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Original article

Risk factors for cancer in patients with primary biliary cholangitis and autoimmune hepatitis and primary biliary cholangitis overlap syndrome

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ABSTRACT

Introduction and objectives: Primary biliary cholangitis (PBC) and autoimmune hepatitis (AIH) and PBC overlap syndrome (AIH/PBC) have been associated with a higher risk of hepatocellular carcinoma (HCC) and extra-hepatic malignancy (EHM). This study aims to assess potential risk factors associated with cancer development in PBC and AIH/PBC.
Materials and methods: The Brazilian Cholestasis Study Group database was reviewed to compare clinical and laboratory features of PBC patients with HCC and EHM with those without cancer.
Results: Among the 752 PBC patients enrolled, 64 of them with AIH/PBC, 87 cancers were identified in 72 patients, including 20 cases of HCC and 67 of EHM. Patients with HCC had a higher prevalence of cirrhosis

Abbreviations: AIC, Akaike information criterion; AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AMA, anti-mitochondrial antibodies; ANA, anti-nuclear antibodies; CAD, concurrent autoimmune diseases; EHM, extrahepatic malignancy; GGT, gamma-glutamyltransferase; HCC, hepatocellular carcinoma; PBC, primary biliary cholangitis; SD, standard deviation; UDCA, ursodeoxycholic acid; ULN, upper limit of normal

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(95% vs. 32.5% of those subjects without cancer, $p \leq 0.001$), smoking (55% vs. 12.3%, $p \leq 0.001$), CREST syndrome (30% vs 7.6%, p=0.003) and prior azathioprine (30% vs 8%, p= 0.005) and prednisone (35% vs 14%, p= 0.018) use, whereas patients with EHM had a higher prevalence of smoking (42.3% vs 12.4% of those subjects without cancer, p= <0.001), AMA positivity (96.6% vs 80.1%, $p \leq 0.001$), azathioprine therapy (21% vs 7.9%, p= 0.01) and concurrent other autoimmune diseases. In multivariate analysis, cirrhosis, obesity and prior azathioprine therapy were independent risk factors for HCC, while Sjogren syndrome and psoriasis were associated with EHM. Fibrates reduced EHM risk.

Conclusions: The prevalence of EHM is higher when compared to HCC in PBC patients. Cirrhosis, obesity, prior azathioprine use, and concurrent autoimmune diseases were significantly associated with cancer in PBC.

1. Introduction

Primary biliary cholangitis (PBC) is a chronic liver disease characterized by progressive immune-mediated destruction of small and medium sized intra-hepatic bile ducts that may lead to cirrhosis and end-stage liver failure. A small subset of patients with PBC may also have clinical, laboratory and histological features of autoimmune hepatitis (AIH) and are better defined as subjects with autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC) overlap syndrome (AIH/PBC). Those patients have worse outcomes when compared to their counterparts with clear-cut PBC or AIH and may benefit from immunosuppressive therapy [1,2]. It is widely recognized that PBC and AIH/PBC may be associated with several concurrent autoimmune diseases (CAD), but their possible association with cancer remains unclear. Previous observational studies reported conflicting results on the risk of both hepatocellular carcinoma (HCC) and extrahepatic malignancy (EHM) in subjects with PBC when compared to the general population, [3–8] but one meta-analysis including several studies concluded that PBC was associated with an increased risk of malignancy [9]. It is worth to mention that inconsistencies among these studies could be explained by limited sample sizes, variations in methodology, heterogeneity in follow-up observation periods while waiting for events, occurrence of different genomic and/or environmental exposures. Therefore, the identification of risk factors related to HCC and EHM in PBC and PBC/AIH patients is extremely important to tailor cancer screening guidelines for those patients in order to improve early diagnosis as well as prognosis. Cirrhosis and male gender have been previously linked to a higher risk of HCC among PBC patients [10–14]. On the other hand, the histological stage and occurrence of CAD were not associated with EHM [15].

