Risk Factors for Survival and the Development of Hepatocellular Carcinoma in Patients with Primary Biliary Cirrhosis

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Abstract

Objective Early diagnosis of hepatocellular carcinoma (HCC) is critical in the management of patients with primary biliary cirrhosis (PBC), since the prognosis of PBC has improved. The aim of this study was to investigate whether HCC development affects the prognosis of PBC and to identify the risk factors for HCC in Japanese patients with PBC.

Methods We compared the survival rates between patients with HCC and those without and analyzed the risk factors for HCC development in 210 patients with PBC who were followed up for a median period of 8.5 years.

Results HCC developed during follow-up in 11 patients (5.2%) and was diagnosed simultaneously at the time of diagnosis of PBC in five patients (2.4%) who were excluded from the analysis. A Kaplan-Meier analysis showed a significant difference in overall survival between the patients who did and did not develop HCC ($p < 0.001$). A multivariate analysis revealed age (OR: 1.08, 95% confidence interval [CI]: 1.03-1.13, $p = 0.001$), the albumin level (OR: 0.24, 95% CI: 0.10-0.56, $p = 0.001$), the total bilirubin level (OR: 1.60, 95% CI: 1.09-2.36, $p = 0.017$) and HCC development (OR: 2.97, 95% CI: 1.24-7.15, $p = 0.015$) to be significant prognostic factors and identified only an advanced histological stage (Scheuer's classification III or IV, OR: 6.27, 95% CI: 1.80-21.83, $p = 0.004$) to be a risk factor associated with HCC.

Conclusion HCC development significantly affects the survival of patients with PBC, and an advanced histological stage is the only risk factor associated with HCC development. These results highlight the important role of liver fibrosis in hepatocarcinogenesis in patients with PBC.

Key words: diabetes mellitus, liver fibrosis, prognosis, survival, ursodeoxycholic acid

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Introduction

Primary biliary cirrhosis (PBC) is a progressive cholestatic liver disease characterized by the presence of highly specific antimitochondrial antibodies, portal inflammation and lymphocyte-dominated destruction of the intralobular bile ducts that eventually leads to cirrhosis (1). The incidence of PBC has increased over recent decades, possibly attributable to augmented testing of liver biochemistry rather

than a rise in disease incidence. The routine use of biochemical screening has also made it possible to diagnose PBC at an earlier stage (2). In addition to early diagnosis, the high prevalence of treatment with ursodeoxycholic acid (UDCA) makes it possible for patients with PBC to live longer. However, the natural history of PBC is still debated and depends on several variables and symptoms of liver disease (3). In general, the risk of cancer development increases as humans live longer, and the development of hepatocellular carcinoma (HCC) is no exception.

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Figure 1. Numbers of patients included and excluded in the retrospective cohorts.

Patients with PBC are considered to be at low risk for the development of HCC (4), although several reports have revealed that PBC is associated with an increased risk of HCC (5-8). Additionally, whether the development of HCC affects the overall survival of patients with PBC remains controversial (5, 7, 9, 10). This matter and the identification of risk factors for HCC development are of importance for improving the prognosis of patients with PBC. There are, however, few studies reporting the risk factors for HCC among patients with PBC (5-7, 9, 11). The age at diagnosis (7, 11), male sex (5, 7, 10, 11), a history of blood transfusions (7, 11), cigarette smoking (6), portal hypertension (11), a more advanced histologic stage of disease (9, 10) and superinfection with hepatitis C virus (HCV) (6) have been reported to be risk factors for HCC in patients with PBC. Such risk factors remain a matter of debate due to recent changes in the nutritional environment and/or lifestyle. For instance, previous studies did not include obesity or diabetes mellitus as clinical parameters for assessing risk factors related to the development of HCC in patients with PBC, even though these parameters have been recognized to be risk factors for the development of HCC (12, 13).

The aim of this study was to determine whether HCC development affects the prognosis of PBC and to identify the risk factors for HCC development in Japanese patients with PBC based on recent clinical evidence.

