Up-regulated YKL-40 is associated with poor prognosis of hepatocellular carcinoma patients with hepatitis B-related cirrhosis

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Submitted: 24 May 2021; **Accepted:** 31 August 2021
Online publication: 17 September 2021

Arch Med Sci
DOI: https://doi.org/10.5114/aoms/141821

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Abstract

Introduction: Hepatocellular carcinoma (HCC) accounts for more than 90% of primary liver cancer, which is the fifth most common cancer and the leading cause of cancer-related death worldwide. Aim of the study was to investigate the clinical significance of YKL-40 in HCC patients with hepatitis B (HBV)-related cirrhosis.

Material and methods: The present prospective observational study included 129 cases of HCC patients with HBV-related cirrhosis between January 2017 and April 2019. Also, 152 patients with only hepatitis B-related cirrhosis and 110 HCC patients with no cirrhosis were enrolled during the same period. Additionally, 100 healthy individuals were enrolled as a control group. Serum YKL-40 levels were determined using the enzyme linked immunosorbent assay (ELISA) method. Levels of serum albumin, total bilirubin, alanine aminotransferase (ALT) and aspartate transaminase (AST) as well as HCC-related biomarkers of α-fetoprotein (AFP), des-γ-carboxy prothrombin (DCP), γ-glutamyltransferase (GCT), α-L-fucosidase (AFU), carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were measured using automatic biochemical analyzers. Patients' demographic and clinical characteristics were collected and analyzed.

Results: The expression of YKL-40 was the highest in HCC patients with HBV-related cirrhosis and the lowest in the healthy controls, and the difference compared with other groups was significant. HCC patients showed markedly higher YKL-40 levels than the HBV-related cirrhosis patients. Patients with higher expression of YKL-40 showed higher rates of TNM stage IV, lymphatic metastasis and Child-Pugh C, as well as higher serum levels of AFP, AFU and CA19-9 than those in the patients with lower levels of YKL-40. YKL-40 level was positively correlated with AFP and AFU. Survival analysis showed that patients with higher expression of YKL-40 had a shorter 1-year survival time than the patients with lower YKL-40.

Conclusion: YKL-40 was elevated in HCC patients with HBV-related cirrhosis and high expression of YKL-40 predicted poor prognosis and shorter 1-year survival.

Key words: YKL-40, HCC, hepatitis B-related cirrhosis, observational study.

Introduction

Hepatocellular carcinoma (HCC) accounts for more than 90% of primary liver cancer, which is the fifth most common cancer and the leading cause of cancer-related death worldwide [1, 2]. Among the risk factors

for HCC, such as excessive alcohol intake, chronic infection with hepatitis B virus (HBV) is one of the most common and main causes for HCC [3, 4]. Hepatitis B virus may induce chronic liver inflammation, immune imbalance, fibrosis and cirrhosis, which can finally lead to HCC [5, 6]. Though early stage HCC patients usually have a good prognosis, HCC patients at an advanced stage suffer from a low 5-year survival rate, less than 5% [7]. Thus, new diagnostic and prognostic biomarkers for HCC are still needed.

Currently, many oncogenes are proven to be associated with HCC. In clinical practice, biomarkers such as α-fetoprotein (AFP) [8], des-γ-carboxy prothrombin (DCP) [9], γ-glutamyltransferase (GCT) [8] and α-L-fucosidase (AFU) [10] are all reported as diagnostic biomarkers in HCC. YKL-40 (chitinase-3-like 1 protein) has been considered as a cancer promotor in many cancers including breast cancer [11], ovarian cancer [12], colorectal cancer [13] and bladder cancer [14]. In early research, YKL-40 was observed to be elevated in fibrosis patients and could be used as a biomarker in fibrosis [15, 16]. However, few studies have focused on the clinical significance of YKL-40 in HCC patients with HBV-related cirrhosis.

In the present study, we conducted an observational study to investigate the role of YKL-40 in HCC patients with HBV-related cirrhosis. This study might provide some novel research targets in HCC in both clinic and basic research.