To gather data on PBC in the highly admixed Brazilian population, the Brazilian Society of Hepatology sponsored a multicenter cooperative consortium named the Brazilian Cholestasis Study Group, with the inclusion of patients with the diagnosis of PBC in hepatology tertiary centers distributed throughout the country. The purpose of the present study was to evaluate the frequency of HCC and EHM in those patients with PBC and AIH/PBC and to investigate potential risk factors associated with cancer development in those subjects.

2. Patients and Methods

The study population comprised adult patients older than 18 years who were diagnosed with PBC between January 1st, 1992 and December 31st, 2020 in 28 different tertiary hepatology centers throughout Brazil. The diagnosis of PBC was considered if the patient fulfilled at least two of the following diagnostic criteria as recommended by the American Association for the Study of Liver Disease guidelines [16]: (i) positive serology for anti-mitochondrial antibodies (AMA); (ii) persistent increase of serum alkaline phosphatase (ALP) levels; and (iii) liver histology compatible with PBC. Autoimmune hepatitis (AIH) and PBC overlap syndrome was considered if the patient satisfied the Paris criteria [17]. Patients in whom the diagnosis could not be confirmed or who had another etiology of liver disease, including alcoholic liver disease, were excluded. AMA status was evaluated by indirect immunofluorescence and all AMA-positive patients had titers ≥ 1:40. Liver histology specimens were available for all patients with AMA-negative PBC. Advanced PBC was defined by the presence of moderate to severe fibrosis (Ludwig stages III or IV) on liver histology (when available) or clinical evidence of cirrhosis.

2.1. Data collection

Each researcher was asked to identify all patients being managed or treated for PBC at their Liver Center at the time of the survey and to fill in a standardized database provided by the Brazilian Cholestasis Study Group. All information collected was reviewed by three independent investigators (GGLC, CAC, MHB). Clinical and laboratory data accrued from medical records at baseline included age at diagnosis, gender, year of diagnosis, year of first symptoms or first biochemical changes and date of the last follow-up. Whenever available liver histology was staged according to the Ludwig system [18]. Other clinical and laboratory features elicited were the presence of concurrent extrahepatic autoimmune diseases, smoking habits, liver enzymes, AMA and antinuclear antibody (ANA) status, use of UDCA, azathioprine, prednisone and/or fibrate treatment, the occurrence of liver decompensation (i.e., ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis), liver transplantation or death. Data on AMA, ANA and liver enzymes, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT) and ALP were collected at baseline. Subjects with PBC or AIH/PBC were treated with UDCA and/or azathioprine and/or prednisone at the local physician's discretion. As previously described, some PBC patients non-responsive to UDCA were treated with fibrates since obeticholic acid is unavailable in Brazil [19].

The duration of follow-up was defined as the interval between the diagnosis and the last visit or the date of an adverse clinical outcome (liver transplantation or death). Cirrhotic patients were submitted to an abdominal ultrasound every six months as part of HCC screening. HCC diagnosis was confirmed by triphasic liver computed tomography, magnetic resonance imaging, or histology, according to the definitions of HCC guidelines. Screening for extrahepatic cancers was performed according to international guidelines at local investigators' discretion. The diagnosis of extrahepatic malignancies was made based on histopathology and/or bone marrow examination as appropriate and confirmed by oncologists from each center.

2.2. Statistical Analysis

Statistical analysis was performed using R software version 4.0.2. Patients were divided into three groups: patients without cancer, those with HCC, and with extrahepatic malignancies. Patients with a history of hepatic and extrahepatic cancers were included in both groups. Continuous variables distribution was assessed by the Anderson-Darling test, and those with Gaussian distribution were expressed as mean and standard deviation, or as the median and

interquartile range (IQR) if skewed distribution. Categorical variables were expressed as absolute numbers and percentages. Univariate analysis was performed using chi-square or Fisher's exact test, as appropriate, for categorical variables. Continuous variables were analyzed by the Student t-test or Mann-Whitney U-test and Brunner-Munzel test, according to the distribution. Univariate logistic regression analysis was used to evaluate candidate predictors of cancer and variable with p-value < 0.2 were further analyzed in multivariate analysis. A conditional forward multivariate analysis was used to identify the risk factors for cancer. To compare and select logistic regression models, we used the well-known Akaike information criterion (AIC). Including different variables in the model provides several possibilities, and AIC attempts to select the model by balancing underfitting (too few variables in the model) and overfitting (too many variables in the model). In all analyses, the significance level was set at p <0.05.

