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

Type
Research paper

Keywords
observational study, HCC, YKL-40, hepatitis B related cirrhosis

Abstract
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To investigate clinical significance of YKL-40 in hepatocellular carcinoma (HCC) patients with hepatitis B (HBV) related cirrhosis.

Material and methods
The present prospective observational study included 129 cases of HCC patients. Besides, 152 patients with only hepatitis B related cirrhosis and 110 HCC patients with no cirrhosis were also enrolled during the same period. Additionally, 100 healthy individuals were enrolled as control. Serum YKL-40 levels were determined using ELISA method. Levels of serum albumin, total bilirubin, alanine aminotransferase (ALT) and aspartate transaminase (AST) as well as HCC related biomarkers of alpha fetoprotein (AFP), des-γ-carboxy prothrombin (DCP), gamma glutamytransferase (GCT-II), α-L-Fucosidase (AFU), CEA and CA19-9 were measured using an automatic biochemical analyzer. 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 control, and the difference was significant compared with other groups. And HCC patients showed markedly higher YKL-40 levels than the HBV-related cirrhosis patients. Patients with higher expression of YKL-40 showed higher ratio of TNM IV, lymphatic metastasis and Child-Pugh C, and 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 patients with higher expression of YKL-40 had shorter 1-year survival time than the patients with lower YKL-40.

Conclusions
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.
Up-regulated YKL-40 is associated with poor prognosis of HCC patients with hepatitis B related cirrhosis

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Running title
YKL-40 predicts poor prognosis of HCC patients with HBV related cirrhosis

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Abstract

Objective: To investigate clinical significance of YKL-40 in hepatocellular carcinoma (HCC) patients with hepatitis B (HBV) related cirrhosis.

Methods: The present prospective observational study included 129 cases of HCC patients with HBV related cirrhosis during January 2017 to April 2019. Besides, 152 patients with only hepatitis B related cirrhosis and 110 HCC patients with no cirrhosis were also enrolled during the same period. Additionally, 100 healthy individuals were enrolled as control. Serum YKL-40 levels were determined using 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 alpha fetoprotein (AFP), des-γ-carboxy prothrombin (DCP), gamma 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 control, and the difference was significant compared with other groups. HCC patients showed markedly higher YKL-40 levels than the HBV-related cirrhosis patients. Patients with higher expression of YKL-40 showed higher ratio of TNM IV stage, 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 patients with higher expression of YKL-40 had 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.

**Keywords** YKL-40, HCC, hepatitis B related cirrhosis, observational study

**Introduction**

Hepatocellular carcinoma (HCC) accounts for more than 90% 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]. HBV 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 well prognosis, HCC patients with advanced stage suffer from low 5-year survival rate less than 5% [7]. Thus, new diagnosis and prognosis biomarkers for HCC are still needed.

Currently, many oncogenes are proven to be associated with HCC. In clinical, biomarkers such as alpha fetoprotein (AFP) [8], des-γ-carboxy prothrombin (DCP) [9], gamma 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], etc. In early researches, YKL-40 was observed to be elevated in fibrosis patients and could be used as a biomarker in fibrosis [15, 16]. However, few studies 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 researches.

Methods and materials

Patients

The present prospective observational study included 129 cases of HCC patients with hepatitis B related cirrhosis who went to our hospital during January 2017 to April 2019. Besides, 152 patients with only hepatitis B related cirrhosis and 110 HCC patients with no cirrhosis were also enrolled during the same period. All patients were diagnosed as 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 received 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 control. 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 manufacture’s instruction. 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. Child-Pugh score was tested 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 normally distribution were expressed as mean ± SD. Comparison for continuous data were analyzed by one-way analysis of variance (ANOVA) following with Tukey post hoc test among three groups. Student t test was used for comparison for two groups. Rates were compared by Chi square test. Pearson’s
correlation was used for analysis of the correlation. Kaplan-Meier (K-M) curve was performed for survival analysis with the log-rank test. \( P < 0.05 \) was considered as statistically significant. All calculations were made using SPSS 22.0 (SPSS Inc., Chicago, USA).

**Results**

*Basic characteristics of all patients*

The basic characteristics of all participants were shown in Table 1. No significant difference was found in age, sex and 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 in HCC patients with HBV-related cirrhosis and HBV-related cirrhosis patients.

