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ORIGINAL ARTICLE

The clinical and laboratory features associated with cancer in patients with primary biliary cholangitis: a longitudinal survey–based study

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Abstract

Objectives To analyze the clinical and laboratory features of primary biliary cholangitis (PBC) patients complicated with cancer, and explore the potential factors associated with cancer.

Methods We consecutively enrolled PBC patients from January 2002 to February 2016 in Peking Union Medical College Hospital and performed a structured interview, systemic rheumatologic evaluation, and laboratory tests. The risk factors associated with cancer were analyzed with univariate and multivariable logistic regression and proportional hazard model.

Results Among the 580 PBC patients enrolled, 51 cancers were identified in 51 patients (8.8%), including 45 (88.2%) solid tumors and 6 (11.8%) hematologic malignancies. Patients with cancer were older (62.1 ± 9.6 vs. 55.4 ± 11.6 years, $p < 0.01$) than patients without cancer. Additionally, positive anti-centromere antibody (ACA) was more frequently observed in patients without cancer (25.9% vs 4.3%, $p = 0.019$) compared with patients with cancer diagnosed after establishing PBC. The median follow-up after the diagnosis of PBC was 4 years (IQR 2.0–6.6). Furthermore, multivariable logistic regression confirmed that older age was associated with cancer in PBC patients (odds ratio (OR) = 1.045, 95% confidence interval (CI): 1.006–1.085), and positive ACA was a protective factor (OR = 0.116, 95% CI: 0.015–0.876). Additionally, proportional hazard model analysis revealed that age was a risk factor (hazard ratio = 1.045, 95% CI: 1.012–1.080), and positive ACA was a protective factor (hazard ratio = 0.232, 95% CI: 0.055–0.977) for cancer.

Conclusions Both solid tumor and hematologic malignancy were prevalent in PBC patients. Older age was associated with cancer, and positive ACA was a protective factor of cancer in PBC patients.

Key Points

- *Patients with PBC could present with both solid tumors and hematologic malignancies.*
- *Multivariable logistic regression and proportional hazard model analysis revealed that age was a risk factor as we know, and positive ACA was a protective factor.*

Key words Cancer · Malignancy · Primary biliary cholangitis · Primary biliary cirrhosis

Background

Primary biliary cholangitis (PBC) is an autoimmune disease characterized with chronic non-suppurative destructive cholangitis, elevated alkaline phosphatase (ALP), and positive anti-mitochondrial antibody (AMA) [1]. PBC is typically presented in the fifth or sixth decade in which the incidence of cancer is significantly increased [2]. Cancer is a common complication of autoimmune diseases such as inflammatory myopathies, Sjogren syndrome, and Behcet's disease [3, 4], suggesting that patients with rheumatic diseases are at risk of cancer. In patients with PBC, many types of cancer have also been reported [5, 6]. Given that PBC is generally an organ-

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specific autoimmune disease primarily affecting the liver, hepatocellular carcinoma (HCC) is the most frequently reported cancer in PBC patients, with a prevalence of 2.4–5.9% [7, 8]. Other cancers, including breast cancer, colorectal cancer, and non-Hodgkin lymphoma, are also reported in PBC patients [9]. However, the clinical characteristics and the prevalence of cancer in PBC patients remain largely unknown.

To address this, we employed a large longitudinal cohort of PBC to characterize the demographic, clinical and laboratory features of the PBC patients with cancer. We further explored the potential risk factors for cancer in patients with PBC by comparing the features of the patients with cancer with those without cancer to promote the early diagnosis and management of cancer in PBC patients.

Methods

Patients

We retrospectively enrolled PBC patients admitted to Peking Union Medical College Hospital (PUMCH) between January 2002 and February 2016. All patients fulfilled the diagnostic criteria of PBC according to the 2009 American Association for the Study of Liver Diseases practice guideline [10, 11].