Materials and Methods

This study was conducted among three series of patients from three different liver disease centers who were treated for a diagnosis of PBC between May 1984 and May 2010. A total of 245 patients were recruited, including 116 patients from Kawasaki Medical School affiliated hospital, 72 patients from Yamaguchi Grand Medical Center and 57 pa-

tients from Kawasaki Hospital. The diagnosis of PBC was established when the patient fulfilled at least one of the following criteria defined by the Intractable Hepato-Biliary Disease Study Group of Japan: (i) laboratory abnormalities consistent with chronic cholestatic liver disease and the presence of chronic nonsuppurative destructive cholangitis, (ii) positive antimicrobial antibodies and a liver histology compatible with PBC, (iii) a medical history and laboratory abnormalities consistent with chronic cholestatic liver disease and positive antimicrobial antibodies. The histological stage was classified according to Scheuer's classification (14). The following 35 patients were excluded from the analysis due to confounding risk factors for HCC or incomplete clinical parameters: hepatitis B surface antigen (HBsAg) positivity in two patients, anti-HCV antibody (anti-HCV) positivity in five patients, a history of excessive alcohol consumption (>40 g/day) in four patients, a lack of follow-up for more than 0.3 years in 12 patients and a lack of pathological diagnosis in 12 patients (Fig. 1).

The diagnosis of diabetes mellitus was made based on a history of antidiabetic medication use, including oral hypoglycemic agents and insulin, since the diagnostic criteria for diabetes mellitus proposed by the Japan Diabetes Society were not applied to all patients due to the lack of several biochemical parameters. The diagnosis of portal hypertension was made based on the presence of esophageal or gastric varices, ascites or splenomegaly. The clinical characteristics at diagnosis of PBC are shown in Table 1. The patients were regularly assessed with biochemical tests every one to four months and followed for a median period of 8.5 (range, 0.3-25.8) years. To determine the presence of HCC, abdominal ultrasonography was performed in all patients without HCC at intervals of four to 12 months. HCC was diagnosed based on the findings of abdominal ultrasonography and confirmed based on the findings of computed tomography (CT), magnetic resonance imaging, hepatic arteri-

Table 1. Clinical Characteristics of Patients at Diagnosis of PBC

Characteristic	Mean $\pm$ SD or frequency (number of analyzed patients)
Age (years)	58 $\pm$ 11 (210)
Gender (Male/Female)	31/179
Body mass index (kg/m ²)	22.4 $\pm$ 3.1 (196)
Blood transfusion (+/-/unknown)	13/192/5
Diabetes mellitus (+/-)	19/191
Portal hypertension (+/-)	39/171
Platelet count ($\times 10^4/\mu\text{L}$)	21.9 $\pm$ 8.2 (210)
ALT (IU/L)	58 $\pm$ 53 (210)
AST (IU/L)	56 $\pm$ 40 (207)
Alkaline phosphatase (IU/L)	523 $\pm$ 434 (207)
γ -GT (IU/L)	230 $\pm$ 233 (207)
Total bilirubin (mg/dL)	0.9 $\pm$ 0.9 (210)
Albumin (g/dL)	3.9 $\pm$ 0.5 (209)
Prothrombin time (%)	82.9 $\pm$ 16.4 (209)
IgM (mg/dL)	410 $\pm$ 279 (203)
Anti-HBc (+/-/unknown)	13/40/157
Histological stage (I or II/III or IV)	169/41
Treatment with UDCA (+/-)	189/21

ALT: alanine aminotransferase, AST: aspartate aminotransferase, γ -GT: γ -glutamyltransferase, Anti-HBc: anti-hepatitis B core antibody, UDCA: ursodeoxycholic acid

ography and/or a fine-needle aspiration liver biopsy.

Overall survival was defined as the period from the day of PBC diagnosis until death, liver transplantation or the last medical examination and compared between the patients who did and did not develop HCC. Laboratory parameters measured at the time of PBC diagnosis were compared to those measured at the time of HCC diagnosis in patients who developed HCC during the follow-up period. The study protocol conformed to the 1975 Declaration of Helsinki Declaration and was approved by the ethics committees of the involved institutions.

Statistical analysis

Baseline continuous variables are expressed as the mean $\pm$ SD. Comparisons between groups were made using the Mann-Whitney test for continuous variables and the χ^2 test with Yates correction or Fisher's exact test for categorical variables. Cumulative survival was calculated using the Kaplan-Meier method, and the differences among the groups were analyzed with the log-rank test. Univariate and multivariate analyses of predictors of survival were performed using the Cox proportional hazards model. A multivariate analysis of predictors for the development of HCC was performed using the logistic regression test. A p value of less than 0.05 was considered to be significant. All analyses described above were performed using the SPSS software package (version 11, SPSS Inc., Chicago, IL).

