Gene Expression **2022** vol. 21(2) | 34–40
DOI: 10.14218/GE.2022.00016

Review Article

Primary Biliary Cholangitis, Liver Transplantation, and Hepatocellular Carcinoma: A Mini-review

Badi Rawashdeh[1*], Allison Couillard[1], Aasem Rawshdeh[2], Hassan Aziz[3], James Esteban[4] and Motaz Selim[1]

[1]Department of General Surgery, Division of Transplant Surgery, Medical College of Wisconsin, Milwaukee, USA; [2]Department of Medicine, Jordanian Royal Medical Services, Amman, Jordan; [3]Department of General Surgery, Division of Transplant Surgery, University of Iowa, Iowa City, USA; [4]Department of Medicine, Division of Gastroenterology and Transplant Hepatology, Medical College of Wisconsin, Milwaukee, USA

Received: September 23, 2022 | **Revised:** November 02, 2022 | **Accepted:** November 28, 2022 | **Published:** December 20, 2022

Abstract

Primary biliary cholangitis (PBC) is an organ-specific chronic autoimmune disease characterized by T-lymphocyte mediated destruction of intrahepatic biliary epithelial cells due to a combination of genetic and possible environmental factors. PBC progresses to hepatic fibrosis and cirrhosis, with the potential of developing hepatocellular carcinoma (HCC) if left untreated. PBC is more common in middle-aged women. It is diagnosed in patients with elevated liver enzymes and the serological hallmark of antimitochondrial antibody (AMA). Early diagnosis and treatment are crucial in improving survival and preventing long-term complications of liver disease. Ursodeoxycholic acid (UDCA) is first-line treatment for PBC. Obeticholic acid (OCA) and fibrates, in combination with UDCA or as monotherapy, may be given to PBC patients with partial or no UDCA response. Liver transplantation has thus been indicated in patients with decompensated cirrhosis or unresectable HCC.

Introduction

Primary biliary cholangitis (PBC) is a chronic autoimmune disease characterized by T-lymphocyte mediated destruction of intrahepatic biliary epithelial cells and a distinctive serologic marker, antimitochondrial antibody (AMA).[1] Histologically, PBC is characterized by infiltration of mononuclear cells and destruction of intrahepatic small bile ducts, followed by liver cirrhosis and, eventually, liver failure.[2] PBC predominantly affects middle-aged women, and the rate of disease progression differs significantly between patients.[1,3] The recent increase in PBC prevalence has been associated with the improvement in mortality due to medical advances leading to earlier disease diagnosis, and earlier introduction of treatment.[4] The diagnosis of PBC is suspected based on cholestatic serum liver tests after exclusion of other causes of liver disease and confirmed with the elevation of AMA.[5]

Keywords: Primary biliary cholangitis; Autoimmune disease; Liver transplantation, Ursodeoxycholic acid.

Abbreviations: ALP, alkaline phosphatase; AMA, antimitochondrial antibody; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; OCA, obeticholic acid; PBC, primary biliary cholangitis; PDC-E2, pyruvate dehydrogenase complex; TB, total bilirubin; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

[*]**Correspondence to:** Badi Rawashdeh, Department of General Surgery, Division of Transplant Surgery, Medical College of Wisconsin, 9200 W Wisconsin Ave, CFAC 2nd Floor, Milwaukee, WI 53226, USA. ORCID: https://orcid.org/0000-0003-4193-4654. Tel: 414-805-6096, Fax: 414-955-0213, E-mail: Brawashdeh@mcw.edu

How to cite this article: Rawashdeh B, Couillard A, Rawshdeh A, Aziz H, Esteban J, Selim M. Primary Biliary Cholangitis, Liver Transplantation, and Hepatocellular Carcinoma: A Mini-review. *Gene Expr* 2022;21(2):34–40. doi: 10.14218/GE.2022.00016.

This article presents an overview of the epidemiology, pathogenesis, natural history, clinical presentation, diagnosis, and treatment of PBC. We received no funding for this work.

Epidemiology

The incidence and prevalence of PBC vary geographically being the highest in Northern and Southeastern Europe and lower in the Asia-Pacific region.[5] In population-based studies of PBC, disease prevalence varied from 4.8 cases per 100,000 people in South Korea[6] to as high as 58.2 cases per 100,000 people in Central Greece.[7] However, it is still unclear whether these geographic differences have been due to true ethnic and environmental differences or variations in study methodologies.[8]

PBC prevalence has also been increasing over time.[1] In Northern England, between 1987 and 1994, prevalence increased from 20 to 33 cases per 100,000 adults, and from 54 to 94 cases per 100,000 women over the age of 40.[9] In Australia, prevalence increased from 1 to 5.1 cases per 100,000 between 1991 and 2004,[10] while in Canada, prevalence increased from 10 to 22.7 cases per 100,000 between 2002 and 2009.[4] In Italy, PBC incidence increased from 1.7 to 5.3 per 100,000 person-years between 2009 and 2015; however, PBC incidence has remained stable in the United States of America, Canada and Sweden.[2,4,11]

In addition, studies have shown a significant transition in global incidence over time. Studies published before 1986 present an annual incidence rate of 0.06–1.37 cases per 100,000 population in comparison to 0.07–4.9 cases per 100,000 population after 1986.[11]

The uptrend in incidence is possibly due to improved detection, diagnosis, and overall survival, but a true increase in disease incidence cannot be excluded.[12]

Middle-aged women comprise the demographic group most commonly affected by PBC. The incidence in women older than 40 years of age is around 0.1%.[13,14] Age-adjusted prevalence per 100,000 persons is 65.4 cases in women and 12.1 cases in men.[3,5,12] While older analyses indicate a 9:1 female-to-male ratio in PBC, recent studies indicate a 5:1 female-to-male ratio[5] and an even lower female-to-male ratio of 2.3:1 was reported in Northern Italy.[15] The sexual dimorphism of PBC is unexplained, but may be due to epigenetic factors affecting the X chromosome and immunological differences that are potentially hormonally mediated.[16] PBC is rare in women under 25 years of age, but cases involving 12- and 16-year-old girls have been reported.[3,14]