*YKL-40 was elevated in HCC patients with hepatitis B related cirrhosis*

Then, 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 (\( P < 0.05 \)). Besides, the healthy control showed the lowest YKL-40 levels, significantly lower than other groups (\( P < 0.05 \)).

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

Then, HCC patients with HBV related cirrhosis were divided into YKL-40 high expression groups and low expression groups according to the mean value of YKL-40 (155.56 ng/ml). The clinical characteristics were analyzed between the two groups. It was found patients with higher expression of YKL-40 showed higher ratio of TNM IV, lymphatic metastasis and Child-Pugh C, and higher serum levels of AFP, AFU and
CA19-9 than those in the patients with lower levels of YKL-40 (all P<0.05, Table 2). No significant difference was observed in other factors. Pearson’s analysis showed YKL-40 level was positively correlated with AFP and AFU in HCC patients with HBV related cirrhosis (Table 3).

**Relationship between YKL-40 and prognosis of HCC patients with hepatitis B related cirrhosis**

Finally, survival analysis was performed using 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 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).

**Discussion**

The diagnosis and treatment of HCC keep being 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 noticed. However, up to now, no study focused on clinical significance of YKL-40 in HCC patients combined with HBV-related cirrhosis. In the present study, we demonstrated 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 condition.

YKL-40 has been regarded as a cancer promotor in many researches. 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 increasing plasma YKL-40 was associated with increased mortality [20]. In a recent research, Holst et al found that elevated YKL-40 level was associated with short overall survival in gliomas patients [21]. Compared to
other cancers, role of YKL-40 in HCC has not been noticed in most researches. Saleh et al demonstrated that YKL-40 levels were associated with chitinase 3-like 1 gene (T/C) polymorphism, and CC genotype, also the highest serum YKL-40 levels predicted the shortest survival rate [22]. Besides, elevated YKL-40 levels are also correlated with clinical outcomes after transcatheter arterial chemoembolization [23]. However, up to now, few other researches 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 upregulated 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 research [27]. Francescone et al reported that YKL-40 induced VEGF expression and promoted endothelial cell angiogenesis in glioblastoma cell line [28]. On the contrary, inhibition of YKL-40 suppressed tumor angiogenesis in cancer development [29]. Besides, in a recent research, 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 be also 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.

The present study also has some limitations. The sample size is small and how YKL-40 influence HCC is still unclear.
In conclusion, we conducted an observational study and found the 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 condition in HCC patients with HBV-related cirrhosis. This study might provide clinical evidence for role of YKL-40 in HCC. More studies need to be performed to further illuminate the underlying mechanisms for YKL-40 in HCC development.

Reference

1. Yang JD, Hainaut P, Gores GJ et al: A global view of hepatocellular carcinoma: trends, risk, prevention and management. Nat Rev Gastroenterol Hepatol 2019, 16(10):589–604.
2. Ringelhan M, Pfister D, O’Connor T et al: The immunology of hepatocellular carcinoma. Nature Immunology 2018, 19(3):222–232.
3. Zhang X, Kang C, Li N et al: Identification of special key genes for alcohol-related hepatocellular carcinoma through bioinformatic analysis. PeerJ 2019, 7:e6375-e6375.
4. Ioannou GN, Green P, Lowy E et al: Differences in hepatocellular carcinoma risk, predictors and trends over time according to etiology of cirrhosis. PLoS One 2018, 13(9):e0204412–e0204412.
5. Chen Y, Tian Z: HBV-Induced Immune Imbalance in the Development of HCC. Front Immunol 2019, 10:2048–2048.
6. An P, Xu J, Yu Y et al: Host and Viral Genetic Variation in HBV-Related Hepatocellular Carcinoma. Front Genet 2018, 9:261–261.
7. Tung SL, Huang WC, Hsu FC et al: miRNA-34c-5p inhibits amphiregulin-induced ovarian cancer stemness and drug resistance via downregulation of the AREG-EGFR-ERK pathway. Oncogenesis 2017, 6(5):e326–e326.
8. Wang Q, Chen Q, Zhang X et al: Diagnostic value of gamma-glutamyltransferase/aspartate aminotransferase ratio, protein induced by vitamin K absence or antagonist II, and alpha-fetoprotein in hepatitis B virus-related hepatocellular carcinoma. World J Gastroenterol 2019, 25(36):5515–5529.
9. Ji J, Wang H, Li Y et al: Diagnostic Evaluation of Des-Gamma-Carboxy Prothrombin versus α-Fetoprotein for Hepatitis B Virus-Related Hepatocellular Carcinoma in China: A Large-Scale, Multicentre Study. PLoS One 2016, 11(4):e0153227–e0153227.
10. Wang K, Guo W, Li N et al: Alpha-1-fucosidase as a prognostic indicator for hepatocellular carcinoma following hepatectomy: a large-scale, long-term study. Br J Cancer 2014, 110(7):1811–1819.
11. Shaker OG, Helmy HS: Circulating bone related markers and YKL-40 versus HER2
and TOP02a in bone metastatic and non-metastatic breast cancer: diagnostic implications. *Clinical Breast Cancer* 2017, 18(3):e321-e328.

