Blood samples at baseline were obtained from each patient. Blood tests and biochemistry including biochemical liver

functions were determined at the clinical laboratory of the hospital. Serum HBV DNA was determined using quantitative real-time polymerase chain reaction. HBsAg, anti-HBs, HBeAg, anti-HBe, and anti-HBc were assayed by enzyme-linked immunosorbent assay. Serum AFP levels (ng/mL) were examined by automated Eleceyes (Hoffman-La Roche Ltd., Basel, Switzerland). Serum PTX3 levels were quantified using The Quantikine Human Pentraxin 3/TSG-14 Immunoassay (R&D Systems China Co., Ltd. Shanghai, China) as described previously.²⁰

Statistical Analysis

Statistical analysis was conducted using SPSS 24.0 software. Quantitative variables were expressed as mean and standard deviation (SD) or median (range). Categorical variables were expressed as absolute or relative frequencies. Continuous variables were compared using the analysis of variance. Categorical variables were compared by Chi-Square test. The prognosis of HBV-related HCC patients according to the serum PTX3 levels was compared by Kaplan-Meier curve and tested by Log rank test. The analysis of factors potentially influencing the prognosis of patients with HBV-related HCC was carried out by univariate and multivariate Cox regression analysis. *P* values less than 0.05 were regarded as statistically significant.

Results

Characteristics of the Participants

One hundred and seven patients with HBV-related HCC were recruited. The demographic and laboratory findings in the 107 patients were shown in Table 1. Of the 107 patients, 92 were males and 15 were females. The age of the patients ranged from 18 to 77 years (average 49.4±10.90 years). The patients were followed-up for a median of 24 months (1–73 months, mean 28.44 months, Table 1).

Serum PTX3 Levels and Overall Survival of HCC Patients

According to the cut-off value of serum PTX3 for HBV-related HCC at baseline determined in previous study,²⁰ the patients were divided into high serum PTX3 level [PTX3 > 9.25ng/mL (n = 85)] and low serum PTX3 level [PTX3 ≤ 9.25ng/mL (n = 22)] groups. The baseline characteristics between patients with PTX3 ≤ 9.25ng/mL and those with PTX3 > 9.25ng/mL are shown in Table 2. The gender, age, HBV DNA, ALT, AST, total bilirubin, albumin, AFP and tumor diameter between the two groups of patients showed

Table 1 Characteristics of the 107 HCC Patients

Variables	
Gender (male/female)	92/15
Age (years)	49.4±10.90 (18–77)
HBV DNA (IU/mL, log)	4.90±1.50
ALT (IU/L)	54 (33–102)
AST (IU/L)	70 (35–150)
TBIL (μmol/L)	26.2 (15.2–46.7)
Albumin (g/L)	33 (29.7–39.1)
AFP (ng/mL)	97.4 (16.8–4886)
PTX3 (ng/mL)	15.6 (9.6–24.3)

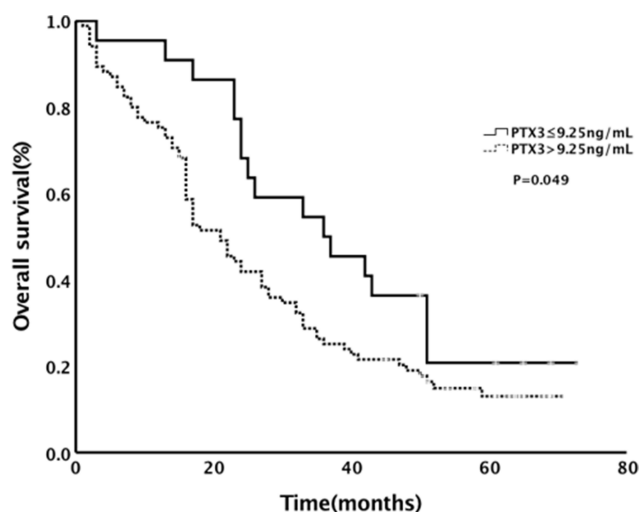
Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; AFP, α-fetoprotein; PTX3, pentraxin 3.

no significant differences. The metastasis occurrence and BCLC stage between the two groups also showed no significant differences. However, the histological differentiation between the low serum PTX3 and high serum PTX3 groups was significantly different ($P < 0.001$, Table 2). Patients with high serum PTX3 levels tended to have more low grade differentiation HCC compared with patients with low serum PTX3 levels.