2.3. Ethical statements

All procedures were conducted in accordance with the ethical standards of the Helsinki Declaration and the study was approved by the Federal University of Minas Gerais Ethics Committee Board (CAAE 98627218.6.1001.5149). Patient consent was waived due to the retrospective nature of this study.

3. Results

3.1. Patient characteristics

The overall cohort was comprised of 752 subjects (92% women; mean age at diagnosis 51.8 ± 12.7 years) either with clear-cut PBC (n=688) or AIH/PBC (n=64). Demographics, and clinical and laboratory features of those patients were previously described [20,21]. Supplementary Table 1 summarizes the features of those subjects with AIH/PBC.

After a mean follow-up of 7.9 ± 6.2 years, 87 cancers were confirmed in 72 patients, including 20 cases of HCC and 67 of EHM. The mean age at cancer diagnosis was 58.4±14.6 years (58.9±14.6 years for HCC and 57.1±12.1 years for EHM). The mean time between PBC diagnosis and cancer development was 9.6 years for HCC and 4.3 years for EHM. Fourteen (19.4%) subjects presented more than one cancer during follow-up [breast cancer and lymphoma (n=2); colorectal cancer and lymphoma (n =1); thyroid cancer and lymphoma (n=1); colorectal cancer and bladder cancer (n=1); sarcoma and thyroid cancer (n=1); breast cancer and thyroid cancer (n=1); breast cancer and gastric cancer (n=1); gastric cancer and thyroid cancer (n=1); thyroid cancer and HCC (n=1); laryngeal cancer and kidney cancer (n=1); thyroid cancer, colorectal cancer and HCC (n=1), thyroid cancer, prostate cancer and HCC (n=1); colorectal cancer, melanoma and HCC (n=1)]. Clinical and laboratory features of those patients without cancer, with HCC or EHM, are summarized in Table 1.

Ninety-five percent of those patients with HCC had cirrhosis at baseline, 65% of them in the Child-Pugh A stage. Most of them (72%) were diagnosed at BCLC stage A. Ninety percent of those HCC patients were submitted to treatment with liver transplantation (20%), resection (15%), radiofrequency ablation (30%), transarterial chemoembolization (25%) and/or systemic therapy (10%).

Extrahepatic solid tumors (n = 60) were common, including 13 breast (21.7%), 11 thyroid (18.3%), 9 colorectal (15%), 4 genitourinary (6.7%) and 23 (38.3%) other cancers. No cases of cholangiocarcinoma were identified. Hematologic malignancies were diagnosed in 7 (9.7%) out of the 72 patients who developed malignancies. All of them are lymphomas.

When compared to patients without cancer, subjects with HCC had more frequent cirrhosis at baseline (95% vs. 32.5% without cancer, $p \leq 0.001$), smoking habits (55% vs. 12.4% of those patients without cancer, p = <0.001) and CREST syndrome (30% vs. 7.5% those patients without cancer, p= 0.003). In addition, they were more commonly treated with azathioprine (30% vs. 7.9% of those patients without cancer, p=0.005) and prednisone (35% vs. 14% of those patients without cancer, p = 0.018), when compared with their counterparts without cancer. As expected, liver transplantation (25% vs. 6.5% of those patients without cancer, p=0.009), overall deaths (50% vs. 16.9% of those patients without cancer, p=0.001) and liver-related deaths (89% vs. 45.7% those patients without cancer, p=0.047) were also more common in those subjects with HCC during follow-up (Table 1).

Likewise, a comparison of clinical and laboratory features of those patients with and without EHM revealed that those subjects with EHM had more frequent smoking habits (42.3% vs 12.4%, $p \leq 0.001$),

Table 1
Clinical and laboratory features of patients with PBC and AIH/PBC with or without cancer (n = 752 patients).