Results

Development of HCC in patients with PBC

Sixteen (7.6%) of the 210 patients with PBC developed HCC. A diagnosis of HCC was made in 11 patients (5.2%)

during follow-up, whereas HCC and PBC were almost simultaneously diagnosed in the remaining five patients (2.4%) who had diabetes mellitus and advanced histological stages, except for a man aged 84 who was potentially at high risk for HCC due to his age. These five patients (three men and two women) were thereafter excluded from the analysis. The clinical and histological features of the 11 patients who developed HCC during follow-up are summarized in Table 2. The HCC incidence according to gender was 3.6% (1/28) in men and 5.6% (10/177) in women. The mean interval between the diagnosis of PBC and the development of HCC was 11.4 $\pm$ 5.7 years. Antibodies to hepatitis B core antigens (anti-HBc) were positive in two patients (18.2%), negative in five patients (45.4%) and unknown in four patients (36.4%), respectively. Six patients (54.5%) and one patient (9.1%) had advanced histological stages (III) and diabetes mellitus at the diagnosis of PBC, respectively. It should be noted that the follow-up period until the development of HCC was significantly longer in the patients with mild histological stages (I or II) (14.8 $\pm$ 4.1 years) than in those with advanced histological stages (III) (8.5 $\pm$ 5.5 years), suggesting a potential risk for HCC development after a long period of time even in patients with a mild histological stage of PBC. Six patients had solitary tumors whose size was less than 30 mm, except for one. These tumors were treated with local ablation, such as percutaneous microwave coagulation therapy, percutaneous ethanol injection or radiofrequency ablation, transarterial chemoembolization (TACE), combination of local ablation and TACE or liver transplantation, in all patients, except one (case 9 in Table 2) who could not be treated due to rupture of HCC.

To determine whether HCC develops as liver damage progresses, laboratory parameters (platelet count, alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, γ -glutamyltransferase, total bilirubin, albumin and prothrombin time) were compared between the two time points of PBC diagnosis and HCC diagnosis in the 11 patients. The serum albumin level, prothrombin activity and platelet count were significantly lower at the time of HCC diagnosis than at the time of PBC diagnosis, suggesting that the development of HCC largely depends on the progression of liver disease (Fig. 2). Patients with PBC who developed HCC had significantly lower cumulative survival rates than those who did not. The 5-, 10-, 15- and 20-year cumulative survival rates of the PBC patients with HCC and those without HCC were 91/98%, 61/87%, 51/83% and 10/80%, respectively (p<0.001, Fig. 3).

Factors associated with survival in patients with PBC

We next investigated the factors associated with survival in patients with PBC in order to determine whether HCC development actually affects the prognosis. In addition to the baseline characteristics of the patients at the time of PBC diagnosis, treatment with UDCA and the development of HCC were incorporated into the parameters used to ana-

Table 2. Characteristics of 11 Patients with PBC who Developed HCC

Case	Age at PBC/HCC diagnosis	Sex	BMI	DM	Anti-HBc	Histological stage at [§]	HCC				Cause of death
							Solitary or multiple	Maximum size (mm) [‡]	Vascular invasion	Therapy [¶]	
1	64/67	M	25.8	-	+	III	Solitary	10	-	PMCT	Sepsis
2	66/75	F	26.9	-	-	III	Multiple	45	-	PEI + TACE	Hepatic failure
3	65/74	F	23.2	-	+	III	Multiple	32	-	TACE	Hepatic failure
4	59/70	F	23.3	+	-	III	Multiple	20	-	REI + TACE	HCC
5	61/75	F	17.8	-	-	II	Multiple	30	-	TACE	Hepatic failure
6	38/55	F	19.5	-	-	I	Solitary	30	-	PEI + TACE	Hepatic failure
7	38/55	F	20.8	-	NA [†]	I	Multiple	15	-	TACE	Hepatic failure
8	58/76	F	23.1	-	-	I	Solitary	30	-	TACE	Hepatic failure
9	64/66	F	22.2	-	NA	III	Solitary	100	+	-	HCC rupture
10	41/49	F	27.7	-	NA	I	Solitary	10	-	Transplantation	Alive
11	48/65	F	24.6	-	NA	III	Solitary	27	-	TACE	Alive

