**Name of journal: World Journal of Gastroenterology**

**ESPS Manuscript NO: 19305**

**Columns: ORIGINAL ARTICLE**

*Observational Study*

Down-regulation of *KIF1B* mRNA in hepatocellular carcinoma tissues correlates with poor prognosis

Yang SZ *et al. KIF1B* expression in HCC patients

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**Author contributions:** Yang SZ, Wang JT and Chen SG designed the research; Yang SZ, Wang JT, Yu WW, Liu Q, and Wu YF performed the research; Yu WW and Liu Q contributed new reagents/analytic tools; Yang SZ, Wang JT, Wu YF and Chen SG analyzed the data; and Yang SZ, Wang JT and Chen SG wrote the paper.

**Ethics approval:** The study protocol was approved by the Ethics Committee of the Yantaishan Hospital.

**Informed consent:** Informed consent was obtained from each patient.

**Conflict-of-interest:** No potential conflicts of interest relevant to this article were reported.

**Data sharing:** No additional data are available.

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**Received:** March 16, 2015

**Peer-review started:** March 17, 2015

**First decision:** March 26, 2015

**Revised:** April 11, 2015

**Accepted:** May 7, 2015

**Article in press:**

**Published online:**

Abstract

**AIM:** To investigated the relationship between kinesin family member 1B (KIF1B) expression and clinicopathologic parameters, and its prognostic value for patients with hepatocellular carcinoma (HCC).

**METHODS:** We assessed KIF1B protein and mRNA expression in HCC tissue and paracarcinomatous (PC) tissue from 68 patients with HCC, using western blot and quantitative real-time reverse transcription-polymerase chain reaction, respectively. We used *t*-tests to analyze relationships between clinicopathological parameters and KIF1B expression, the Kaplan–Meier method to analyze survival outcomes, and the log-rank test to compare survival differences between groups.

**RESULTS:** Mean protein and mRNA levels of KIF1B were similar in HCC tissues to those in PC tissues. HCC tissues with vein invasions had significantly lower KIF1B protein levels (2.30 ± 0.82 RU) than did those without vein invasions (2.77 ± 0.84; *P* < 0.05). KIF1B protein levels in HCC tissues from patients with recurrence during the follow-up were significantly lower than from those without recurrence (2.31 ± 0.92 *vs* 2.80 ± 0.80, *P* < 0.05). However, KIF1B protein and mRNA expression in HCC patients had no statistical association with other clinicopathologic parameters. Ratios of *KIF1B* mRNA expression in HCC tissues to those in PC tissues were correlated with overall survival (13.5 *vs* 20 mo, *P* < 0.05) and disease-free survival (11.5 *vs* 19.5 mo, *P* < 0.05).

**CONCLUSION:** Down-regulation of KIF1B mRNA in HCC tissues was associated with poor prognosis. The further large-scale clinical studies are needed to confirm whether KIF1B could serve as a liver cancer prognostic marker.

**Key words:** Liver cancer; Clinicopathologic correlation; Kinesin family member 1B; Tumor progression; Survival

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**Core tip:**Expression of kinesin family member 1B (KIF1B) protein and mRNA did not significantly differ between hepatocellular carcinoma (HCC) tissues and paracarcinomatous tissues. KIF1B protein levels in HCC tissues were inversely correlated with recurrence and tumor vein invasion. Furthermore, ratios of *KIF1B* mRNA in HCC tissues to paracarcinomatous tissues correlated with overall survival and disease-free survival for patients with HCC. Down-regulation of *KIF1B* mRNA in HCC tissues was associated with poor prognosis.

Yang SZ, Wang JT, Yu WW, Liu Q, Wu YF, Chen SG. Down-regulation of *KIF1B* mRNA in hepatocellular carcinoma tissues correlates with poor prognosis. *World J Gastroenterol* 2015; In press

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third most common cause of cancer-related deaths worldwide[1,2]. An estimated 782500 new liver cancer cases and 745500 deaths occurred worldwide during 2012, with China alone accounting for about 50% of the total number of cases and deaths[3]. It imposes high social and medical burdens, especially in societies with high incidences of viral hepatitis infection[4]. Most HCC patients are diagnosed beyond the stage at which surgical options are suitable, and thus have poor prognoses. However, patients at the same stage may have different prognoses[5] because many factors affect outcomes such as clinicopathologic parameters[6-13] and emerging biomarkers[10,14-19]. In this study, we explore how kinesin family member 1B (KIF1B) affects the long-term survival outcomes in patients with HCC who undergo surgical treatment.