Material and methods

Patients

The present prospective observational study included 129 cases of HCC patients with hepatitis B-related cirrhosis who attended our hospital between January 2017 and April 2019. Also, 152 patients with only hepatitis B-related cirrhosis and 110 HCC patients with no cirrhosis were enrolled during the same period. All patients were diagnosed with primary HCC for the first time and received no chemotherapy, radiotherapy or other anti-cancer treatments before the study. The diagnosis of HCC was confirmed by imaging and histological analysis for all patients. The diagnosis of hepatitis B was made according to the criteria of the Chinese Society of Hepatology and Chinese Society of Infectious Diseases, Chinese Medical Association at 2015 [17]. The diagnosis of hepatitis B-related cirrhosis was made according to the guideline of the Chinese management of clinical diagnosis, evaluation and antiviral therapy for HBV-related cirrhosis [18]. The following patients were excluded: patients with other hepato-virus such as hepatitis C, patients with other cancers or cancer history, patients with autoimmune diseases, patients who underwent surgery within half a year before the study and patients with severe cardiovascular, renal or central diseases. All patients who met the above inclusion criteria during the study period were consecutively enrolled. Additionally, 100 healthy individuals who came for routine physical examination were enrolled as controls. Written informed consent was obtained from all patients. The present study was approved by the ethical committee of Tongling People's Hospital.

Measurement of YKL-40 and other laboratory factors

The fasting peripheral venous blood samples (5 ml) were collected within 24 h after admission for all patients. Serum levels of YKL-40 were determined by enzyme linked immunosorbent assay (ELISA) using a human YKL-40 kit (LifeSpan Biosciences, Seattle, WA, USA, intra-assay: CV% < 10% inter-assay: CV% < 10%, sensitivity 0.1 ng/ml, detection range 10–250 ng/ml) according to the manufacturer's instructions. A routine whole blood test was conducted for all patients. Levels of serum albumin, total bilirubin, alanine aminotransferase (ALT) and aspartate transaminase (AST) as well as HCC-related biomarkers of AFP, DCP, GCT and AFU were measured using an automatic biochemical analyzer (Hitachi 7600, Hitachi Corporation, Japan). Levels of CEA and CA19-9 were measured by a Roche Applied Science automatic electrochemical luminescence analyzer (Roche Applied Science, Germany).

Data collection and follow-up

Patients' demographic characteristics were collected and analyzed, including age, sex, BMI and medical history. The Child-Pugh score was determined for all patients with cirrhosis. Clinical characteristics including TNM stage and metastasis condition were recorded. The patients' survival condition was followed up for 1 year after admission for all patients. The survival duration was defined from the admission to the death or the last follow-up.

Statistical analysis

The distribution of the data was analyzed by Kolmogorov-Smirnov analysis. The continuous measurement data with normal distribution were expressed as mean ± SD. Comparisons for continuous data were analyzed by one-way analysis of variance (ANOVA) followed with the Tukey post hoc test among three groups. Student's t test was used for comparison for two groups. Rates were compared by the chi square test. Pearson's correlation was used for analysis of the correlation.

Table I. Basic characteristics of all patients

Variables	HCC with HBV-related cirrhosis, *n* = 129	HCC with no cirrhosis, *n* = 110	HBV-related cirrhosis, *n* = 152	Healthy, *n* = 100	*P*-value
Age [years]	60.09 ±11.40	62.20 ±10.69	60.26 ±11.64	62.69 ±10.28	0.169*
Sex, female (%)	57 (44.19)	49 (44.54)	61 (40.13)	44 (44.00)	0.914*
BMI [kg/m^2]	22.03 ±2.35	21.87 ±2.36	21.78 ±2.41	21.70 ±2.46	0.747*
HBV infection, *n* (%)	129 (100)	82 (74.54)	152 (100)	–	–
TNM stage, *n* (%)					
I–II	68 (52.71)	60 (54.55)	–	–	0.794#
III–IV	61 (47.29)	50 (45.45)	–	–	
Lymphatic metastasis, *n* (%)	76 (58.91)	69 (62.73)	–	–	0.580#
Child-Pugh score, *n* (%)					
A	54 (41.86)	–	48 (43.64)	–	0.966&
B	44 (34.11)	–	36 (32.73)	–	
C	31 (24.03)	–	26 (23.64)	–	