Variables	PBC and AIH/PBC		
	Without cancer (n=680)	HCC (n=20)	EHM (n=67)
Demographics			
Age at diagnosis (years)	51.3±12.5	49.8±14.4	53.0±11.9
Age at first symptoms (years)	48.4±12.9	42.4±16.2	51.6±10.0
Female gender	93.5%	90%	89.8%
Baseline Clinical Features			
Pruritus	44%	55%	42.3%
Fatigue	33.5%	35%	28.8%
Weight loss	1.18%	55%	62.7%
Cirrhosis at diagnosis	32.6%	95%*	40.3%
Esophageal/gastric varices	31.76%	75%	30.6%
Concurrent autoimmune diseases			
Hashimoto's thyroiditis	17.4%	15%	32.2%#
Sjogren's syndrome	8.1%	20%	23.7%#
CREST syndrome	7.6%	30%*	18.6%#
Rheumatoid arthritis	4.26%	10%	6.9%
Celiac Disease	1.2%	0%	3.4%
Psoriasis	2.2%	5%	5.0%
Vitiligo	1.3%	0%	5.1%
Comorbidities			
Hypertension	28.2%	30%	30.5%
Diabetes	16.2%	20%	11.8%
Smoking	12.4%	55%*	42.3%#
Obesity	10.4%	20%	18.6%
Baseline laboratory features			
AMA-positive	80.1%	95%	96.6%#
PBC specific ANA-positive	74%	80%	54.2%
Immunoglobulin M (mg/dL)	359±271	359±271	397±237
ALP X ULN	4.16±4.45	4.6±5.1	4.41±4.54
GGT X ULN	11.7±11.6	9.8±6.3	11.2±22.6
AST X ULN	2.68±2.22	2.5±1.6	2.36±2.49
ALT X ULN	2.8±2.6	2.3±1.4	2.2±1.8
Bilirubin x ULN	1.29±2.25	1.17±0.58	1.67±3.78
Treatment and outcomes			
Treatment with UDCA	96.3%	100%	98.5%
Treatment with UDCA + fibrates	23%	10%	10.2%#
Treatment with azathioprine	7.9%	30%*	21%#
Treatment with prednisone	14%	35%*	32%
Follow up time (years)	7.19±6.2	11.8±7.9	11.6±7.5
Liver transplantation during follow-up	6.5%	25%*	5%
Overall deaths	16.9%	50%*	23.7%
Liver-related deaths	45.7%	89%*	50%

Data is presented as mean ± standard deviation or percentage; patients with HCC and EHM were included in both groups; n; number of cases; PBC; primary biliary cholangitis; AIH; autoimmune hepatitis; AIH/PBC; autoimmune hepatitis and primary biliary cholangitis overlap syndrome; AST; aspartate aminotransferase; ALT; alanine aminotransferase; AMA; anti-mitochondrial antibodies; ANA; anti-nuclear antibody; ALP; alkaline phosphatase; GGT; gamma-glutamyltransferase; EHM; extra-hepatic malignancy; HCC, hepatocellular carcinoma; PBC; primary biliary cholangitis; UDCA; ursodeoxycholic acid; ULN; upper limit of normal.

* p <0.05 patients with HCC vs. subjects without cancer.

\# p <0.05 patients with EHM vs. subjects without cancer.

Table 2
Multivariate variables associated with either HCC or EHM in subjects with PBC and AIH/PBC.

Variables	Multivariate Analysis		
	OR	95%CI	*p*-value
HCC			
Cirrhosis	42.4	4.1-438	0.002
Obesity	8.41	1.2-57	0.03
Prior azathioprine use	7.8	1.42-43.3	0.02
EHM			
Sjogren's syndrome	4.3	1.14-16.2	0.031
Psoriasis	18.1	1.2-268.5	0.035
Prior fibrate use	0.10	0.02-0.5	0.005

OR: odds ratio; CI: confidence interval; AIH/PBC: autoimmune hepatitis and primary biliary cholangitis overlap syndrome; HCC: hepatocellular carcinoma; EHM: extra-hepatic malignancy; PBC: primary biliary cholangitis.