Pathogenesis and genetics

PBC is strongly associated with the loss of immune tolerance against the E2 component of the pyruvate dehydrogenase complex (PDC-E2) causing dysregulation of the innate and adaptive immune system resulting in a targeted immune response directed against the biliary epithelial cells.[17] A highly specific AMAs is present in high titers in patients with PBC and target the PDC-E2 in cholangiocytes causing apoptosis of the biliary epithelial cells.[1,13] Furthermore, PBC is also characterized by heavy infiltration of autoreactive CD4+ and CD8+ T cells that target intrahepatic biliary epithelial cells, thus causing chronic inflammation and ultimately hepatic cirrhosis.[13,18] Moreover, the presence of granulomatous inflammation, polyclonal immunoglobulin M production, and cytokine responses emphasize the role of innate immune response in the pathogenesis of PBC.[17]

Hereditary susceptibility is a crucial contributing element in the pathogenesis of PBC.[1] Genetic predisposition is supported by significant concordance in monozygotic twins. The familial risk of PBC for women with one affected first-degree relative is higher than for women with no affected relatives.[1] Furthermore, the risk of PBC was found to be higher with an increasing degree of familial relationships.[19]

Growing evidence has suggested that environmental factors, in combination with genetic predisposition, play an essential role in disease development.[5,19] Nevertheless, there have been no definite environmental factors singled out. However, there is an association between urinary tract infections and PBC, which have been potentially caused by molecular mimicry between human and Escherichia coli PDC-E2.[5,20–22] Case-control studies have also demonstrated that xenobiotic modification of PDC-E2 with chemicals abundantly found in daily life, such as lipsticks, hair dyes, and nail polish may have a role in developing immunogenic neoantigens and breaking immune tolerance in PBC.[5] A history of smoking or hormone replacement therapy has also been linked to an increased risk of PBC.[18]

Natural history

Early diagnosis of PBC through AMA and treatment with ursodeoxycholic acid (UDCA) have significantly transformed the natural history of PBC in the last few decades.[3,5,14,23,24] Before AMA's recognition as the serological signature of PBC,[25] most patients were diagnosed in the advanced stages of cirrhosis.[5,14,26] In the pre-UDCA era, the median time to develop advanced hepatic fibrosis from the time of diagnosis was approximately two years.[27]

Other prospective studies showed the median time from early presentation of PBC to histologically confirmed cirrhosis to be four years.[27,28] Asymptomatic patients have better outcomes than symptomatic patients.[24] In 1994, Mahl *et al.* found that the median survival of symptomatic patients is 7.5 years in comparison to a median survival of 16 years for asymptomatic patients.[29] However, a newer study showed that asymptomatic patients have 50–70% 10-year survival, while symptomatic patients have a median survival of 5–10 years from presentation.[30] At the present time, PBC can be diagnosed in the asymptomatic stage in patients with elevated liver enzymes. Receiving treatment at earlier stages results in a more positive prognosis.[14,21,31] The five-year probability of liver failure in PBC-associated cirrhosis is 15–20%. Patients who develop cirrhosis and portal hypertension have worse outcomes. Three-year survival after the development of esophageal varices is 59%, and 46% after a first variceal bleed.[3]

Portal hypertension, as seen by esophageal varices, appears to be a common finding in PBC patients' follow-up and progresses rapidly during disease advancement. Previous research found 20–82% of PBC patients affected.[32–34] PBC portal hypertension studies are scarce. Thus, portal hypertension's natural history and development of PBC patients are still not well known. Without treatment, portal hypertension may not improve; however, UDCA stabilizes or reduces portal pressure in certain patients.[33] Portal pressure might be greatly elevated in the early stages of a disease.[34] In fact, gastrointestinal bleeding due to portal hypertension occurs in around half of patients, and may be the first sign of PBC.[32,34]

In a population-based PBC study from the USA, the median time to progression from AMA positivity to persistent elevation of liver chemistries was six years (range of 1–20 years).[35] Other studies showed that the median survival of asymptomatic AMA-positive persons is better than in symptomatic patients with PBC. The mortality rate was 63% in the symptomatic group compared to 20% in the asymptomatic group. Nevertheless, the survival was worse than expected relative to the general population.[36]

Studies indicate potential gender-based differences in patient outcomes. One of the most widely recognized clinical characteristics of PBC is a strong female preponderance.[37] Multiple studies showed that male gender is associated with a delay in diagnosis and, as a result, an increased age at PBC identification.[37–39] Multiple studies have shown that fatigue is more likely to be associated with female sex at the time of PBC presentation.[37] Additionally, several studies demonstrated that an inadequate response to UDCA is more prevalent in males than in females.[38,40] However, other researches have shown that sex difference has no impact on UDCA therapy response.[7,41] On the other hand, gender did not affect OCA therapy response in one trial.[42] Multiple studies from Northern Italy, Canada, and the Netherlands also described higher mortality rates in males with PBC than females,[4,15,43] which is possibly related to poorer response to UDCA in males or a higher likelihood of asymptomatic PBC in men that may delay diagnosis.[38] One study found that disease severity was higher in Black and Hispanic Americans.[44,45]

Clinical presentation

Common clinical manifestations vary from fatigue, pruritus, and weakness to major life-threatening complications secondary to end-stage liver failure. Nonetheless, the most common mode of presentation is asymptomatic patients diagnosed by laboratory work.[1,18] Extrahepatic manifestations of PBC are generally autoimmune in nature and occur in up to 63% of patients with the most common being Sjogren's syndrome, thyroid dysfunction, and systemic sclerosis.[45]

Diagnosis

PBC is diagnosed by history, physical exam, laboratory tests, and liver biopsy. The diagnosis of PBC should be suspected when there is an elevation of serum alkaline phosphatase (ALP), clinical signs, and symptoms of cholestasis, such as jaundice and pruritus, and cirrhosis without cause.[1,46] In addition, PBC patients often have elevations of aminotransferases and elevated immunoglobulins, mainly immunoglobulin M.[1]

As such, a diagnosis of PBC can be made if two of three objective criteria are met: Positive AMA at titers, unexplained elevated ALP ≥1.5 times the upper normal value for over 24 weeks, and pathology from liver biopsy demonstrating portal-tract inflammation and bile duct destruction.[47] AMA is highly sensitive and specific for PBC and is positive in >95% of patients.[5] Other autoantibodies associated with PBC include antinuclear antibody, anti-sp100, and anti-gp210.[48]