**P-value was calculated using ANOVA for continuous data and using the χ^2 test for rates among all four groups. #P-value was calculated using Student's t-test for continuous data and using the χ^2 test for rates between patients of HCC with HBV-related cirrhosis and patients of HCC with no cirrhosis. &P-value was calculated using Student's t-test for continuous data and using the χ^2 test for rates between HCC with HBV-related cirrhosis and patients with HBV-related cirrhosis.*
BMI – body mass index, HBV – hepatitis B virus

A Kaplan-Meier (K-M) curve was created for survival analysis with the log-rank test. $P < 0.05$ was considered as statistically significant. All calculations were performed using SPSS 22.0 (SPSS Inc., Chicago, USA).

Results

Basic characteristics of all patients

The basic characteristics of all participants are shown in Table I. No significant difference was found in age, sex or BMI in all participants. The TNM stage and lymphatic metastasis ratio showed no significant difference between HCC patients with or without HBV-related cirrhosis. The Child-Pugh score showed no significant difference between HCC patients with HBV-related cirrhosis and HBV-related cirrhosis patients.

YKL-40 was elevated in hepatocellular carcinoma patients with hepatitis B-related cirrhosis

The measurement of YKL-40 showed that the expression of YKL-40 was the highest in HCC patients with HBV-related cirrhosis, which was remarkably higher than other groups ($p < 0.05$, Figure 1). YKL-40 levels were also markedly higher in HCC patients than the HBV-related cirrhosis patients ($p < 0.05$). The healthy controls showed the lowest YKL-40 levels, significantly lower than other groups ($p < 0.05$).

Higher YKL-40 levels were correlated with clinical outcomes of hepatocellular carcinoma patients with hepatitis B-related cirrhosis

The HCC patients with HBV-related cirrhosis were divided into a YKL-40 high expression group and a low expression group according to the mean value of YKL-40 (155.56 ng/ml). The clinical characteristics were analyzed between the two groups. It was found that patients with higher expression of YKL-40 showed higher rates of TNM IV, lymphatic metastasis and Child-Pugh C, and higher serum levels of AFP, AFU and CA19-9 than those

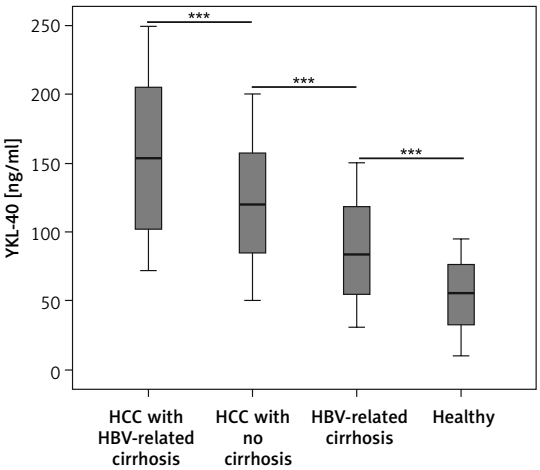

Figure 1. Expression of YKL-40 in different patients and healthy controls

in the patients with lower levels of YKL-40 (all $p < 0.05$, Table II). No significant difference was observed in other factors. Pearson's analysis showed that YKL-40 level was positively correlated with AFP and AFU in HCC patients with HBV-related cirrhosis (Table III).

Table II. Relationship between YKL-40 and clinical characteristics of hepatocellular carcinoma (HCC) patients with hepatitis B-related cirrhosis