A structured interview including demographics, disease duration, clinical manifestation, history with dyslipidemia, smoking and thyroid diseases, systemic rheumatologic examination including anti-mitochondrial antibody (AMA), M2 subtype of AMA, anti-centromere antibody (ACA), anti-nuclear antibody (ANA), erythrocyte sedimentation rate (ESR), immunoglobulin M, immunoglobulin G, and immunoglobulin A, and laboratory tests including ALP, γ-glutamyl transpeptidase (GGT), total bilirubin, albumin, were performed in all patients. All variables were collected at the diagnosis of PBC, and histological findings (if available) at the diagnosis of cancer were collected. The diagnosis of cancer was based on histopathology and bone marrow examination as appropriate.

Statistical analysis

Enumeration data were expressed by percentage. Kolmogorov-Smirnov test was used to verify whether the data followed the normal distribution. Data of normal distribution and data of non-normal distribution were expressed by mean ± standard deviation (SD) and median and interquartile range (IQR), respectively. Continuous and categorical variables were compared by the independent samples *t*-test and Pearson χ^2 test, respectively. Non-parametric test was used for non-normal distributed data. Univariate logistic regression analysis was used to evaluate candidate predictors of cancer, and variables with *p*-value < 0.1 were further analyzed in the multivariate analysis. A conditional forward stepwise multivariate stepwise analysis was used to identify the risk factors for cancer. Proportional hazard model was further used for patients diagnosed of cancer after diagnosis of PBC to analyze risk factors. A two-sided *p*-value < 0.05 was considered statistically significant. All statistical analysis was performed using SPSS 22.0 (SPSS Inc, Chicago, IL, USA).

Results

Clinical features of the PBC patients

We enrolled 580 PBC patients, including 508 (87.6%) females, with a mean age of 56.0 ± 11.6 years. Among them, AMA was positive in 530 (91.4%) patients, and hepatic pathology was available in 140 patients. Median ALP and γ-glutamyl transpeptidase (GGT) was 203U/L (IQR 127–390) and 200U/L (IQR 103–422), respectively. Elevated immunoglobulin M (IgM) (> 2.5 g/L) was observed in 61.0% patients, with a median of 4.26 g/L (IQR 3.45–6.14). Additionally, anti-centromere antibody (ACA) was positive in 138/554 (24.9%) patients (Table 1), and the median erythrocyte sedimentation rate (ESR) was 40mm/h (21–67). Cirrhosis secondary to PBC was documented in 161 (27.8%) patients, and all the patients were decompensated with esophagogastric varices, splenomegaly, ascites, or more than one of the complications. Three hundred seventy-six patients (64.8%) had a normal liver, and 43 patients (7.4%) had liver echogenicity on ultrasound evaluation. Autoimmune hepatitis (AIH) was complicated in 6 (1.0%) patients. All patients received ursodesoxycholic acid (UDCA) treatment, 309 patients (53.3%) received glucocorticoid, and 84 patients (14.5%) patients received immunosuppressant. The median follow-up of all patients from the diagnosis of PBC was 4 years (IQR 2.0–6.6).

A total of 51 cancers were confirmed in 51 patients (8.8%), including 44 females (86.3%). Solid tumors (n = 45) were common, including colorectal cancer (n = 7), breast cancer (n = 7), gastric cancer (n = 5), HCC (n = 4), papillary thyroid carcinoma (n = 4), cervical cancer (n = 4), lung cancer (n = 3), periampullary carcinoma (n = 2), and kidney cancer (n = 2). Among the hematologic malignancies (n = 6), multiple myeloma (MM) (n = 2) and non-Hodgkin's lymphoma (n = 2) were followed by macroglobulinemia (n = 1) and leukemia (n = 1) (Table 2). In 29 (56.9%) patients, the cancers were diagnosed after the diagnosis of PBC, and the cancers were presented at or prior to the diagnosis of PBC in 10 (19.6%) and 12 patients (23.5%), respectively.