Liver biopsy is not necessary for the diagnosis and work-up of PBC unless there is a concern of AMA-negative PBC, autoimmune hepatitis (AIH) overlap, or an alternative or concomitant liver disease. Histopathologic examinations have demonstrated granulomatous non-suppurative small duct cholangitis, ductopenia, and ductal proliferation, which may be accompanied by varying stages of hepatic fibrosis.[18,49]

Hepatobiliary imaging is a useful adjunctive diagnostic tool in PBC to exclude other causes of cholestasis, such as primary sclerosing cholangitis or biliary obstruction, to evaluate cirrhosis and portal hypertension, as well as to screen for hepatocellular carcinoma (HCC) in patients with cirrhosis. In cases of cirrhosis secondary to PBC, computed tomography may show heterogeneous hepatic parenchyma, hepatic surface nodularity, enlarged left hepatic and caudate lobes, and an atrophic right hepatic lobe, or stigmata of portal hypertension, such as splenomegaly, ascites, portosystemic collaterals, and umbilical vein recanalization. Computed tomography in PBC may demonstrate hypoattenuation around intrahepatic portal vein branches representing periportal edema, which is a non-specific finding. Likewise, magnetic resonance imaging provides higher resolution images of the biliary system and liver parenchyma, where lace-like fibrosis and periportal halo may be seen in PBC and have a sensitivity of 69%.[50] Periportal halo sign refers to a hypointense signal surrounding portal vein branches on T2-weighted and post-contrast T1-weighted imaging, particularly in the portal venous phase, and represents periportal fibrosis. Periportal T2 hyperintensity on T2 imaging can also be seen, which represents periportal edema.[50]

Management

PBC is universally progressive in the absence of medical treatment. The goal of treatment is to alleviate bile ductular inflammation and damage through tight regulation of bile acid synthesis and metabolism, thereby reducing the rate of disease progression to cirrhosis and reducing the risk of needing liver transplantation.[5,13]

UDCA has been first-line therapy for PBC for decades.[47,51] This has improved the biochemical parameters, pathological features, and survival rates.[51] Second-line therapies such as obeticholic acid (OCA) or fibric acid derivatives are added on to UDCA in patients who are partial responders, or as replacement therapy in patients who are intolerant to UDCA.

Treatment response is assessed after one year of treatment through liver chemistries, specifically ALP and total bilirubin (TB). Almost all treatment responders do so within six-nine months of treatment, typically starting within a few weeks of treatment initiation. There are several response criteria for PBC, the majority of which require a reduction of ALP below a predefined cut-off level. Lower levels of ALP and bilirubin are associated with significantly better long-term survival. PBC patients whose ALP dropped to <2 times the upper limit of normal (ULN) and TB to <1 times ULN after one year of treatment have 10-year survival of 84% (*vs.* 62% if ALP >2 times ULN) and 86% (*vs.* 41% if TB >1 times ULN), respectively.[46] A cohort study from the Global PBC Study Group shows that patients able to achieve normal ALP and TB have the best transplant-free survival, thus treatment of PBC should aim for normalization instead of just improvement in liver biochemistries.[52] Among patients with poor response to UCDA, 30% develop complications after 10 years.[35]

Ursodeoxycholic acid

UDCA, also known as ursodiol, has been used in traditional Chinese medicine for hundreds of years.[44] UDCA is a hydrophilic dihydroxy bile acid that can modify the disease course of PBC through the following presumed mechanisms: 1) Modification of the bile acid pool, specifically replacement of cytotoxic endogenous hydrophobic bile acids with a less toxic hydrophilic bile acid,[13] 2) immunomodulation by reducing hepatocellular and biliary expression of major histocompatibility complete class I and class II proteins,[53] and 3) stimulation of choleresis by upregulating anion exchanger-2 expression on the surface of cholangiocytes.[13] Since USA Food and Drug Administration (FDA) approval in 1994, UDCA remains the first-line therapy for PBC and has transformed the natural course of the disease.[5,13,54] The recommended dose of UDCA is 13–15 mg/kg/day typically in two divided doses.[5]

UDCA, especially if administered in the early stages of PBC, significantly delays histological progression to cirrhosis and improves transplant-free survival.[55,56] Moreover, transplant-free survival after eight years of UDCA treatment is 61%.[44] Transplant-free survival of UDCA-treated PBC patients was much improved compared to patients with no treatment or insufficient biochemical response to UDCA.[55–57] Boberg *et al.* demonstrated that UDCA could extend the life expectancy of PBC patients by an additional 2.2 years.[58] Hence, survival of UDCA-treated patients with PBC, when provided in early stages of the disease, is equivalent to age- and sex-matched healthy subjects.[30] Therefore, UDCA is generally safe. Side effects include hair thinning, weight gain, and diarrhea.

Carbone *et al.* showed that males expressed an inferior response to UDCA therapy.[59] Age at diagnosis also independently correlated with the response to UDCA; patients presenting at a younger age were significantly more likely to be nonresponders and more likely to be symptomatic.[59] Another study concluded that Hispanics with PBC had a decreased response to UDCA and experienced portal hypertension more commonly than non-Hispanic patients.[3]

Approximately 20–40% of patients with PBC exhibit incomplete biochemical responses to UDCA with a persistently elevated level of alkaline phosphatase.[13] The outcomes of partial responders are worse than full responders;[56] therefore, adding a second-line therapeutic agent should be considered for those patients.[5,55,57]

Obeticholic acid

OCA is a synthetically modified bile acid that is a selective farnesoid X (FXR) activator.[13] OCA increases the bile salt exporter protein expression, which increases bile acid flow and secretion.[60] OCA also has anti-inflammatory and antifibrotic effects.[61] In 2016, OCA received accelerated approval from the USA FDA for treatment of patients with PBC who are partial responders, nonresponders, or intolerant to UDCA.[31,62]

In a randomized placebo-controlled phase 3 trial, Nevens *et al.*

found that for 12 months, OCA, either with UDCA or as monotherapy, improved the ALP and the TB levels among PBC patients with an inadequate response to UDCA or unacceptable UDCA side effects.[61]