Recently, a single nucleotide polymorphism, rs17401966, located at intron 24 of KIF1B, was associated with the susceptibility to hepatitis B virus (HBV)-related HCC in a genome-wide association study[20]. Several studies confirmed that KIF1B affects the progression from HBV infection to HCC[20,21]. However, expression of KIF1B protein and mRNA in tumors and paracarcinomatous (PC) tissues of HCC patients were not described in existing studies. We therefore retrospectively investigated the relationship between KIF1B expression and clinicopathologic parameters, and its predictive value for HCC prognosis.

MATERIALS AND METHODS

## Patients and samples

We collected resected tumor and matched PC specimens from 68 HCC patients, which were immediately frozen in liquid nitrogen and stored at −80 °C until further testing. PC tissue was defined as liver tissue collected 2–5 cm away from the tumor border. All patients were treated with surgery in the Department of Hepatobiliary Surgery, Yantaishan Hospital, between January 2012 and June 2012. The diagnosis of HCC was made based on guidelines from the Chinese Society of Hepatology and Chinese Society of Infectious Diseases, Chinese Medical Association[22]. Patients who received other treatment (TACE, RFA or others) before surgery or have other tumor diseases were excluded from this study. The study protocol was approved by the Ethics Committee of the Yantaishan Hospital. Informed consent was obtained from each patient.

Cinfection, tumor size, number of tumor nodules, histopathological classification, vein invasion, recurrence status, and patient survival time. Vein invasion found during pathological examination indicated tumor infiltration in the portal venous and/or hepatic veins. We monitored recurrence with ultrasound, computed tomography scan, and magnetic resonance imaging.

## Western blot analysis

HCC and PC tissues were homogenized and treated with RIPA lysis buffer (Dingguo, Beijing, China); the extracted proteins were resolved by 4%–12% acrylamide gradient gel. After electrophoresis, samples were transferred to a polyvinylidene fluoride membrane using iBlot fast transfer electric transfer (Invitrogen, IL, United States). Membranes were blocked at room temperature for 1 h by 5% milk, and incubated with a primary antibody against KIF1B or GAPDH (1:1000, Abcam, MA, United States) at 4 °C overnight, followed by TBST washing three times, a secondary antibody (1:8000, Abcam) incubation at room temperature for 2 h, TBST washing three times, and exposure to film with the ECL kit (Pierce, CA, United States). KIF1B-specific signals were quantified from X-ray films using a scanner with BandScan 4.30 densitometry software, and expressed as integrated intensity units relative to the GAPDH signals. The results were analyzed by physicians in a blinded manner.

## Quantitative real-time reverse transcription-polymerase chain reaction

Total RNA was extracted from HCC and PC tissues with the Trizol method. The retroviral reverse transcriptase kit (Takara, Tokyo, Japan) was used to synthesize cDNA with the reaction conditions of 37 °C for 60 min and 95 °C for 3 min. Primers were sense: 5′-TTTCCAGCACTTAATGAAAACACATAG-3′; antisense: 5′-CAAAGTTAAATTTCCCTGCTTTGAA-3′ for the *KIF1B* gene, and sense: 5′-GAAGGTGAAGGTCGGAGTC -3′; antisense: 5′-GAAGATGGTGATGGGATTTC -3 ′ for *GAPDH*. Real-time PCR was performed with the 7500 real-time quantitative PCR instrument (Applied Biosystems, CA, United States) at the following condition: 95 °C for 20 s, 60 °C for 30 s, and 72 °C for 30 s for 40 cycles. Data were normalized using the *GAPDH* housekeeping gene and were expressed as 2−ΔCt.

## Patients follow-up

We obtained follow-up data after discharge for all 68 HCC patients by direct communication with the patients or their relatives, or by reviewing hospital records. Disease-free survival (DFS) was measured from the date of hepatectomy until tumor recurrence. Overall survival (OS) was measured from the date of hepatectomy until death or the last follow-up point. The last follow-up evaluation was censored on December 31, 2014, or up to the time of death.