Comparison of PBC patients with or without cancer

PBC patients with cancer were older (62.1 ± 9.6 vs. 55.4 ± 11.6 years, $p < 0.01$) compared with those without cancer. No

Table 1 Clinical and laboratory features of the PBC patients with or without cancer

Parameters	Total (N = 580)	Cancer (N = 51)	No cancer (N = 529)	*p-value*
Age (year)	56.0 ± 11.6	62.1 ± 9.6	55.4 ± 11.6	0.000*
Female-n (%)	508 (87.6)	44 (86.3)	464 (87.7)	0.766
Duration of PBC (year)-median (IQR)	2.0 (0.6–5.0)	1.3 (0.2–5.0)	2.0 (0.7–5.0)	0.714
Liver Biochemical Tests				
ALP(U/L)-median (IQR)	203 (127–390)	214 (158–300)	202 (126–399)	0.550
GGT(U/L)-median (IQR)	200 (103–422)	200 (78–420)	199 (107–427)	0.446
TBil(μmol/L)-median (IQR)	18.6 (10.9–32.5)	20.6 (11.2–32.2)	18.5 (10.9–32.6)	0.708
Alb(g/L)-mean ± SD	36.2 ± 6.4	35.5 ± 6.5	36.3 ± 6.4	0.415
Autoantibodies				
Positive AMA-n(%)	530 (91.4)	48 (94.1)	482 (91.1)	0.466
Positive AMA-M2-n(%)	530 (91.4)	48 (94.1)	480 (90.7)	0.420
Positive ACA-n(%)	138/554 (24.9)	5/41 (12.2)	133/513 (25.9)	0.050
Positive ANA-n(%)†	248 (42.8)	16 (31.4)	232 (43.9)	0.085
ESR (mm/h)-median (IQR)	40 (21–67)	42 (25–77)	40 (20–67)	0.444
IgM (g/L)-median (IQR)	3.24 (1.90–4.76)	2.99 (1.36–4.89)	3.26 (2.00–4.76)	0.223
IgG (g/L)-median (IQR)	16.30 (12.5–20.2)	16.20 (12.70–21.02)	16.43 (12.49–20.13)	0.937
IgA (g/L)-median (IQR)	2.98 (2.12–4.30)	3.13 (1.81–4.64)	2.98 (2.14–4.28)	0.708
Dyslipidemia-n (%)	21 (3.6)	2 (3.9)	19 (3.6)	0.904
Smoking-n (%)	52 (9.0)	6 (11.8)	46 (8.7)	0.464
Thyroid diseases-n (%)‡	60 (10.3)	7 (13.7)	53 (10.0)	0.406

IQR interquartile range, *ALP* alkaline phosphatase, *GGT* γ-glutamyl transpeptidase, *TBil* total bilirubin, *Alb* albumin, *AMA* anti-mitochondrialantibody, *AMA-M2* M2 subtype of anti-mitochondrial antibody, *ACA* anti-centromere antibody, *ANA* anti-nuclear antibody, *ESR* erythrocyte sedimentation rate, normal range < 20 mm/h, *IgM* immunoglobulin M, *IgG* immunoglobulin G *IgA* immunoglobulin A.

* $p < 0.05$ between patients with cancer and patients without cancer.

† PBC specific ANA: rim-like/membranous pattern, and multiple nuclear dots.

‡ Including hyperthyroidism, hypothyroidism, subclinical hypothyroidism, thyroiditis, and nodular goiter

significant difference was observed in gender, duration of PBC, liver biochemical tests, autoantibodies profile, ESR, and immunoglobulins levels (Table 1).

We further compared the clinical features of patients diagnosed with cancer after the diagnosis of PBC (n = 29) with patients without cancer (n = 529). Consistently, we found that the patients with cancer were also older (60.8 ± 10.2 vs 55.4 ± 11.6 years, p = 0.04). In addition, the patients without cancer had a higher prevalence of ACA (25.9% vs 4.3%, p = 0.019) (Table 3). To further confirm this finding, we also compared the features of patients with cancer (n = 29) with age- and sex-matched patients without cancer (n = 116). Again, positive ACA was more frequently observed in patients without cancer (25.9% vs 4.3%, p = 0.024) (Online Resource 1).