The American Association for the Study of Liver Diseases and European Association for the Study of the Liver clinical practice guidelines recommend either a combination of OCA and UDCA therapy for patients with PBC with an inadequate biochemical response to UDCA, or OCA monotherapy for patients who are intolerant of UDCA as second-line treatment.[23,47]

Several trials have raised concerns about the adverse effects of OCA. Dose-related increases in the incidence and severity of pruritus were noted; mostly at doses higher than 10 mg.[61,62] Other studies showed that among patients with compensated PBC cirrhosis, OCA usage correlated with an increased risk of hepatic decompensation.[13,31] Patients with a constant elevation of serum liver enzymes should discontinue OCA, particularly if there is evidence of hepatic decompensation.[31] Thus, during the initial months of therapy, patients should have a close follow-up of their liver enzyme levels, including serum bilirubin, ALT, AST, and ALP, to weigh the efficacy versus safety.[60]

Fibrates

Fibrates are agonists of peroxisome proliferator-activated receptor and pregnane X receptor that reduce de novo bile acid synthesis and upregulate bile acid transporters.[63] Fibrates are currently only approved as lipid-lowering agents by the US FDA.[13]

In several uncontrolled randomized trials, fibrates improved the treatment response to UDCA.[23,63,64] In a prospective placebo-controlled trial, adding bezafibrate for two years to UDCA partial responders significantly improved the ALP levels. Additionally, 67% in the bezafibrate group had normal ALP levels at the end of treatment; furthermore, 60% of the median reduction from the baseline in the ALP level was observed in three months.[65] In a large Japanese retrospective study of treatment effects in patients with PBC, the addition of bezafibrate to UDCA was associated with a lower need for liver transplantation.[2]

Cancado *et al.* showed that 50% of UDCA nonresponders treated with add-on ciprofibrate or bezafibrate had a biochemical response at one year.[66] The combination of UDCA and bezafibrate decreased mortality and improved transplant-free survival compared with patients on UDCA monotherapy.[5,66] Pruritus was also significantly improved by bezafibrate in subjects with PBC.[67]

Liver transplantation

As for any other indication for liver transplantation, a careful assessment of risks versus benefits for the patient should be undertaken. The aim of liver transplantation is to improve the patient's survival and/or quality of life. PBC patients who develop cirrhosis are at a disadvantage in both those areas. Recent guidelines of the American Association for the Study of Liver Diseases have recommended referring patients for liver transplantation evaluation when their Model For End-Stage Liver Disease is higher than 14.[47] Patients can be referred to transplant evaluation with medically refractory complications of portal hypertension (*e.g.* ascites, hepatic encephalopathy, or variceal bleeding), and/or unresectable HCC within transplant criteria. The most recently published national data in the USA has shown that the rate of liver transplantation for cholestatic liver diseases remained unchanged between 2010 (8.6% of all transplantations) and 2020 (8.3%).[68]

The technique of liver transplantation for PBC does not vary from the standard technique for other indications for liver transplantation. Either live or deceased donor organs can be used. The graft would be revascularized using the standard techniques. Biliary construction with choledochocholedochostomy can be performed when technically feasible since the disease mostly affects the intrahepatic biliary radicles.[69] Roux-en-Y hepaticojejunostomy would also be performed in live donor or segmental liver transplant, or in other situations, such as donor/recipient duct size mismatch or adhesions and scarring around the native bile duct. The rate of biliary anastomotic complications (*e.g.* leakage or stricture) is comparable between liver transplantations done for PBC and other liver diseases at 10–25%.[70]

Overall, survival after liver transplantation for PBC is similar to slightly better than for other liver transplantation indications with one, three and five-year patient survival rates of 94%, 91%, and 86%, respectively.[71] Current overall patient survival rates after liver transplantation are 93.6% at one year, 86.9% at three years, and 81.2% at five years, respectively.[68]

PBC recurrence after transplantation is estimated at 22% at five years and 36% at 10 years post-liver transplantation. Younger age at transplantation, tacrolimus used for immunosuppression, and biochemical evidence of cholestasis in the first-year post-transplantation are associated with a higher risk of post-transplantation recurrence. PBC recurrence may lead to graft loss, re-transplantation, or death. In a study of 785 liver transplantation recipients, the time-dependent hazard ratio of graft loss in patients with PBC recurrence was 2.01 (95% confidence interval (CI) 1.16–3.51; p = 0.01).[72] Use of UDCA after liver transplantation is associated with a reduced risk of PBC recurrence.[73]

Hepatocellular carcinoma

Considerable evidence has demonstrated that PBC increases the risk of HCC.[74] Autoimmune liver illnesses in general also raise the risk of HCC, but at a lesser rate than other liver diseases.[75] The incidence of HCC in PBC, particularly in patients with severe fibrosis, varied widely between 1.9–14%.[74] In addition, studies found a combined relative risk of HCC that ranged from 10.8 to 26.8% when compared to that of the general population.[76] Despite the fact that PBC is primarily a female disease, women with PBC cirrhosis had a lower incidence of HCC than men, estrogen may prevent hepatocellular carcinoma by suppressing the cytokines and interleukin-6.[74,76] HCC in PBC is linked to advanced age, male sex, and comorbidities.[74] Additional risk factors for HCC in PBC include concomitant diabetes and obesity (body mass indexes).[77] However, advanced liver fibrosis is the most significant risk factor,[74,76] yet some PBC patients develop HCC without advanced cirrhosis.[74]

Till now, the only indication for HCC screening on which all scientific societies agree has been in patients with cirrhosis; nevertheless, hypoalbuminemia, thrombocytopenia, and signs of portal hypertension are all risk factors for the development of HCC.[76] These indicate advanced PBC, thus supporting the HCC screening suggestion for PBC with cirrhosis.[74,76] US with or without AFP testing every six months is the recommended screening modality for HCC in PBC,[78] as this is less helpful in the early stages of HCC. However, the sensitivity increases when AFP is included.[78]

The biochemical response to UDCA and HCC development are inconsistent. It is still not known whether or to what extent treatment with UDCA lowers the risk of HCC in patients with PBC.[74,76] HCC development is linked to a biochemical nonresponse to UDCA.[79] Likewise, in another study of cirrhotic PBC patients, UDCA response was not linked with HCC development.