Variables	Patients with low expression of YKL-40, *n* = 67	Patients with high expression of YKL-40, *n* = 62	*P*-value*
Age [years]	59.10 ±10.99	61.16 ±11.82	0.308
Sex, female (%)	25	22	
BMI [kg/m^2]	22.00 ±2.37	22.07 ±2.35	0.869
TNM stage, *n* (%)			
I–II	55 (82.09)	13 (20.97)	< 0.001
III–IV	12 (17.91)	49 (79.03)	
Lymphatic metastasis, *n* (%)	24 (35.82)	52 (83.87)	< 0.001
Child-Pugh score, *n* (%)			
A	30 (44.78)	22 (32.83)	0.083
B	28 (41.79)	18 (29.03)	0.059
C	9 (13.43)	22 (35.48)	< 0.001
Albumin [g/l]	37.05 ±4.42	36.96 ±4.07	0.898
Total bilirubin [µmol/l]	59.22 ±25.11	57.07 ±27.27	0.642
ALT [U/l]	169.00 ±84.56	167.57 ±71.01	0.917
AST [U/l]	207.32 ±82.71	190.92 ±92.39	0.289
AFP [ng/ml]	252.87 ±100.10	218.01 ±98.07	0.048
DCP [ng/ml]	5.46 ±2.08	5.34 ±2.07	0.759
GCT [U/L]	256.05 ±121.80	281.47 ±124.35	0.243
AFU [U/L]	129.16 ±44.53	99.83 ±42.81	< 0.001
CEA [U/L]	45.10 ±20.01	45.89 ±22.92	0.834
CA19-9 [ng/ml]	135.55 ±47.60	117.69 ±46.01	0.032

**P-value was calculated using Student's t-test for continuous data and using the chi square test for rates between the two groups. BMI – body mass index, ALT – alanine aminotransferase, AST – aspartate transaminase, AFP– α-fetoprotein, DCP – des-γ-carboxy prothrombin, GCT – γ-glutamyltransferase, AFU – α-L-fucosidase, CEA – carcinoembryonic antigen, CA19-9 – carbohydrate antigen 19-9*

Table III. Correlation among YKL-40 and other cancer biomarkers in hepatocellular carcinoma (HCC) patients with HBV-related cirrhosis

		YKL-40	AFP	AFU	CA19-9	DCP	GCT	CEA
YKL-40	Pearson correlation	1	–0.250	–0.314	–0.163	–0.012	0.053	0.026
	P-value	–	0.004	< 0.001	0.065	0.889	0.544	0.762
AFP	Pearson correlation	–0.250	1	0.110	–0.37	–0.003	0.098	–0.182
	P-value	0.004	–	0.214	0.674	0.972	0.268	0.039
AFU	Pearson correlation	–0.314	0.110	1	–0.017	0.040	–0.123	–0.141
	P-value	< 0.001	0.214	–	0.846	0.654	0.165	0.111
CA19-9	Pearson correlation	–0.163	–0.037	–0.017	1	–0.040	–0.087	0.105
	P-value	0.065	0.674	0.846	–	0.655	0.324	0.235
DCP	Pearson correlation	–0.012	–0.003	0.040	–0.040	1	0.123	0.075
	P-value	0.889	0.972	0.654	0.655	–	0.166	0.395
GCT	Pearson correlation	0.054	0.098	–0.123	–0.087	0.123	1	0.025
	P-value	0.544	0.268	0.165	0.324	0.166	–	0.776
CEA	Pearson correlation	0.027	–0.182	–0.141	0.105	0.075	0.025	1
	P-value	0.762	0.039	0.111	0.235	0.395	0.776	–

AFP – α-fetoprotein, AFU – α-L-fucosidase, CA19-9 – carbohydrate antigen 19-9, DCP – des-γ-carboxy prothrombin, GCT – γ-glutamyltransferase, CEA – carcinoembryonic antigen

Relationship between YKL-40 and prognosis of hepatocellular carcinoma patients with hepatitis B-related cirrhosis

Finally, survival analysis was performed using a K-M curve. We found that patients with higher expression of YKL-40 had shorter 1-year survival time than the patients with lower YKL-40 ($p < 0.05$, Figure 2). The mortality rate of the YKL-40 higher group (26/62, 41.94%) was also higher than the YKL-40 lower group (18/67, 26.87%); the difference was significant ($p = 0.025$).