## Statistical analysis

Values are presented as mean ± SD or median (range). The Student’s *t*-test was used to evaluate differences in KIF1B protein and mRNA expression between HCC and PC tissues. Spearman correlation coefficients were used to analyze relationships between expression levels of KIF1B protein and mRNA in HCC. The Student’s *t*-test was used to analyze relationships between KIF1B expression level and clinicopathologic parameters. Bivariate correlations were used to analyze the association between survival time and KIF1B protein and mRNA. OS and DFS was calculated by the Kaplan–Meier method and analyzed by the log-rank test. All tests were two-tailed; *P* < 0.05 was considered significant. The SPSS package 13.0 (SPSS Inc., Chicago, IL, United States) was used for all analyses.

RESULTS

## Patient characteristics

The mean age of the HCC patients was 58.4±10.9 years; 83.8% (57/68) were male, and 80.9% (55/68) had HBV infections. Nineteen HCC patients had at least one tumor nodule larger than 5 cm. Tumors were well differentiated in 25 patients, and moderately or poorly differentiated in 32 and 11 patients, respectively. The median follow-up time was 16.5 mo (range: 1–36 mo). HCC recurred in 34 patients over a median recurrence time of 13.5 mo. During the follow-up, 31 patients died, with a mean survival time of 16.8 ± 9.4 mo.

## KIF1B protein and mRNA expression in HCC and PC tissues

The mean KIF1B protein level in HCC tissues was 2.55 ± 0.87 RU higher, but not significantly so, than that in PC tissues (2.38 ± 0.92 RU). The mean *KIF1B* mRNA level in HCC tissues (1.47 ± 0.29) was also similar to that in PC tissues (1.48 ± 0.29). KIF1B protein and mRNA expression did not significantly differ between HCC and PC tissues (Figure 1).

## Correlation between KIF1B expression and clinicopathological features

KIF1B protein expression in HCC tissues with vein invasion was significantly lower (2.30 ± 0.82 RU) than in those without vein invasion (2.77 ± 0.84, *P* = 0.033). *KIF1B* mRNA expression in HCC tissues with vein invasion (1.41 ± 0.25) was also lower than in those without vein invasion (1.50 ± 0.30), but not significantly so. However, ratios of *KIF1B* mRNA expression in HCC/adjacent PC tissues with vein invasions were significantly lower (0.89 ± 0.29) than those without vein invasions (1.11 ± 0.33, *P* = 0.009).

KIF1B protein levels in HCC tissues from patients who experienced recurrence during the follow-up (2.31 ± 0.92) were significantly lower than in those without recurrence (2.80 ± 0.80, *P* = 0.022). *KIF1B* mRNA levels were slightly lower, but not significantly so, in the recurrence group. Ratios of HCC/PC *KIF1B* mRNA expression in patients with recurrence during the follow-up (0.96 ± 0.31) were significantly lower than those without recurrence (1.11 ± 0.29, *P* = 0.043).

We found no correlation between KIF1B protein or mRNA expression and other clinicopathologic parameters, including patient age, sex, hepatitis B virus, liver function, tumor differentiation, tumor size, and number of tumor nodules (Table 1).

Bivariate correlations were used to analyze the association between survival time and KIF1B protein and mRNA. We found ratios of *KIF1B* mRNA expression in HCC/adjacent PC tissues were correlated with OS and DFS, with respective Pearson correlations of 0.941 and 0.988 (*P* < 0.001 for both). This indicates that down-/up-regulated *KIF1B* mRNA in HCC tissues is relevant to HCC prognosis. Kaplan–Meier survival curves and log-rank tests showed that down-regulated *KIF1B* mRNA in HCC tissues was associated with poor prognosis. Median OS for the down-regulated group was 13.5 mo, significantly shorter than for the up-regulated group at 20 mo (*P* < 0.05; Figure 2). Median DFS for down- and up-regulated groups were 11.5 months and 19.5 months, respectively (*P* < 0.05; Figure 3).

DISCUSSION

*KIF1B* is located on chromosome 1p36, and belongs to the kinesin superfamily of intermediate filaments of cytoskeletal structures that are responsible for intracellular vesicular transport[23]. *KIF1B* encodes two alternatively spliced isoforms, KIF1Ba and KIF1Bb, and both isoforms form homodimers and transport mitochondria and synaptic vesicle precursors, respectively[24]. *KIF1B* has been shown to act as a tumor suppressor in multiple cancers, including aggressive neuroblastoma, pheochromocytoma, colon, liver, brain, breast, and other cancers, by acting on various inhibitors of cell proliferation and activators of apoptosis[25,26]. *KIF1B* knockdown in rat sympathetic neurons prevents apoptosis following nerve growth factor withdrawal, indicating that KIF1B plays a crucial role in neuronal apoptosis upon nerve growth factor limitation[27].