In a Natarajan meta-analysis, UDCA did not reduce the HCC risk in PBC patients with or without cirrhosis.[76]

Compared to other chronic liver diseases with HCC, PBC-associated HCC has a poor prognosis. Without treatment, HCC with PBC had a median survival of 36 months, and liver transplantation has the highest survival rate.[74] Currently, the indications for liver transplantation for HCC in PBC are comparable to those for any other form of chronic liver disease with HCC.[80,81] HCC treatment options are also varied with multiple different algorithms published and practiced by different centers; therefore, HCC management should ideally be done through a multidisciplinary approach.[82] Additionally, a detailed discussion on the treatment approach to HCC is beyond the scope of this review. In the USA, liver transplantation for HCC in patients with PBC follows the same rules set by the United Network for Organ Sharing for all liver transplantations for HCC that is the tumors have to be within the Milan criteria, or downstaged to within the Milan criteria to be eligible for the exception points.

Summary

In conclusion, PBC is an immune-mediated destruction of small intrahepatic bile ducts due to a combination of genetic and possible environmental factors. Left untreated, PBC progresses to hepatic fibrosis, cirrhosis, and potentially HCC. PBC also has a predilection for middle-aged women. AMA is the serologic signature of PBC. PBC is diagnosed in patients with chronic cholestasis, a positive AMA, and/or liver biopsy showing suppurative cholangitis. PBC is commonly asymptomatic, but is sometimes symptomatic with fatigue, pruritus, xerostomia, and abdominal pain being the most commonly reported symptoms. PBC may also be accompanied by extrahepatic or other autoimmune conditions, such as hypothyroidism, connective tissue disease, osteodystrophy, and hyperlipidemia. Early diagnosis and treatment are crucial in improving survival and preventing long-term complications of liver disease. UDCA is the first-line treatment for PBC and improves transplant-free survival. OCA and fibrates, in combination with UDCA or as monotherapy, may be used in PBC patients who are partial responders, nonresponders, or intolerant to UDCA. Biochemical improvement, defined as an alkaline phosphatase reduction to normal or up to <1.67 times the upper limit of normal, is the goal of medical treatment, as it is associated with the best patient outcomes. Liver transplantation is indicated in patients who develop decompensated cirrhosis or unresectable HCC.

Acknowledgments

None.

Funding

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Literature review and writing (BR); Drafting the article (AC); Critical revision (AR, HA, JE and MS).

References

[1] Zhao Y, Yin Z, Du H, Huang K, Zhang F, Chen H. The latest research trends in primary biliary cholangitis: a bibliometric analysis. Clin Exp Med 2022. doi:10.1007/s10238-022-00825-0, PMID:35389157.

[2] Tanaka A, Hirohara J, Nakano T, Matsumoto K, Chazouillères O, Takikawa H, *et al*. Association of bezafibrate with transplant-free survival in patients with primary biliary cholangitis. J Hepatol 2021;75(3):565–571. doi:10.1016/j.jhep.2021.04.010, PMID:33882268.

[3] Imam MH, Lindor KD. The natural history of primary biliary cirrhosis. Semin Liver Dis 2014;34(3):329–333. doi:10.1055/s-0034-1383731, PMID:25057955.

[4] Myers RP, Shaheen AA, Fong A, Burak KW, Wan A, Swain MG, *et al*. Epidemiology and natural history of primary biliary cirrhosis in a Canadian health region: a population-based study. Hepatology 2009;50(6):1884–1892. doi:10.1002/hep.23210, PMID:19821525.

[5] Tanaka A. Current understanding of primary biliary cholangitis. Clin Mol Hepatol 2021;27(1):1–21. doi:10.3350/cmh.2020.0028, PMID:33264835.

[6] Jeong SH. Current epidemiology and clinical characteristics of autoimmune liver diseases in South Korea. Clin Mol Hepatol 2018;24(1):10–19. doi:10.3350/cmh.2017.0066, PMID:29307132.

[7] Gatselis NK, Zachou K, Lygoura V, Azariadis K, Arvaniti P, Spyrou E, *et al*. Geoepidemiology, clinical manifestations and outcome of primary biliary cholangitis in Greece. Eur J Intern Med 2017;42:81–88. doi:10.1016/j.ejim.2017.05.006, PMID:28535947.

[8] Kanth R, Shrestha RB, Rai I, VanWormer JJ, Roy PK. Incidence of Primary Biliary Cholangitis in a Rural Midwestern Population. Clin Med Res 2017;15(1-2):13–18. doi:10.3121/cmr.2017.1351, PMID:28487448.

[9] James OF, Bhopal R, Howel D, Gray J, Burt AD, Metcalf JV. Primary biliary cirrhosis once rare, now common in the United Kingdom? Hepatology 1999;30(2):390–394. doi:10.1002/hep.510300213, PMID:10421645.

[10] Sood S, Gow PJ, Christie JM, Angus PW. Epidemiology of primary biliary cirrhosis in Victoria, Australia: high prevalence in migrant populations. Gastroenterology 2004;127(2):470–475. doi:10.1053/j.gastro.2004.04.064, PMID:15300579.

[11] Lu M, Zhou Y, Haller IV, Romanelli RJ, VanWormer JJ, Rodriguez CV, *et al*. Increasing Prevalence of Primary Biliary Cholangitis and Reduced Mortality With Treatment. Clin Gastroenterol Hepatol 2018;16(8):1342–1350.e1. doi:10.1016/j.cgh.2017.12.033, PMID:29277621.

[12] Lazaridis KN, Talwalkar JA. Clinical epidemiology of primary biliary cirrhosis: incidence, prevalence, and impact of therapy. J Clin Gastroenterol 2007;41(5):494–500. doi:10.1097/01.mcg.0000225653.07932.8f, PMID:17450033.

[13] Gulamhusein AF, Hirschfield GM. Primary biliary cholangitis: pathogenesis and therapeutic opportunities. Nat Rev Gastroenterol Hepatol 2020;17(2):93–110. doi:10.1038/s41575-019-0226-7, PMID:31819247.