AMA positivity (96.6% vs 80.1% of those patients without cancer, $p \leq 0.001$), concurrent autoimmune diseases, particularly CREST syndrome (18.6% vs 7.6% of those patients without cancer, $p \leq 0.006$), Hashimoto thyroiditis (32.2% vs 17.4% of those patients without cancer, $p \leq 0.001$) and Sjogren's syndrome (23.7% vs 8.1% of those patients without cancer, $p \leq 0.001$) when compared to their counterparts without cancer. Regarding prior employment of immunosuppressive drugs, azathioprine use was more commonly observed in those subjects with EHM (21% vs 8% of those subjects without cancer, $p=0.01$) (Table 1). When compared to their counterparts without EHM, patients with EHM had higher overall mortality rates, but the difference was not statistically different (Table 1). Subjects with AIH/PBC had no increase in the risk of both HCC (p= 0.724) and EHM (p= 0.07) when compared to their counterparts with clear-cut PBC.

On multivariate analysis (Table 2), cirrhosis, obesity and prior azathioprine therapy were independently associated with HCC development, whereas Sjogren's syndrome and psoriasis were independently correlated with EHM. On the other hand, prior fibrate therapy was shown to be protective against EHM.

4. Discussion

Little is known about cancer risk in patients with PBC. Identifying risk factors for malignancies in PBC might impact clinical management and cancer surveillance strategies. In this study, we observed a considerably high frequency (9.6%) of cancer, including solid and hematologic malignancies, in patients with PBC. Furthermore, we identified that cirrhosis, obesity and azathioprine therapy were independent risk factors for HCC, while extrahepatic autoimmunity, particularly Sjogren's syndrome and psoriasis, was associated with a higher risk for EHM. Surprisingly, fibrate therapy was found to be a possible protective factor against EHM in PBC.

Mounting evidence suggests that PBC patients are more prone to cancer in comparison to the general population. Liang *et al.* have previously demonstrated that PBC was closely associated with a greater risk of overall cancer and HCC [9,22]. In this respect, HCC is the most common primary malignant tumor of the liver and has been frequently reported in patients with advanced PBC [13,23,24]. Several risk factors were associated with an increased risk of HCC in PBC patients, including male gender, older age, type 2 diabetes, concurrent viral hepatitis, advanced histological stage at diagnosis and non-response to UDCA [10–14,25].

In our study, cirrhosis was strongly associated with HCC, indicating that it is necessary to rigorously screen PBC patients with advanced fibrosis or cirrhosis for HCC. As previously reported by Zhang *et al* [26], obesity was also associated with HCC development in subjects with PBC in the present study. Several studies highlighted a close association between obesity and HCC, especially in patients with non-alcoholic fatty liver disease. Mechanisms relating obesity to HCC seem to correlate with adipose tissue remodeling, alteration in the gut microbiome, genetic factors, endoplasmic reticulum stress, oxidative stress and epigenetic changes [27]. Furthermore, we identified that azathioprine also increases HCC risk. Immunosuppressants are classically related to susceptibility to cancer development since these medications inhibit proper tumor surveillance by the immune system [28]. In this respect, azathioprine therapy has been implicated as a risk factor for several malignancies, including skin cancer and lymphoma. Although large cohort studies have failed to show any association between HCC and prior azathioprine use, there is biological plausibility given azathioprine's known hepatotoxicity and mutagenicity potential [29,30]. Arber *et al.* demonstrated that azathioprine might increase liver cell turnover in animal models, a finding that might be implicated in carcinogenesis [31]. Furthermore, several authors also reported HCC in patients using azathioprine without liver disease [32]. It is also possible to speculate that the observed increased risk of HCC seen in our patients with PBC treated with immunosuppressants could reflect a difficult-to-treat subpopulation of patients with more advanced disease and higher inflammatory activity, favoring the occurrence of HCC. It is important to highlight that in our cohort most patients with PBC used azathioprine in the nineties, a period in which therapeutic responses in randomized clinical trials were still conflicting [33]. Therefore, those patients had longer periods of follow-up, which could impact the overall prevalence of cancer.