The overall survivals of the patients according to PTX3 levels were shown in Figure 1. HCC patients with high serum PTX3 levels ($PTX3 > 9.25\text{ng/mL}$) had a significantly shorter overall survival time than HCC patients with low serum PTX3 levels ($PTX3 \leq 9.25\text{ng/mL}$) ($P = 0.049$, Figure 1).

Factors Associated with the Overall Survival of HCC Patients

Univariate analysis showed that higher total bilirubin, lower albumin, and higher PTX3 levels were significant

**Figure 1** Overall survivals of hepatocellular carcinoma patients according to serum pentraxin 3 (PTX3) levels.

risk factors associated with shorter overall survival of HCC patients ($P < 0.001$, $P = 0.041$ and $P < 0.001$, respectively). Multivariate analysis showed that total bilirubin [hazard ratio (HR): 1.933, 95% confidence interval (CI): 1.075–3.536] and serum PTX3 (HR: 1.058, 95% CI: 1.031–1.085) levels were independent risk factors related to the overall survival of HCC patients ($P = 0.032$ and $P < 0.001$, respectively, Table 3, Figure 2).

Discussion

HCC remains one of the most deadly malignancies, and the prognosis of HCC is poor in many patients.⁵ Clinically, prognostic biomarkers are useful for predicting the progression of the disease and may be used to plan the

Table 2 Comparison of the Baseline Characteristics Between Patients with $PTX3 \leq 9.25\text{ng/mL}$ and Patients with $PTX3 > 9.25\text{ng/mL}$

Variables	$PTX3 \leq 9.25\text{ng/mL}$ (n=22)	$PTX3 > 9.25\text{ng/mL}$ (n=85)	P
Gender (male/female)	20/2	72/13	0.455
Age (years)	52.8±11.26	48.56±10.69	0.080
HBV DNA (IU/mL, log)	4.71±1.60	4.95±1.48	0.481
ALT (IU/L)	55 (7–765)	53 (10–603)	0.326
AST (IU/L)	53 (23–647)	74 (15–1348)	0.179
TBIL (μmol/L)	26.2 (12.6–409.4)	25.3 (1.5–727.2)	0.799
Albumin (g/L)	34.1 (23.5–49)	33.3 (21.1–51.3)	0.445
AFP (ng/mL)	99.4 (2.51–84,150)	97.4 (2.01–325,900)	0.954
Tumor diameter (mm)	35.5±13.1	34.7±12.7	0.981
Metastasis (yes/no)	17/5	65/20	0.937
BCLC stage (0/A/B/C/D)	3/13/4/2/0	14/38/13/11/9	0.481
Histology (I/II/III)	3/3/7	14/16/0	<0.001

Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; AFP, α-fetoprotein; PTX3, pentraxin 3.

Table 3 Univariate and Multivariate Analysis of Factors Associated with the Overall Survival of HCC Patients

	n	Overall Survival (%)			Univariate Analysis	Multivariate Analysis	
		1 Year	2 Year	3 Year	P	HR (95% CI)	P
Gender							
Male	92	83	32	15	0.289	1.050 (0.531–2.074)	0.889
Female	15	60	20	13			
Age (years)							
≤ 55	70	80	34	14	0.855	1.005 (0.640–1.579)	0.982
> 55	37	78	24	16			
HBV DNA (IU/mL)							
≤10 ⁴	59	83	36	13	0.874	1.006 (0.858–1.180)	0.937
>10 ⁴	48	78	28	15			
ALT (IU/L)							
≤ 40	36	89	37	18	0.524	1.174 (0.661–2.084)	0.584
> 40	71	75	27	13			
AST (IU/L)							
≤ 40	29	97	36	28	0.150	1.087 (0.572–2.066)	0.798
> 40	78	73	28	10			
TBIL (μmol/L)							
≤ 40	74	93	38	18	<0.001	1.933 (1.075–3.536)	0.032
> 40	33	47	13	6			
Albumin (g/L)							
≤ 32	48	75	27	7	0.041	0.681 (0.399–1.163)	0.159
> 32	59	83	33	21			
AFP (ng/mL)							
≤200	58	84	38	14	0.104	1.348 (0.851–2.135)	0.203
>200	49	73	21	15			
PTX3 (ng/mL)							
≤ 9.25	22	95	50	21	<0.001	1.058 (1.031–1.085)	<0.001
> 9.25	85	75	25	13			
MELD score							
≤ 15	93	84	32	13	0.524	1.097 (0.487–2.471)	0.823
> 15	14	50	21	21			
Child-pugh grade							
A	55	95	35	18	0.061	1.128 (0.655–2.267)	0.533
B+C	52	73	29	14			

Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; AFP, α-fetoprotein; PTX3, pentraxin 3; HR, hazard ratio; 95% CI, 95% confidence interval.

management strategies for the patients. Therefore, the identification of prognostic biomarkers is of important clinical value for HCC.

Previous study showed that high PTX3 level was an independent risk factor of HCC and related to HCC differentiation, and serum PTX3 levels could highly discriminate HCC from non HCC diseases in chronic HBV infection.²⁰ This study evaluated the role of serum PTX3

levels in the prognosis of HBV-related HCC patients, showing that increased serum PTX3 levels were associated with poor prognosis of HCC patients. These results support the involvement of PTX3 in the development and progression of HBV-related HCC, suggesting that the determination of PTX3 levels may possess not only a diagnostic value but also a prognostic value for HBV-related HCC.

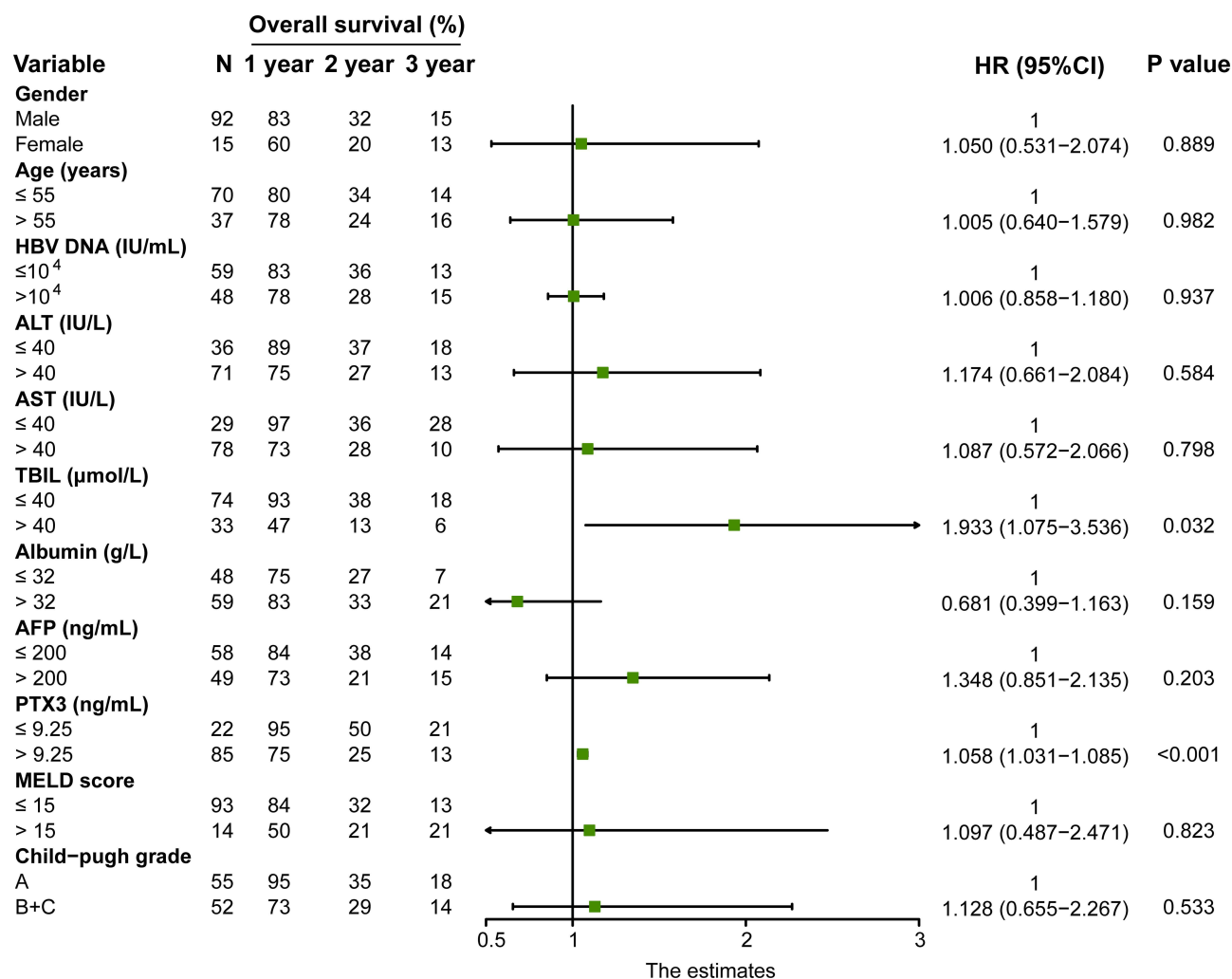


Figure 2 Associations of factors with the overall survival of HCC patients by multivariate Cox regression analysis.

Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; AFP, α -fetoprotein; PTX3, pentraxin 3; HR, hazard ratio; 95% CI, 95% confidence interval.

The mechanisms of PTX3 in carcinogenesis and tumor progression have not been completely elucidated. Chronic inflammation is a key factor in the initiation and progression of cancer.^{23,24} PTX3 plays a complex regulatory role in inflammation including cancer-related inflammation.¹⁶ Innate immune responses including humoral innate immune responses are involved in cancer.^{24,25} PTX3, a evolutionarily conserved humoral pattern recognition molecule,^{13,26} links innate immunity, inflammation, tissue repair, and cancer¹⁶ and may impose important influences on tumor initiation, angiogenesis and metastasis via immune-regulation.²⁷ Increased PTX3 expression has been indicated to be related to poor prognosis in many cancers including breast,²⁸ lung,²⁹ gastric,³⁰ pancreatic³¹ and prostate³² cancers. In HCC, inflammation is an essential constituent of the tumor microenvironment that