[14] Al-Harthy N, Kumagi T. Natural history and management of primary biliary cirrhosis. Hepat Med 2012;4:61–71. doi:10.2147/HMER.S25998, PMID:24367233.

[15] Lleo A, Jepsen P, Morenghi E, Carbone M, Moroni L, Battezzati PM, *et al*. Evolving Trends in Female to Male Incidence and Male Mortality of Primary Biliary Cholangitis. Sci Rep 2016;6:25906. doi:10.1038/srep25906, PMID:27192935.

[16] Smyk DS, Rigopoulou EI, Pares A, Billinis C, Burroughs AK, Muratori L, *et al*. Sex differences associated with primary biliary cirrhosis. Clin Dev Immunol 2012;2012:610504. doi:10.1155/2012/610504, PMID:22693524.

[17] Li H, Guan Y, Han C, Zhang Y, Liu Q, Wei W, *et al*. The pathogenesis, models and therapeutic advances of primary biliary cholangitis. Biomed Pharmacother 2021;140:111754. doi:10.1016/j.biopha.2021.111754, PMID:34044277.

[18] Hirschfield GM, Heathcote EJ, Gershwin ME. Pathogenesis of cholestatic liver disease and therapeutic approaches. Gastroenterology 2010;139(5):1481–1496. doi:10.1053/j.gastro.2010.09.004, PMID:20849855.

[19] Örnolfsson KT, Olafsson S, Bergmann OM, Gershwin ME, Björnsson ES. Using the Icelandic genealogical database to define the familial risk of primary biliary cholangitis. Hepatology 2018;68(1):166–171. doi:10.1002/hep.29675, PMID:29159924.