KIF1B is reportedly associated with gastric cancer invasion[28], which suggests that KIF1B has a function in cancer progression. Zhang *et al*[20]showed *KIF1B* contributed distinctly to the progression from chronic HBV infection to HCC. However, the exact function of KIF1B in HCC is unclear; conditional knockout models may be necessary to further investigate its role in hepatocarcinogenesis.

KIF1B expression in HCC tissues and its relationship with tumor progression and prognosis are not widely reported. The present study found that KIF1B protein was expressed in cancer tissues and PC tissues of patients with HCC, with no significant differences in expression levels. We observed no significant correlation between the expression level of KIF1B protein and mRNA in HCC samples. Genetic polymorphisms and epigenetic factors may have contributed to the difference.

An important result of the current study was that KIF1B protein expression was associated with vein invasion and tumor recurrence status. These factors are highly correlated with invasion and metastasis of HCC[29-31]. Our results indicate that more invasive tumors have lower KIF1B protein expression, and by extension, that KIF1B has a suppressive function in HCC. We also found that KIF1B protein expression showed no significant pattern when the subjects and their specimens were stratified by sex, age, liver function, HBV, number of tumor nodules, tumor size, and tumor differentiation. These factors might not affect KIF1B expression, or might do so only subtly.

Unlike the protein results, *KIF1B* mRNA expression had no correlation to any tested clinicopathologic features. Interestingly, correlation analysis showed that ratios of *KIF1B* mRNA expression in HCC/PC pairs had a significant negative correlation with OS and DFS. HCC patients were divided into two groups: patients with down-regulated expression (higher *KIF1B* mRNA expression in PC tissues than in HCC tissues) and those with up-regulated expression (higher *KIF1B* mRNA expression in HCC tissues than in PC tissues). The down-regulated *KIF1B* mRNA group had longer DFS than the up-regulated *KIF1B* mRNA group. In addition, patients with down-regulated *KIF1B* mRNA had increased risk of recurrence and significantly reduced OS.

Our results show that *KIF1B* is a liver cancer suppressor gene. *KIF1B* mRNA levels may be prognostic biomarkers.

In conclusion, this is the first investigation of the KIF1B expression at both protein and mRNA levels with clinicopathologic features of HCC. Expression of the KIF1B protein and mRNA did not differ between HCC tissues and PC tissues. KIF1B protein levels in HCC tissues from patients with recurrence during the follow-up were significantly lower than in those without recurrence. HCC tissues with vein invasions had significantly lower KIF1B protein levels than those without vein invasions. Ratios of *KIF1B* mRNA relative expression in HCC tissues to PC tissues were correlated with OS and DFS. Based on the down-regulation of *KIF1B* mRNA in HCC, we propose that the manipulation of KIF1B expression in HCC patients might have therapeutic implications. However, related reports, especially on KIF1B functions and mechanisms of regulation in normal and HCC tissues, are limited and warrant further study. The further large-scale clinical studies are needed to confirm whether KIF1B could serve as a liver cancer prognostic marker.

**COMMENTS**

***Background***

An estimated 782500 new liver cancer cases and 745500 deaths occurred worldwide during 2012, with China alone accounting for about 50% of the total number of cases and deaths. Most HCC patients are diagnosed beyond the stage at which surgical options are suitable, and thus have poor prognoses. However, patients at the same stage may have different prognoses because many factors affect outcomes such as clinicopathologic parameters and emerging biomarkers. In this study, we explore how kinesin family member 1B (KIF1B) affects the long-term survival outcomes in patients with HCC who undergo surgical treatment.

***Research frontiers***

Recently, a single nucleotide polymorphism, rs17401966, located at intron 24 of KIF1B, was associated with the susceptibility to hepatitis B virus (HBV)-related HCC in a genome-wide association study. Several studies confirmed that KIF1B affects the progression from HBV infection to HCC. However, expression of KIF1B protein and mRNA in tumors and paracarcinomatous (PC) tissues of HCC patients were not described in existing studies. The authors therefore retrospectively investigated the relationship between KIF1B expression and clinicopathologic parameters, and its predictive value for HCC prognosis.