12. Høgdall E, Johansen J, Kjaer S *et al*: High plasma YKL-40 level in patients with ovarian cancer stage III is related to shorter survival. *Oncology Reports* 2003, 10(5):1535-1538.

13. Tarpgaard LS, Guren TK, Glimelius B *et al*: Plasma YKL-40 in Patients with Metastatic Colorectal Cancer Treated with First Line Oxaliplatin-Based Regimen with or without Cetuximab: RESULTS from the NORDIC VII Study. *PLoS One* 2014, 9(2):e87746.

14. Tschir dewahn S, Reis H, Niedworok C *et al*: Prognostic effect of serum and tissue YKL-40 levels in bladder cancer. *Urologic Oncology* 2014, 32(5):663-669.

15. Berres ML, Papen S, Pauels K *et al*: A functional variation in CHI3L1 is associated with severity of liver fibrosis and YKL-40 serum levels in chronic hepatitis C infection. *Journal of Hepatology* 2009, 50(2):0-376.

16. Yan L, Deng Y, Zhou J *et al*: Serum YKL-40 as a biomarker for liver fibrosis in chronic hepatitis B patients with normal and mildly elevated ALT. *Infection* 2018, 46(3):385-393.

17. Hou JL: The guideline of prevention and treatment for chronic hepatitis B: a 2015 update. *Chinese journal of hepatology* 2015, 23(12):888-905.

18. Y O: Management of clinical diagnosis, and antiviral therapy for HBV-related cirrhosis. *Chinese Journal of Hepatology* 2014, 22(5):327-335.

19. Bian B, Li L, Yang J *et al*: Prognostic value of YKL-40 in solid tumors: a meta-analysis of 41 cohort studies. *Cancer Cell Int* 2019, 19:259-259.

20. Hafsa I, Jens H, Lisbet RH *et al*: Measured and genetically predicted plasma YKL-40 levels and melanoma mortality. *European journal of cancer (Oxford, England: 1990)* 2019, 121:74-84.

21. Holst CB, Christensen IJ, Skjøth-Rasmussen J *et al*: Systemic Immune Modulation in Gliomas: Prognostic Value of Plasma IL-6, YKL-40, and Genetic Variation in YKL-40. *Front Oncol* 2020, 10:478-478.

22. Saleh AA, Alhanafy, A. M., Elbahr, O., & El-Hefnawy, S. M.: Chitinase 3-like 1 gene (T/C) polymorphism and serum YKL-40 levels in patients with hepatocellular carcinoma. *Meta Gene* 2020, 24:100686.

23. Zhu C-B, Wang C, Chen L-L *et al*: Serum YKL-40 independently predicts outcome after transcatheter arterial chemoembolization of hepatocellular carcinoma. *PLoS One* 2012, 7(9):e44648.

24. Kang KF, Shi XC, Chen XW: Relationships between PTTG and VEGF Expression and Cancer Angiogenesis in Hepatocellular Carcinoma. *The Practical Journal of Cancer* 2007, 22(2):161-163.

25. Mao CS, Yin H, Ning HB *et al*: Levels of HBx, VEGF, and CEACAM1 in HBV-related hepatocellular carcinoma and their correlation with cancer prognosis. *Eur Rev Med Pharmacol Sci* 2017, 21(17):3827-3833.