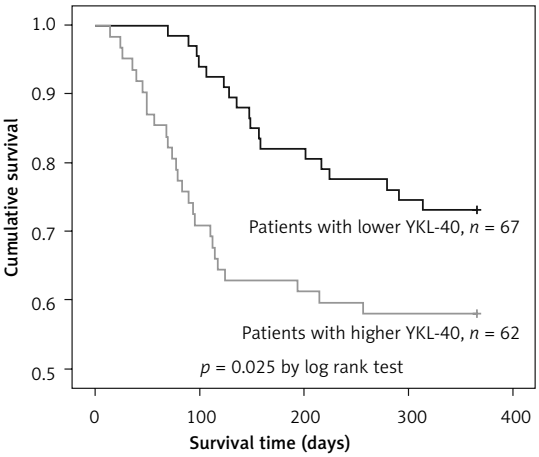

Figure 2. Kaplan-Meier curve for 1-year mortality in patients with high or low YKL-40 levels

Discussion

The diagnosis and treatment of HCC continue to pose a clinical challenge. Despite current advances, new biomarkers and research targets are still needed. In recent years, the role of YKL-40 in cancer development has been noted. However, up to now, no study has focused on the clinical significance of YKL-40 in HCC patients combined with HBV-related cirrhosis. In the present study, we found that YKL-40 was elevated in HCC patients with HBV-related cirrhosis, and was associated with patients' TNM stage, lymphatic metastasis, AFP and AFU and CA19-9 levels, as well as patients' 1-year survival.

YKL-40 has been regarded as a cancer promotor in many studies. In a meta-analysis, the authors reported that elevated YKL-40 levels were associated with poor prognosis in gastrointestinal tumors, ovarian cancer, melanoma, lung cancer, urologic neoplasms and glioblastoma, but not breast cancer [19]. In melanoma patients in a cohort study, it was also observed that increasing plasma YKL-40 was associated with increased mortality [20]. In a recent study, Holst *et al*. found that elevated YKL-40 level was associated with short overall survival in gliomas patients [21]. Compared to other cancers, the role of YKL-40 in HCC has not been investigated in most research. Saleh *et al*. reported that YKL-40 levels were associated with chitinase 3-like 1 gene (T/C) polymorphism and CC genotype, and the highest serum YKL-40 levels predicted the shortest survival rate [22]. Furthermore, elevated YKL-40 levels were correlated with clinical outcomes after transcatheter arterial chemoembolization [23]. However, up to now, few other studies have focused on the role of YKL-40 in HCC and its relationship with HBV-related cirrhosis. In this research, we also observed that YKL-40 was up-regulated in HCC patients, especially in HCC patients with HBV-related cirrhosis. The levels of YKL-40 were associated with patients' TNM stage, lymphatic metastasis and cancer biomarkers, as well as patients' prognosis.

HBV-related cirrhosis is one of the risk factors for HCC. In HBV-related cirrhosis, the tumor-related angiogenesis signaling pathways, such as vascular endothelial growth factor (VEGF) and pituitary tumor transforming gene (PTTG) signaling pathways, are activated and overexpressed [24–26]. Except for the abnormal expression of YKL-40 in cancer, YKL-40 is also found to be associated with tumor-related angiogenesis. Shao *et al*. concluded that YKL-40 acts as an angiogenic factor to promote tumor angiogenesis in a review [27]. Francescone *et al*. reported that YKL-40 induced VEGF expression and promoted endothelial cell angiogenesis in a glioblastoma cell line [28]. On the other hand, inhibition of YKL-40 suppressed tumor angiogenesis in cancer development [29]. Moreover, in a recent study, YKL-40 was found to be elevated in accordance with the progression of liver fibrosis and could be used as a biomarker in liver fibrosis patients [30]. Since angiogenesis is one of the important factors in HBV-related cirrhosis, the relationship between YKL-40 and HBV might also be related to the function of YKL-40 in angiogenesis. Thus, we can speculate that in HCC patients with HBV-related cirrhosis, YKL-40 might also promote cancer development by promoting cancer angiogenesis. However, this hypothesis needs more basic studies to confirm it.

The present study also has some limitations. The sample size was small, and it is still unclear how YKL-40 influences HCC.

In conclusion, we conducted an observational study and found that increased YKL-40 levels were associated with patients' TNM stage, lymphatic metastasis, AFP, AFU and CA19-9 levels, as well as patients' 1-year survival in HCC patients with HBV-related cirrhosis. This study might provide clinical evidence for the role of YKL-40 in HCC. More studies need to be performed to further illuminate the underlying mechanisms for YKL-40 in HCC development.

Conflict of interest

The authors declare no conflict of interest.

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