We also compared the clinical features of patients with HCC and those with extrahepatic cancer (non-HCC). The patients with HCC had a longer disease duration (10.0 (7.0–16.0) vs 1.0 (0.21–2.0) years, p = 0.013), higher total bilirubin level (median, 71.5 vs 16.0 μmol/L, p = 0.028), and higher prevalence of cirrhosis (75% vs 24.4%, p = 0.033) and ACA (50.0% vs 6.5%, p = 0.010) (Online Resource 2), compared with patients with non-HCC.

Risk factors associated with cancer in PBC patients

We first used the data of 29 patients with cancer diagnosed after established PBC and 529 patients without cancer to identify potential factors associated with cancer. We found that older age (odds ratio (OR) = 1.042, 95% confidence interval (CI): 1.008–1.077) was potentially associated with cancer, which was confirmed by multivariate logistic regression analysis (OR = 1.045, 95% CI: 1.006–1.085). Furthermore, multivariate logistic regression analysis showed that positive ACA (OR = 0.116, 95% CI: 0.015–0.876) was associated with a lower risk of cancer (Table 4), adjusted with age, gender, and ACA. Finally, we used proportional hazard model to analyze risk factors. Again, we found that age was a risk factor (hazard ratio = 1.045, 95% CI: 1.012–1.080), and positive ACA was a protective factor (hazard ratio = 0.232, 95% CI: 0.055–0.977) for cancer in PBC patients (Fig. 1).

Table 2 Types of cancers in PBC patients

Cancers	*N* (%)
Solid tumor	45 (88.2)
Colorectal cancer	7 (13.7)
Gastric cancer	5 (9.8)
Hepatocellular carcinoma	4 (7.8)
Periampullary carcinoma	2 (4.0)
Breast cancer	7 (13.7)
Cervical cancer	4 (7.8)
Lung cancer	3 (5.9)
Kidney cancer	2 (4.0)
Papillary thyroid carcinoma	4 (7.8)
Other malignancies*	7 (13.7)
Hematologic malignancy	6 (11.8)
Non-Hodgkin's lymphoma	2 (4.0)
Multiple myeloma	2 (4.0)
Macroglobulinemia	1 (2.0)
Leukemia	1 (2.0)

* Includes cholangiocarcinoma (n = 1), pancreatic cancer (n = 1), small intestine cancer (n = 1), ovarian cancer (n = 1), choriocarcinoma (n = 1), prostate cancer (n = 1), bladder cancer (n = 1)

Discussion

In this study, we investigated a longitudinal cohort of PBC and observed that a considerable portion (8.8%) of patients with PBC were complicated with cancer, including solid tumor and hematologic malignancy. We further identified that older age and positive ACA were the risk factor and the protective factor associated with cancer in PBC patients.

Accumulating evidence has suggested that patients with autoimmune diseases are prone to cancer compared with the general populations. Yan L et al show that PBC patients have a significantly higher risk of cancer compared with the general population (pooled rate ratio (RR), 1.55; 95% CI: 1.28–1.83) [9]. Hemminki et al report that PBC is the second most common disease in 16 autoimmune diseases with an increased risk for cancer of unknown primary [3]. In our study, we confirmed that PBC patients had increased risk of cancer, compared with the age-standardized incidence rate of the general population (168.7/100,000 per year) in China [2]. Therefore, PBC patients were at risk of cancer and should be routinely monitored for cancer.