[20] Burroughs AK, Rosenstein IJ, Epstein O, Hamilton-Miller JM, Brumfitt W, Sherlock S. Bacteriuria and primary biliary cirrhosis. Gut 1984;25(2):133–137. doi:10.1136/gut.25.2.133, PMID:6363217.
[21] Gershwin ME, Selmi C, Worman HJ, Gold EB, Watnik M, Utts J, *et al*. Risk factors and comorbidities in primary biliary cirrhosis: A controlled interview-based study of 1032 patients. Hepatology 2005;42(5):1194–202. doi:10.1002/hep.20907, PMID:16250040.
[22] Corpechot C, Chrétien Y, Chazouillères O, Poupon R. Demographic, lifestyle, medical and familial factors associated with primary biliary cirrhosis. J Hepatol 2010;53(1):162–169. doi:10.1016/j.jhep.2010.02.019, PMID:20471130.
[23] European Association for the Study of the Liver. EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. J Hepatol 2017;67(1):145–172. doi:10.1016/j.jhep.2017.03.022, PMID:28427765.
[24] Lee YM, Kaplan MM. The natural history of PBC: has it changed? Semin Liver Dis 2005;25(3):321–326. doi:10.1055/s-2005-916323, PMID:16143947.
[25] Walker JG, Doniach D, Roitt IM, Sherlock S. Serological Tests in Diagnosis of Primary Biliary Cirrhosis. Lancet 1965;1(7390):827–831. doi:10.1016/s0140-6736(65)91372-3, PMID:14263538.
[26] Murillo Perez CF, Goet JC, Lammers WJ, Gulamhusein A, van Buuren HR, Ponsioen CY, *et al*. Milder disease stage in patients with primary biliary cholangitis over a 44-year period: A changing natural history. Hepatology 2018;67(5):1920–1930. doi:10.1002/hep.29717, PMID:29220537.
[27] Janmohamed A, Trivedi PJ. Patterns of disease progression and incidence of complications in primary biliary cholangitis (PBC). Best Pract Res Clin Gastroenterol 2018;34-35:71–83. doi:10.1016/j.bpg.2018.06.002, PMID:30343713.
[28] Christensen E, Crowe J, Doniach D, Popper H, Ranek L, Rodés J, *et al*. Clinical pattern and course of disease in primary biliary cirrhosis based on an analysis of 236 patients. Gastroenterology 1980;78(2):236–246. PMID:7350046.
[29] Mahl TC, Shockcor W, Boyer JL. Primary biliary cirrhosis: survival of a large cohort of symptomatic and asymptomatic patients followed for 24 years. J Hepatol 1994;20(6):707–713. doi:10.1016/s0168-8278(05)80139-4, PMID:7930469.
[30] Lindor KD, Gershwin ME, Poupon R, Kaplan M, Bergasa NV, Heathcote EJ;, *et al*. Primary biliary cirrhosis. Hepatology 2009;50(1):291–308. doi:10.1002/hep.22906, PMID:19554543.
[31] John BV, Schwartz K, Levy C, Dahman B, Deng Y, Martin P, *et al*. Impact of Obeticholic acid Exposure on Decompensation and Mortality in Primary Biliary Cholangitis and Cirrhosis. Hepatol Commun 2021;5(8):1426–1436. doi:10.1002/hep4.1720, PMID:34430786.
[32] Lebrec D, Sicot C, Degott C, Benhamou JP. Portal hypertension and primary biliary cirrhosis. Digestion 1976;14(3):220–226. doi:10.1159/000197934, PMID:1085267.
[33] Huet PM, Vincent C, Deslauriers J, Coté J, Fenyves D, Matsutani S, *et al*. Portal hypertension in primary biliary cirrhosis (PBC): A reversible condition? Yes, but not in all UDCA treated patients. Hepatol Res 2009;39(10):1032–8. doi:10.1111/j.1872-034X.2009.00550.x, PMID:19796042.
[34] Warnes TW, Roberts SA, Smith A, Cope VM, Vales P, Haboubi NY, *et al*. Portal hypertension in primary biliary cholangitis: prevalence, natural history and histological correlates. Eur J Gastroenterol Hepatol 2021;33(12):1595–1602. doi:10.1097/MEG.0000000000002033, PMID:33323761.
[35] Mayo MJ. Natural history of primary biliary cirrhosis. Clin Liver Dis 2008;12(2):277–288. doi:10.1016/j.cld.2008.02.012, PMID:18456180.
[36] Nyberg A, Lööf L. Primary biliary cirrhosis: clinical features and outcome, with special reference to asymptomatic disease. Scand J Gastroenterol 1989;24(1):57–64. doi:10.3109/00365528909092240, PMID:2928724.
[37] Invernizzi F, Cilla M, Trapani S, Guarino M, Cossiga V, Gambato M, *et al*. Gender and Autoimmune Liver Diseases: Relevant Aspects in Clinical Practice. J Pers Med 2022;12(6):925. doi:10.3390/jpm12060925, PMID:35743710.
[38] Carbone M, Mells GF, Pells G, Dawwas MF, Newton JL, Heneghan MA, *et al*. Sex and age are determinants of the clinical phenotype of primary biliary cirrhosis and response to ursodeoxycholic acid. Gastroenterology 2013;144(3):560–569. doi:10.1053/j.gastro.2012.12.005, PMID:23246637.
[39] Kim KA, Ki M, Choi HY, Kim BH, Jang ES, Jeong SH. Population-based epidemiology of primary biliary cirrhosis in South Korea. Aliment Pharmacol Ther 2016;43(1):154–162. doi:10.1111/apt.13448, PMID:26526639.
[40] Cheung AC, Lammers WJ, Murillo Perez CF, van Buuren HR, Gulamhusein A, Trivedi PJ, *et al*. Effects of Age and Sex of Response to Ursodeoxycholic Acid and Transplant-free Survival in Patients with Primary Biliary Cholangitis. Clin Gastroenterol Hepatol 2019;17(10):2076–2084.e2. doi:10.1016/j.cgh.2018.12.028, PMID:30616022.
[41] John BV, Aitcheson G, Schwartz KB, Khakoo NS, Dahman B, Deng Y, *et al*. Male Sex Is Associated With Higher Rates of Liver-Related Mortality in Primary Biliary Cholangitis and Cirrhosis. Hepatology 2021;74(2):879–891. doi:10.1002/hep.31776, PMID:33636012.
[42] D'Amato D, De Vincentis A, Malinverno F, Viganò M, Alvaro D, Pompili M, *et al*. Real-world experience with obeticholic acid in patients with primary biliary cholangitis. JHEP Rep 2021;3(2):100248. doi:10.1016/j.jhepr.2021.100248, PMID:33681748.
[43] ter Borg PC, Schalm SW, Hansen BE, van Buuren HR, Dutch PBC Study Group. Prognosis of ursodeoxycholic Acid-treated patients with primary biliary cirrhosis. Results of a 10-yr cohort study involving 297 patients. Am J Gastroenterol 2006;101(9):2044–2050. doi:10.1111/j.1572-0241.2006.00699.x, PMID:16848809.
[44] Patel A, Seetharam A. Primary Biliary Cholangitis: Disease Pathogenesis and Implications for Established and Novel Therapeutics. J Clin Exp Hepatol 2016;6(4):311–318. doi:10.1016/j.jceh.2016.10.001, PMID:28003721.
[45] Chalifoux SL, Konyn PG, Choi G, Saab S. Extrahepatic Manifestations of Primary Biliary Cholangitis. Gut Liver 2017;11(6):771–780. doi:10.5009/gnl16365, PMID:28292174.
[46] Lammers WJ, van Buuren HR, Hirschfield GM, Janssen HL, Invernizzi P, Mason AL, *et al*. Levels of alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with primary biliary cirrhosis: an international follow-up study. Gastroenterology 2014;147(6):1338–1349. doi:10.1053/j.gastro.2014.08.029, PMID:25160979.
[47] Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases. Hepatology 2019;69(1):394–419. doi:10.1002/hep.30145, PMID:30070375.
[48] Nakamura M, Kondo H, Mori T, Komori A, Matsuyama M, Ito M, *et al*. Anti-gp210 and anti-centromere antibodies are different risk factors for the progression of primary biliary cirrhosis. Hepatology 2007;45(1):118–127. doi:10.1002/hep.21472, PMID:17187436.
[49] Ruiz A, Lemoinne S, Carrat F, Corpechot C, Chazouillères O, Arrivé L. Radiologic course of primary sclerosing cholangitis: assessment by three-dimensional magnetic resonance cholangiography and predictive features of progression. Hepatology 2014;59(1):242–250. doi:10.1002/hep.26620, PMID:23857427.
[50] Haliloglu N, Erden A, Erden I. Primary biliary cirrhosis: evaluation with T2-weighted MR imaging and MR cholangiopancreatography. Eur J Radiol 2009;69(3):523–527. doi:10.1016/j.ejrad.2007.11.003, PMID:18313877.
[51] Kawata K, Joshita S, Shimoda S, Yamashita Y, Yamashita M, Kitsugi K, *et al*. The ursodeoxycholic acid response score predicts pathological features in primary biliary cholangitis. Hepatol Res 2021;51(1):80–89. doi:10.1111/hepr.13584, PMID:33080094.
[52] Murillo Perez CF, Harms MH, Lindor KD, van Buuren HR, Hirschfield GM, Corpechot C, *et al*. Goals of Treatment for Improved Survival in Primary Biliary Cholangitis: Treatment Target Should Be Bilirubin Within the Normal Range and Normalization of Alkaline Phosphatase. Am J Gastroenterol 2020;115(7):1066–1074. doi:10.14309/ajg.0000000000000557, PMID:32618657.
[53] Trauner M, Graziadei IW. Review article: mechanisms of action and therapeutic applications of ursodeoxycholic acid in chronic liver diseases. Aliment Pharmacol Ther 1999;13(8):979–996. doi:10.1046/j.1365-2036.1999.00596.x, PMID:10468672.
[54] Tang R, Wei Y, Li Y, Chen W, Chen H, Wang Q, *et al*. Gut microbial profile is altered in primary biliary cholangitis and partially restored after UDCA therapy. Gut 2018;67(3):534–541. doi:10.1136/gutjnl-2016-313332, PMID:28213609.
[55] Achufusi TGO, Safadi AO, Mahabadi N. Ursodeoxycholic Acid. Stat-