***Innovations and breakthroughs***

KIF1B expression in HCC tissues and its relationship with tumor progression and prognosis are not widely reported. The present study found that KIF1B protein was expressed in cancer tissues and PC tissues of patients with HCC, with no significant differences in expression levels. The authors observed no significant correlation between the expression level of KIF1B protein and mRNA in HCC samples. Genetic polymorphisms and epigenetic factors may have contributed to the difference.

An important result of the current study was that KIF1B protein expression was associated with vein invasion and tumor recurrence status. These factors are highly correlated with invasion and metastasis of HCC. The results indicate that more invasive tumors have lower KIF1B protein expression, and by extension, that KIF1B has a suppressive function in HCC.

Unlike the protein results, KIF1B mRNA expression had no correlation to any tested clinicopathologic features. Interestingly, correlation analysis showed that ratios of KIF1B mRNA expression in HCC/PC pairs had a significant negative correlation with OS and DFS. The down-regulated KIF1B mRNA group had longer DFS than the up-regulated KIF1B mRNA group. In addition, patients with down-regulated KIF1B mRNA had increased risk of recurrence and significantly reduced OS.

***Applications***

This study suggested that KIF1B is a liver cancer suppressor gene. KIF1B mRNA levels may be prognostic biomarkers for HCC.

***Terminology***

HCC patients were divided into two groups: patients with down-regulated expression (higher KIF1B mRNA expression in PC tissues than in HCC tissues) and those with up-regulated expression (higher KIF1B mRNA expression in HCC tissues than in PC tissues).

***Peer-review***

This is a good retrospective study in which the authors investigated the relationship between KIF1B expression and clinicopathologic parameters, and its predictive value for HCC prognosis. The results are interesting and suggest that KIF1B mRNA levels may be prognostic biomarkers for HCC.

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**P-Reviewer:** El-Emshaty HM, Pinero F, Xu Y **S-Editor:** Qi Y

**L-Editor: E-Editor:**

**Figure 1 kinesin family member 1B protein expression in hepaztocellular carcinoma patients.** Western blotting for kinesin family member 1B (KIF1B) expression in HCC tissues and PC tissues. GAPDH was used as the internal loading control. HCC: Hepatocellular carcinoma; PC: Paracarcinomatous.



**Figure 2 Overall (A) and disease-free (B) survival** **of patients with hepaztocellular carcinoma after surgical resection by *KIF1B* mRNA expression in their tissues** **(*P* < 0.05; log-rank test).**



**A**



**B**

**Table 1 Correlation among clinicopathological features in 68 patients with hepatocellular carcinoma, and kinesin family member 1B protein and mRNA expression in their hepatocellular carcinoma and paracarcinomatous tissues**