remarkably influences HCC development and progression. Immunologic mechanisms including humoral immunity play a critical role in the development and progression of HCC.³³ PTX3 was also shown to be significantly related to liver disease severity and malignant biological behaviors including high-serum levels of aminotransferases, γ -glutamyl transferase and total bilirubin in HCV-related HCC patients.³⁴ The strong correlation between PTX3 overexpression and HCC suggests the role of PTX3 in immunologic dysregulation and inflammation during the hepatocarcinogenesis and HCC progression.^{18–20,34} It should be noted that there is a study showing that PTX3 is not related to disease severity in cirrhosis and HCC patients.³⁵ However, this study included relatively small number of cirrhosis (n=35) and HCC (n=31) patients.³⁵ More other studies confirmed the potential of PTX3 as

a biomarker in evaluating the disease severity and prognosis of cirrhosis³⁶ and HCC.^{18–20,34} The present study showed that increased serum PTX3 levels were associated with poor prognosis of HBV-related HCC and high PTX3 level was an independent factor associated with a reduced survival time of HCC patients. These findings added further information for the role of serum PTX3 in predicting the prognosis of malignancies.

AFP is the most commonly used biomarker of HCC but it is not suitable to detect and predict the prognosis of AFP-negative HCC.³⁷ The present study showed that serum PTX3 levels are associated with the prognosis of HCC, suggesting the potential of applying serum PTX3 levels as a prognostic biomarker for HBV-related HCC including AFP-negative HCC.

This study has several limitations. The sample size of the study is small. The study was carried out with no validation group and subgroup analysis according to therapeutic approaches. The HCC in the analyzed patients was only associated with HBV. Therefore, further studies are needed to validate the findings of this study.

In conclusion, this study showed that elevated serum PTX3 levels are associated with poor prognosis of HBV-related HCC, supporting the involvement of PTX3 in the disease progression and the potential of using serum PTX3 as a prognostic biomarker for HCC including AFP-negative HCC. Studies in large sample size of HCC patients related to various etiologies are required to confirm these results.

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Disclosure

The authors report no conflicts of interest in this work.

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