Cancer is a common complication of autoimmune diseases and several studies have shown that patients with rheumatic diseases are at increased risk for malignancy. In our study, Sjogren's syndrome or psoriasis increased the risk of EHM in subjects with PBC, while fibrate use seemed to be protective. Sjogren's syndrome has been associated with a higher incidence of lymphoma, thyroid cancer, lung cancer, multiple myeloma, cancers of the unknown site and skin cancers [22,34]. Similarly, studies have previously demonstrated that patients with psoriasis are at an increased risk of cancer and cancer-related mortality, which is primarily driven by colorectal, kidney, laryngeal, liver, lymphoma, skin, esophageal, oral cavity, and pancreatic cancers [35,36]. The explanation for the increased risk of cancer in psoriasis is still unknown but seems not to be related to photo- and biological therapies. Finally, the role of fibrates in the reduction of EHM development among PBC patients is not clear and should be interpreted with more caution. These patients may have had a shorter period of follow-up since off-label fibrate use for PBC was introduced in Brazil only in the last decade. It is also possible that add-on treatment with fibrates might have a protective effect boosting treatment responses to drug therapy. Besides that, we usually prescribe fibrates for patients with less advanced liver disease, since we consider high bilirubin levels or decompensated cirrhosis as relative contra-indications to fibrates. It is worth mentioning that one previous meta-analysis provided no evidence for an association between fibrates and cancer in cohorts of patients without the liver disease [37].

Much controversy remains about the frequency of EHM in patients with PBC when compared to the general population [3–8]. Although we cannot estimate cancer incidence compared with the Brazilian population, the overall prevalence of cancer was high in our cohort and similar to those reported in Italy and Spain [15]. Not surprisingly, extra-hepatic cancers were more common than HCC, since HCC is primarily seen in patients with cirrhosis, which comprised about a third of our patient cohort, and EHM included several types of cancer in a much larger susceptible population. On the other hand, a lower rate of HCC in autoimmune liver diseases compared with viral hepatitis has been recently described [38]. Interestingly, in this study, HCC patients had a longer period from symptom manifestation to definite PBC diagnosis than individuals with EHM and probably suffered a delay to start treatment leading to more fibrosis.

Our study has some limitations inherent to its retrospective design. However, its large multicenter sample size and the long follow-up observation period are important strengths of this work. Furthermore, since PBC is a rare and slowly progressive disease, retrospective studies are fundamental to understanding its natural history and generating new hypotheses to be prospectively tested. Unfortunately, incidence could not be calculated to compare our data to the Brazilian national cancer database. On the other hand, according to the National Institute of Cancer (INCA) database, the most frequent types of cancer in Brazil, except for non-melanoma skin cancer, are prostate (29.2%), colorectal (9.1%), lung (7.9%), stomach (5.9%) and oral cavity (5.0%) in men, and breast (29.7%), colorectal (9.2%), cervix (7.4%), lung (5.6%) and thyroid (5.4%) in women [39]. Therefore, the high prevalence of thyroid neoplasia in our cohort of patients with PBC is at least intriguing. Finally, the wide confidence intervals about the estimates themselves indicate a high variability, which is probably associated with the small number of events observed. In this way, data should be interpreted with caution until a large meta-analysis on this topic is performed.

5. Conclusions

Cancer, both HCC and EHM, is a common complication of PBC. Extra-hepatic neoplasms prevalence is higher than HCC on a long-term follow-up. We identified that cirrhosis, obesity and azathioprine therapy are independent risk factors for HCC, while Sjogren's syndrome and psoriasis are associated with extra-hepatic cancers in PBC patients. Fibrate therapy may be a protective factor against EHM in this population, although the mechanisms underlying such a relationship remain unclear. Large new prospective studies are necessary to further confirm these data and evaluate the potential effectiveness of cancer surveillance programs for different subsets of patients with PBC.

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Declaration of Competing Interests

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.aohep.2023.101105.

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