|  |  |  |
| --- | --- | --- |
|  |  | **KIF1B** |
|  |  | **protein** | **mRNA** |
| Clinicopathological features | N | HCC tissue | PC tissues | HCC/PC | HCC tissue | PC tissues | HCC/PC |
| Age (yr) |  |  |  |  |  |  |  |
| ≥ 50 | 54 | 2.59 ± 0.53 | 2.50 ± 0.43 | 1.19 ± 0.10 | 1.44 ± 0.24 | 1.49 ± 0.23 | 1.01 ± 0.05 |
| < 50 | 14 | 2.63 ± 0.92 | 2.26 ± 0.80 | 1.31 ± 0.63 | 1.48 ± 0.30 | 1.44 ± 0.26 | 1.07 ± 0.35 |
| Sex |  |  |  |  |  |  |  |
| Male | 57 | 2.62 ± 0.88 | 2.39 ± 0.90 | 1.27 ± 0.63 | 1.49 ± 0.29 | 1.48 ± 0.29 | 1.05 ± 0.31 |
| Female | 11 | 2.20 ± 0.70 | 2.30 ± 0.97 | 1.16 ± 0.63 | 1.39 ± 0.28 | 1.50 ± 0.26 | 0.98 ± 0.37 |
| Child classification |  |  |  |  |  |  |  |
| A | 54 | 2.59 ± 0.91 | 2.50 ± 0.89 | 1.19 ± 0.63 | 1.44 ± 0.29 | 1.49 ± 0.28 | 1.01 ± 0.32 |
| B | 14 | 2.40 ± 0.64 | 1.91 ± 0.85 | 1.4 8± 0.60 | 1.58 ± 0.27 | 1.45 ± 0.28 | 1.13 ± 0.27 |
| Hepatitis B virus |  |  |  |  |  |  |  |
| Positive | 55 | 2.55 ± 0.90 | 2.43 ± 0.93 | 1.28 ± 0.62 | 1.45 ± 0.28 | 1.48 ± 0.28 | 1.02 ± 0.30 |
| Negative | 13 | 2.59 ± 0.70 | 2.16 ± 0.84 | 1.38 ± 0.65 | 1.58 ± 0.34 | 1.50 ± 0.28 | 1.10 ± 0.37 |
| Differentiation |  |  |  |  |  |  |  |
| Well | 25 | 2.53 ± 0.95 | 2.22 ± 0.86 | 1.31 ± 0.68 | 1.54 ± 0.28 | 1.46 ± 0.30 | 1.11 ± 0.33 |
| Moderately | 32 | 2.52 ± 0.76 | 2.47 ± 0.98 | 1.20 ± 0.58 | 1.43 ± 0.28 | 1.49 ± 0.27 | 0.99 ± 0.30 |
| Poorly | 11 | 2.69 ± 0.90 | 2.45 ± 0.77 | 1.27 ± 0.66 | 1.42 ± 0.32 | 1.51 ± 0.28 | 0.98 ± 0.30 |
| Tumor size (cm) |  |  |  |  |  |  |  |
| >3 | 48 | 2.56 ± 0.85 | 2.42 ± 0.91 | 1.24 ± 0.64 | 1.46 ± 0.31 | 1.47 ± 0.27 | 1.03 ± 0.32 |
| ≤3 | 20 | 2.55 ± 0.90 | 2.27 ± 0.93 | 1.28 ± 0.63 | 1.49 ± 0.23 | 1.51 ± 0.31 | 1.05 ± 0.31 |
| Tumor nodule |  |  |  |  |  |  |  |
| Solitary | 45 | 2.57 ± 0.91 | 2.35 ± 0.93 | 1.27 ± 0.64 | 1.50 ± 0.28 | 1.48 ± 0.29 | 1.06 ± 0.31 |
| Multiple | 23 | 2.52 ± 0.77 | 2.44 ± 0.87 | 1.21 ± 0.62 | 1.42 ± 0.31 | 1.48 ± 0.27 | 1.00 ± 0.32 |
| Vein invasion |  |  |  |  |  |  |  |
| Positive | 22 | 2.30 ± 0.82 | 2.33 ± 0.97 | 1.21 ± 0.60 | 1.41 ± 0.25 | 1.50 ± 0.31 | 0.89 ± 0.29 |
| Negative | 46 | 2.77 ± 0.841 | 2.40 ± 0.89 | 1.27 ± 0.65 | 1.50 ± 0.30 | 1.47 ± 0.27 | 1.11 ± 0.333 |
| Recurrence status |  |  |  |  |  |  |  |
| Yes | 34 | 2.31 ± 0.92 | 2.59 ± 0.93 | 1.14 ± 0.63 | 1.42 ± 0.27 | 1.55 ± 0.31 | 0.96 ± 0.31 |
| No | 34 | 2.80 ± 0.802 | 2.17 ± 0.85 | 1.36 ± 0.61 | 1.52 ± 0.30 | 1.42 ± 0.24 | 1.11 ± 0.294 |

1Hepatocellular carcinoma (HCC) tissues with vein invasions had a significantly less KIF1B protein (2.30 ± 0.82 RU) than did those without vein invasions (2.77 ± 0.84, *P* = 0.033); 2HCC tissues from patients with recurrence during the follow-up had significantly lower KIF1B protein levels (2.31±0.92) than did those without recurrence (2.80 ± 0.80, *P* = 0.022); 3Ratios of *KIF1B* mRNA expression in HCC tissues to PC tissues of patients with vein invasions (0.89 ± 0.29) were significant lower than those without vein invasions (1.11 ± 0.33, *P* = 0.009); 4Ratios of *KIF1B* mRNA expression in HCC tissues to PC tissues of patients with recurrence during the follow-up (0.96 ± 0.31) were significant lower than those without recurrence (1.11 ± 0.29, *P* = 0.043).