26. Mathonnet M, Descottes B, Valleix D *et al*: VEGF in hepatocellular carcinoma and surrounding cirrhotic liver tissues. *World journal of gastroenterology:
27. Shao R: YKL-40 acts as an angiogenic factor to promote tumor angiogenesis. *Front Physiol* 2013, 4:122-122.

28. Francescone RA, Scully S, Faibish M et al: Role of YKL-40 in the angiogenesis, radioresistance, and progression of glioblastoma. *J Biol Chem* 2011, 286(17):15332-15343.

29. Faibish M, Francescone R, Bentley B et al: A YKL-40–Neutralizing Antibody Blocks Tumor Angiogenesis and Progression: A Potential Therapeutic Agent in Cancers. *Molecular Cancer Therapeutics* 2011, 10(5):742-751.

30. Kumagai E, Mano Y, Yoshio S et al: Serum YKL-40 as a marker of liver fibrosis in patients with non-alcoholic fatty liver disease. *Sci Rep* 2016, 6:35282.
Figure Legends:

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

**Figure 2.** K-M curve for 1-year mortality in patients with high or low YKL-40 levels.

**Table legends**

**Table 1.** Basic characteristics of all patients

| Variables | HCC with HBV-related cirrhosis, n=110 | HCC with no HBV-related cirrhosis, n=152 | HBV-related cirrhosis, n=152 | Healthy, n=100 | P value |
|-----------|----------------------------------------|------------------------------------------|-----------------------------|----------------|---------|

11
|                      | n=129                                      |
|----------------------|-------------------------------------------|
| **Age, year**        | 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/m²**       | 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 (%)** | -  -  -  - 0.794# |
| I~II                 | 68 (52.71)  60 (54.55)  -  - |
| III~IV               | 61 (47.29)  50 (45.45)  -  - |
| **Lymphatic metastasis, n (%)** | 76 (58.91)  69 (62.73)  -  - 0.580# |
| **Child-Pugh score, n (%)** | -  -  -  - 0.966& |
| A                    | 54 (41.86)  -  48 (43.64)  -  |
| 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 Chi square test for rates among all four groups; #P value was calculated using Student t test for continuous data and using Chi square test for rates between patients of HCC with HBV-related cirrhosis and patients of HCC with no cirrhosis; &P value was calculated using Student t test for continuous data and using Chi square test for rates between HCC with HBV-related cirrhosis and patients of HBV-related cirrhosis.
Table 2. Relationship between YKL-40 and clinical characteristics of 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, year                          | 59.10±10.99                                 | 61.16±11.82                                 | 0.308     |
| Sex, female (%)                    | 25                                          | 22                                          |           |
| BMI, kg/m²                         | 22.00±2.37                                  | 22.07±2.35                                  | 0.869     |
| TNM stage, n (%)                   |                                             |                                             | <0.001    |
| I–II                               | 55 (82.09)                                  | 13 (20.97)                                  |           |
| 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, μ mol/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    |
|                  | YKL-40 | AFP  | AFU  | CA19-9 | DCP  | GCT  | CEA  |
|------------------|--------|------|------|--------|------|------|------|
| **YKL-40**       |        | -0.250 | -0.314 | -0.163 | -0.012 | 0.053 | 0.026 |
| **AFP**          | -0.250 | 1     | 0.110 | -0.37  | -0.003 | 0.098 | -0.182 |
| **AFU**          | <0.001 | 0.214 | 1     | -0.017 | 0.040 | -0.123 | -0.141 |
| **CA19-9**       | -0.163 | -0.037 | -0.017 | 1   | -0.040 | -0.087 | 0.105 |
| **DCP**          | -0.012 | -0.003 | 0.040 | -0.040 | 1   | 0.123 | 0.075 |
| **GCT**          | 0.054  | 0.098 | -0.123 | -0.087 | 0.123 | 1   | 0.025 |
| **CEA**          | 0.027  | -0.182 | -0.141 | 0.105 | 0.075 | 0.025 | 1   |

*P value was calculated using Student t test for continuous data and using Chi square test for rates between the two groups.

Table 3. Correlation among YKL-40 and other cancer biomarkers in HCC patients with HBV related cirrhosis
| P  | 0.762 | 0.039 | 0.111 | 0.235 | 0.395 | 0.776 | -    |
|----|-------|-------|-------|-------|-------|-------|------|

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