Given that liver is the primary organ targeted by PBC, HCC has been frequently reported in PBC, with an incidence of 0.76–5.9% [7, 8, 12]. Previous studies report that the incidence of HCC is 4.13–5.2% in PBC patients in China [6, 13], and the other cancers were rarely reported. In our study, we discovered not only HCC (n=4) but also more extra-hepatic cancer (n=49) in PBC patients. As it takes time to develop from cirrhosis to HCC, the most reason for this discrepancy may be the median observation period, sample size, regional and racial differences, previous hepatitis B and C infections, alcohol intake, and other basic hepatic diseases. Patients with HCC had a longer disease course, a higher level of total bilirubin, and a higher incidence of liver cirrhosis. Melanie et al

Table 3 Comparison of clinical and laboratory features of the PBC patients with cancer and without cancer

Parameters	Cancer# (N = 29)	No cancer (N = 529)	p-value
Age (year)	60.8 ± 10.2	55.4 ± 11.6	0.014*
Female-n (%)	25 (86.2)	464 (87.7)	0.810
Duration of PBC (year)-median (IQR)	3.0 (1.0–6.5)	2.0 (0.7–5.0)	0.433
Liver biochemical tests			
ALP(U/L)-median (IQR)	204 (156–316)	202 (126–399)	0.835
GGT(U/L)-median (IQR)	194 (60–328)	199 (107–427)	0.234
TBil(μmol/L)-median (IQR)	16.2 (10.3–33.9)	18.5 (10.9–32.6)	0.951
Alb(g/L)-mean ± SD	35.9 ± 6.2	36.3 ± 6.4	0.770
Autoantibodies			
Positive AMA-n(%)	27 (93.1)	482 (91.1)	0.713
Positive AMA-M2-n(%)	27 (93.1)	480 (90.7)	0.667
Positive ACA-n(%)	1/23 (4.3)	133/513 (25.9)	0.019*
ESR (mm/h)-median (IQR)	53 (23–75)	40 (20–67)	0.385
IgM (g/L)-median (IQR)	2.26 (1.29–3.97)	3.26 (2.00–4.76)	0.160
IgG (g/L)-median (IQR)	16.20 (12.39–21.20)	16.43 (12.49–20.13)	0.948
IgA (g/L)-median (IQR)	2.11 (1.76–4.56)	2.98 (2.14–4.28)	0.275

* $p < 0.05$ between patients with cancer and patients without cancer

The cancers were diagnosed after the onset of PBC

Table 4 Univariate (unadjusted) and multivariate (adjusted) logistic regression analysis of risk factors associated with cancer diagnosed after PBC onset in PBC patients

	Univariate (unadjusted)		Multivariate (adjusted)	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age	1.042 (1.008–1.077)	0.015	1.045 (1.006–1.085)	0.023
Positive ACA	0.135 (0.018–1.014)	0.052	0.116 (0.015–0.876)	0.037

OR odds ratio, *CI* confidence interval

also find that the risk for HCC was significantly higher in PBC patients with cirrhosis [14]. It is presumed that the chronic inflammation-repair of cirrhosis potentially drives the oncogenesis of HCC. And similar to our study, Deutsch et al also report that extra-hepatic cancer is more common than HCC in PBC patients, 7.0% patients with extrahepatic malignancies and 3.8% with HCC, with a 10-year risk of 13 and 4%, respectively [14]. Consistently, in a study of 208 patients with PBC, 6 (6/208, 2.9%) breast cancer were documented in 11 extra-hepatic cancer, and additionally, the incidence of breast cancer is 4.4-folder ($p < 0.01$) higher than that in general population [15]. Taken together, for the monitoring of cancers in PBC patients, we should not only focus on HCC but also on extra-hepatic cancers.

Plasma cell dyscrasia was the most common hematologic malignancy in our study, including macroglobulinemia and MM, which is previously reported in PBC [16–18]. Persistent elevated IgM level is frequently observed in PBC patients, suggesting chronic hyperactivation of IgM-producing B cells and plasma cells. In the setting of chronic activation of B cells and plasma cells, a polyclonal gammopathy might eventually evolve into the monoclonal gammopathy. Besides, aberrant cellular and humoral immune, the major players in the pathogenesis of PBC, might impair immune surveillance and hinder the clearance of neoplastic cells [16].