BMI: body mass index, DM: diabetes mellitus, Anti-HBc: anti hepatitis B core antibody, †NA: unknown, §at the diagnosis of PBC, ‡tumor sizes in cases 2, 3, 4, 5 and 7 represent the largest ones among multiple tumors. ¶PMCT: percutaneous microwave coagulation therapy, PEI: percutaneous ethanol injection, TACE: transarterial chemoembolization, RFA: radiofrequency ablation

Figure 2. Serum albumin levels, platelet counts and prothrombin activity at diagnosis of primary biliary cirrhosis (PBC) and hepatocellular carcinoma (HCC) in the patients with PBC who developed HCC. The results are shown as box plot profiles. The bottom and top edges of the boxes are the 25th and 75th percentiles, respectively. *: p<0.05

lyze the factors associated with the survival of patients with PBC. However, we did not incorporate the response to treatment with UDCA into these parameters due to a lack of established biochemical criteria for the response to UDCA allowing for prediction of the prognosis. Treatment with UDCA (600 mg daily) was started within six months from diagnosis of PBC in 186 patients (91%). The reason why UDCA was not administered in the remaining 19 patients was unknown. The duration of UDCA treatment was almost the same as the follow-up period, since almost all of the patients continued taking UDCA due to a lack of moderate to severe adverse effects.

A univariate analysis identified age, portal hypertension, platelet count, AST, the total bilirubin and albumin levels, prothrombin activity, advanced histological stage (Scheuer criteria III or IV) and HCC development to be significant predictors of survival in patients with PBC (Table 3). Among these predictors, a multivariate analysis revealed age (OR: 1.08, 95% CI: 1.03-1.13, p=0.001), the total bilirubin (OR: 1.60, 95% CI: 1.09-2.36, p=0.017) and albumin levels (OR: 0.24, 95% CI: 0.10-0.56, p=0.001) and HCC development (OR: 2.97, 95% CI: 1.24-7.15, p=0.015) to be significant factors associated with survival in patients with PBC (Table 3).

Patients without HCC	194	142	75	36	9	1
Patients with HCC	11	10	6	5	1	-

Figure 3. Cumulative survival curves for the patients with primary biliary cirrhosis who developed hepatocellular carcinoma (HCC) and those who did not. The solid and broken lines indicate patients with HCC and those without HCC, respectively. Log-rank test $p < 0.001$

Factors associated with the development of HCC in patients with PBC

As the development of HCC has been demonstrated to be significantly associated with survival in patients with PBC, it is important to determine screening targets for HCC to improve the prognosis for patients with PBC. In this study, the patients with PBC who developed HCC had lower platelet counts ($p = 0.008$), lower albumin levels ($p = 0.02$) and more advanced histological stages of disease (Scheuer criteria III or IV) ($p = 0.005$) at the time of PBC diagnosis than those who did not (Table 4). A multivariate analysis identified only an advanced histological stage (Scheuer criteria III or IV) (OR: 6.27, 95% CI: 1.80-21.83, $p = 0.004$) as being a predictor of the development of HCC in patients with PBC (Table 5).

Discussion

The frequency of HCC development in patients with PBC is estimated to be around 3% (0.7-3.6%) according to recent and relatively large cohort studies conducted in European countries, the United States and Japan, although this frequency increases as the histological stage progresses (5-10, 15, 16). In this study 5.2% of the patients with PBC developed HCC during follow-up and 2.4% of the patients had HCC simultaneously at the time of PBC diagnosis. The incidence of HCC was slightly higher in the present study than that reported in previous studies; however, it is unknown whether this difference is significant. The higher incidence of HCC observed in the present study may be ex-

plained by the relatively longer period of follow-up in a restricted number of institutions. Such situations potentially include less drop out patients during the follow-up period.