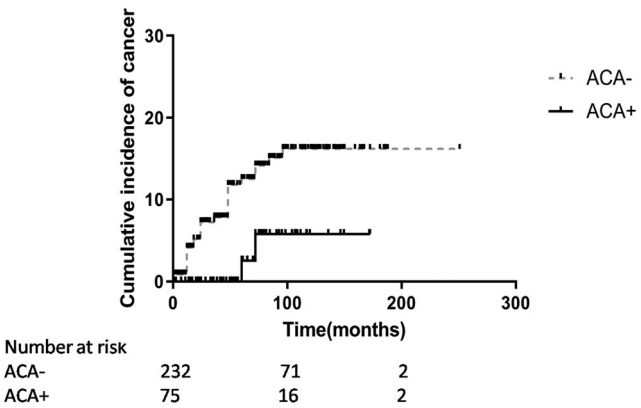

Fig. 1 Cumulative incidence of cancer in patients with or without ACA Patients with positive ACA had a lower cumulative incidence of cancer. ACA was a protective factor (hazard ratio = 0.232, 95% CI: 0.055–0.977, $p = 0.046$) for cancer in PBC patients

We confirmed that older age was associated with cancer in PBC patients. Similarly, Harada K et al find that older age (> 54 years) was associated with HCC in patients with PBC [19]. Many studies confirm that older age is a risk factor for cancer [20], which is partially explained by the increasing incidence of cancer with aging [2]. We confirmed that older age was associated with cancer in PBC patients. Age is also the risk factors for other autoimmune diseases such as scleroderma. We speculated that cell senescence and attenuated immune surveillance were the key factors contributing to the age-related cancer development in PBC [21, 22].

We also found that positive ACA was a protective factor of cancer in PBC patients. ACA is commonly observed in patients with scleroderma (28.2%) [23], PBC (30%) [24], and primary Sjogren's syndrome (pSS) (13.4%) [25]. In patients with scleroderma (SSc), ACA is a well-known protective factor of renal crisis and interstitial lung disease [26, 27]. Some study report that SSc patients with ACA have a lower incidence of cancer than those with anti-RNA polymerase antibodies [28]. Conversely, Higuchi et al. analyzed 43 SSc patients without CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome and found that positive ACA was a risk factor for cancers [29]. However, the prevalence of ACA (16%) in this study was lower than reported in SSc patients (28.2%) [23], and ACA test was unavailable in 28% patients, which might compromise the finding of this study. Therefore, ACA might be a protective factor of cancer in multiple autoimmune diseases. $CD8^+$ T cells from ACA-positive SSc patients produced a trend of higher level of IFN-γ than those from anti-nuclear antibody (ANA)-positive patients. Given $CD8^+$ T cells as a key player in antitumor immunity, we speculated that ACA-positive PBC patients might have stronger $CD8^+$ T cell response against cancer, which potentially contributed to the tumor protection of ACA. However, the underlying mechanism remains elusive [30].

Our study has limitations. First, the study was conducted in a single national referral medical center, and consequently the cohort might not be representative of patients in general medical centers. However, given the low prevalence of PBC (49.2/100,000) [31], it is difficult to enroll PBC patients in general medical centers. Second, we did not adjust other common confounding factors in the analysis; therefore, the effect of the factors associated with cancer might be overestimated.

Third, the patients were followed for a median of 4 years, which might be insufficient for the exposure of cancer and underestimate the incidence of cancer. To address this, we are continuously monitoring the cohort.

Conclusions

In summary, we confirmed that cancer was a common complication in PBC patients. Older age is associated with cancer, while positive ACA is the protective factor of cancer. PBC patients, especially older patients, should be routinely evaluated for cancer.

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Author contribution Fengchun Zhang and Hua Chen designed the study. Li Wang, Yunyun Fei, and Suying Liu prepared the material. Sainan Bian collected and analyzed the data. Sainan Bian drafted the manuscript. Hua Chen revised the manuscript with other authors' input. All authors read and approved the final manuscript.

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Data availability All data generated or analyzed during this study are included in this published article and its supplementary information files.

Compliance with ethical standards

Ethics approval The study has been approved by the ethics committee of PUMCH and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent for publication Approved by all authors.

Disclosures None.

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