HCC was demonstrated to develop as liver damage progressed in the patients with PBC, as indicated by significant decreases in the serum albumin levels, prothrombin activity and platelet counts at the time of HCC development. These results are consistent with a previous observation of a Japanese study group in which all patients had progressed to an advanced histological stage (Scheuer criteria III or IV) by the time of HCC development (7). We also found that HCC development is a significant risk factor for survival in patients with PBC. Because the PBC patients had already progressed to an advanced histological stage at the time of HCC diagnosis, these results appear to be reasonable and are consistent with those of a study from Spain and Italy (9) and a recent Japanese report based on a nationwide survey (10). In fact, the six PBC patients with HCC (6/9, 67%) evaluated in the present study died of hepatic failure (Table 2). In some of the patients with HCC, it was difficult to determine whether the cause of death was hepatic failure or HCC. Therefore, deaths resulting from progressive hepatic failure related to portal venous invasion or rupture of HCC were defined as deaths caused by HCC. Deaths resulting from progressive hepatic failure during the course of treatment for HCC without portal venous invasion were defined as deaths caused by hepatic failure.

In contrast to PBC, HCC development ($n = 19$) was not found to be a significant risk factor for survival in patients with alcoholic liver cirrhosis ($n = 103$) who were followed during almost the same period as those followed in this study and who developed hepatic failure within a relatively short period of time unless they stopped drinking alcohol (unpublished data). The long-term clinical course of PBC may also account for the association between HCC development and a poor prognosis in patients with PBC. In addition to HCC development, age, the albumin level and the total bilirubin level at onset of PBC were selected as significant prognostic factors in patients with PBC in the present study. These results are in part consistent and in part inconsistent with those of previous studies (7, 17), most likely due to the different backgrounds of the patients studied.

That the majority (90%) of patients were treated with UDCA may account for why we did not find any differences in survival between the treated patients and the untreated patients. However, a limitation of this study is that the response to treatment with UDCA could not be incorporated into the analytic factors for survival. The response to UDCA has been reported to be associated with a better prognosis among PBC patients with moderately advanced disease compared with patients with mild disease (18), who accounted for the majority (80%) of the patients in the present study. Recent biochemical criteria for predicting the outcomes of patients with early PBC at low risk for long-term development of liver cirrhosis (19) may be useful for assessing whether the response to UDCA treatment affected the

Table 3. Univariate and Multivariate Analyses of Predictors for Survival in Patients with PBC

Variables	Univariate			Multivariate		
	Hazard ratio	95% CI	p value	Hazard ratio	95% CI	p value
Age (years)	1.09	1.04-1.14	<0.001	1.08	1.03-1.13	0.001
Male	1.65	0.63-4.34	0.31			
Body mass index (kg/m ²)	0.92	0.81-1.05	0.24			
Blood transfusion	1.19	0.28-5.03	0.62			
Diabetes mellitus	3.70	1.56-7.14	0.009			
Portal hypertension	3.34	1.93-7.04	0.002			
Platelet count (× 10 ⁴ /μL)	0.92	0.87-0.97	0.003			
ALT (IU/L)	1.00	0.99-1.00	0.64			
AST (IU/L)	1.01	1.00-1.01	0.04			
Alkaline phosphatase (IU/L)	1.00	1.00-1.00	0.24			
γ-GT (IU/L)	1.00	1.00-1.00	0.87			
Total bilirubin (mg/dL)	2.03	1.50-2.76	<0.001	1.60	1.09-2.36	0.017
Albumin (g/dL)	0.13	0.06-0.27	<0.001	0.24	0.10-0.56	0.001
Prothrombin time (%)	0.94	0.91-0.96	<0.001			
IgM (mg/dL)	1.00	1.00-1.00	0.12			
Anti-HBc	0.83	0.23-3.00	0.27			
Histological stage III or IV	5.10	2.40-10.66	<0.001			
Treatment with UDCA	3.35	0.45-24.78	0.24			
Development of HCC	5.15	2.31-11.49	<0.001	2.97	1.24-7.15	0.015

ALT: alanine aminotransferase, AST: aspartate aminotransferase, γ-GT: γ-glutamyltransferase, Anti-HBc: anti hepatitis B core antibody, UDCA: ursodeoxycholic acid, HCC: hepatocellular carcinoma

Table 4. Comparison of Clinical Characteristics at Diagnosis of PBC between Patients who Developed HCC and Those who Did Not

Variables	Patients with HCC	Patients without HCC	p value
Number of patients	11	194	
Age (years)	58 ± 11	58 ± 10	0.91
Gender (Male/Female)	1/10	27/167	0.54
Body mass index (kg/m ²)	23.6 ± 2.7	22.3 ± 3.1	0.10
Blood transfusion (+/-)	1/10	11/178	0.50
Diabetes mellitus (+/-)	1/10	14/180	0.58
Portal hypertension (+/-)	4/7	33/161	0.12
Platelet count (× 10 ⁴ /μL)	16.0 ± 7.5	22.5 ± 8.0	0.008
ALT (IU/L)	47 ± 29	59 ± 55	0.66
AST (IU/L)	60 ± 36	55 ± 40	0.40
Alkaline phosphatase (IU/L)	468 ± 338	518 ± 432	0.72
γ-GT (IU/L)	127 ± 86	236 ± 238	0.08
Total bilirubin (mg/dL)	1.6 ± 1.7	0.9 ± 0.6	0.11
Albumin (g/dL)	3.6 ± 0.6	4.0 ± 0.5	0.02
Prothrombin time (%)	76.8 ± 14.0	83.6 ± 16.5	0.30
IgM (mg/dL)	479 ± 393	405 ± 273	0.91
Anti-HBc (+/-/unknown)	2/6/3	11/30/153	0.65
Histological stage (I or II/III or IV)	5/6	163/31	0.005
Treatment with UDCA (+/-)	11/0	175/19	0.33

ALT: alanine aminotransferase, AST: aspartate aminotransferase, γ-GT: γ-glutamyltransferase, Anti-HBc: anti hepatitis B core antibody, UDCA: ursodeoxycholic acid

survival of patients with PBC in this study.

Diabetes mellitus was demonstrated to increase the risk of HCC in a large cohort of patients without concomitant liver disease (12) and in a cohort of patients with hepatitis C, hepatitis B or alcoholic cirrhosis (20, 21). However, these previous studies did not include diabetes mellitus as a clinical parameter for assessing risk factors related to the devel-

Table 5. Multivariate Analysis of Predictors for Development of HCC in Patients with PBC

Variables	Odds ratio	95% CI	p value
Histological stage III or IV	6.27	1.80-21.83	0.004

opment of HCC in patients with PBC (5-7, 9-11). We did not find any associations between diabetes mellitus and the development of HCC, although the proportion of patients with diabetes mellitus (9%) in this study was relatively small. Although a link between insulin resistance and metabolic hepatocarcinogenesis has been reported (22), the contribution of diabetes mellitus to the development of HCC in patients with chronic liver diseases may vary according to the etiology of liver disease.

We did not identify male sex to be a significant factor associated with HCC development in patients with PBC, which is inconsistent with the results of some previous studies (5, 7, 10, 11). In particular, the discrepancy between the present study and a recent Japanese nationwide study (10) may be explained by at least three factors. First, the patient sample size was much smaller in this study than in the nationwide survey. Second, the present study included more patients with an advanced histological stage of disease (Scheuer criteria III or IV) (18%) than the nationwide survey (12%), although other clinical parameters, such as age, gender and the frequency of treatment with UDCA, were similar between the two studies. Third, the exclusion criterion regarding a history of excessive alcohol consumption (>40 g/day) employed in this study may be associated with this discrepancy since the nationwide survey did not clearly

exclude patients with a history of excessive alcohol consumption. As shown in a previous study (9), we also found only an advanced histological stage (Scheuer's classification III or IV) to be a risk factor associated with the development of HCC in patients with PBC. Considering that cholangiocytes, not hepatocytes, are primarily affected and liver fibrosis progresses as the histological stage advances in PBC, these results indeed highlight the important role of liver fibrosis in hepatocarcinogenesis in patients with PBC. In addition, it should be noted that the follow-up period until the development of HCC was significantly longer in the patients with a mild histological stage (I or II) than in those with an advanced histological stage (III or IV). These results suggest a potential risk for HCC development after a long period of time, even in PBC patients with a mild histological stage of disease at the time of diagnosis.

In conclusion, the development of HCC has been demonstrated to affect the survival of Japanese patients with PBC. Considering that the prognosis of PBC has improved in general as a result of early diagnosis and the use of UDCA, the early diagnosis of HCC is also crucial for obtaining a better prognosis for patients with PBC. Therefore, strict surveillance for HCC is necessary among patients with PBC who are in the advanced stage of disease.

The authors state that they have no Conflict of Interest (COI).

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