Pearls Publishing; 2022. PMID:31424887.
[56] Harms MH, van Buuren HR, Corpechot C, Thorburn D, Janssen HLA, Lindor KD, *et al*. Ursodeoxycholic acid therapy and liver transplant-free survival in patients with primary biliary cholangitis. J Hepatol 2019;71(2):357–365. doi:10.1016/j.jhep.2019.04.001, PMID:30980847.
[57] Bahar R, Wong KA, Liu CH, Bowlus CL. Update on New Drugs and Those in Development for the Treatment of Primary Biliary Cholangitis. Gastroenterol Hepatol (NY) 2018;14(3):154–163. PMID:29928160.
[58] Boberg KM, Wisløff T, Kjøllesdal KS, Støvring H, Kristiansen IS. Cost and health consequences of treatment of primary biliary cirrhosis with ursodeoxycholic acid. Aliment Pharmacol Ther 2013;38(7):794–803. doi:10.1111/apt.12435, PMID:23915021.
[59] Carbone M, Nardi A, Flack S, Carpino G, Varvaropoulou N, Gavrila C, *et al*. Pretreatment prediction of response to ursodeoxycholic acid in primary biliary cholangitis: development and validation of the UDCA Response Score. Lancet Gastroenterol Hepatol 2018;3(9):626–634. doi:10.1016/S2468-1253(18)30163-8, PMID:30017646.
[60] National Institute of Diabetes and Digestive and Kidney Diseases. Obeticholic Acid. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Bethesda; 2012.
[61] Nevens F, Andreone P, Mazzella G, Strasser SI, Bowlus C, Invernizzi P, *et al*. A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis. N Engl J Med 2016;375(7):631–643. doi:10.1056/NEJMoa1509840, PMID:27532829.
[62] Kulkarni AV, Tevethia HV, Arab JP, Candia R, Premkumar M, Kumar P, *et al*. Efficacy and safety of obeticholic acid in liver disease-A systematic review and meta-analysis. Clin Res Hepatol Gastroenterol 2021;45(3):101675. doi:10.1016/j.clinre.2021.101675, PMID:33722778.
[63] Honda A, Ikegami T, Nakamuta M, Miyazaki T, Iwamoto J, Hirayama T, *et al*. Anticholestatic effects of bezafibrate in patients with primary biliary cirrhosis treated with ursodeoxycholic acid. Hepatology 2013;57(5):1931–1941. doi:10.1002/hep.26018, PMID:22911624.
[64] Hegade VS, Khanna A, Walker LJ, Wong LL, Dyson JK, Jones DEJ. Long-Term Fenofibrate Treatment in Primary Biliary Cholangitis Improves Biochemistry but Not the UK-PBC Risk Score. Dig Dis Sci 2016;61(10):3037–3044. doi:10.1007/s10620-016-4250-y, PMID:27435324.
[65] Corpechot C, Chazouillères O, Rousseau A, Le Gruyer A, Habersetzer F, Mathurin P, *et al*. A Placebo-Controlled Trial of Bezafibrate in Primary Biliary Cholangitis. N Engl J Med 2018;378(23):2171–2181. doi:10.1056/NEJMoa1714519, PMID:29874528.
[66] Cançado GGL, Couto CA, Guedes LV, Braga MH, Terrabuio DRB, Cançado ELR, *et al*. Fibrates for the Treatment of Primary Biliary Cholangitis Unresponsive to Ursodeoxycholic Acid: An Exploratory Study. Front Pharmacol 2022;12:818089. doi:10.3389/fphar.2021.818089, PMID:35126149.
[67] de Vries E, Bolier R, Goet J, Parés A, Verbeek J, de Vree M, *et al*. Fibrates for Itch (FITCH) in Fibrosing Cholangiopathies: A Double-Blind, Randomized, Placebo-Controlled Trial. Gastroenterology 2021;160(3):734–743. doi:10.1053/j.gastro.2020.10.001, PMID:33031833.
[68] Kwong AJ, Kim WR, Lake JR, Smith JM, Schladt DP, Skeans MA, *et al*. OPTN/SRTR 2019 Annual Data Report: Liver. Am J Transplant 2021;21(Suppl 2):208–315. doi:10.1111/ajt.16494, PMID:33595192.
[69] Selmi C, Bowlus CL, Gershwin ME, Coppel RL. Primary biliary cirrhosis. Lancet 2011;377(9777):1600–1609. doi:10.1016/S0140-6736(10)61965-4, PMID:21529926.
[70] Moy BT, Birk JW. A Review on the Management of Biliary Complications after Orthotopic Liver Transplantation. J Clin Transl Hepatol 2019;7(1):61–71. doi:10.14218/JCTH.2018.00028, PMID:30944822.
[71] Liberal R, Zen Y, Mieli-Vergani G, Vergani D. Liver transplantation and autoimmune liver diseases. Liver Transpl 2013;19(10):1065–1077. doi:10.1002/lt.23704, PMID:23873751.
[72] Montano-Loza AJ, Hansen BE, Corpechot C, Roccarina D, Thorburn D, Trivedi P, *et al*. Factors Associated With Recurrence of Primary Biliary Cholangitis After Liver Transplantation and Effects on Graft and Patient Survival. Gastroenterology 2019;156(1):96–107. doi:10.1053/j.gastro.2018.10.001, PMID:30296431.
[73] Bosch A, Dumortier J, Maucort-Boulch D, Scoazec JY, Wendum D, Conti F, *et al*. Preventive administration of UDCA after liver transplantation for primary biliary cirrhosis is associated with a lower risk of disease recurrence. J Hepatol 2015;63(6):1449–1458. doi:10.1016/j.jhep.2015.07.038, PMID:26282232.
[74] Sy AM, Ferreira RD, John BV. Hepatocellular Carcinoma in Primary Biliary Cholangitis. Clin Liver Dis 2022;26(4):691–704. doi:10.1016/j.cld.2022.06.011, PMID:36270724.
[75] McGee EE, Castro FA, Engels EA, Freedman ND, Pfeiffer RM, Nogueira L, *et al*. Associations between autoimmune conditions and hepatobiliary cancer risk among elderly US adults. Int J Cancer 2019;144(4):707–717. doi:10.1002/ijc.31835, PMID:30155920.
[76] Natarajan Y, Tansel A, Patel P, Emologu K, Shukla R, Qureshi Z, *et al*. Incidence of Hepatocellular Carcinoma in Primary Biliary Cholangitis: A Systematic Review and Meta-Analysis. Dig Dis Sci 2021;66(7):2439–2451. doi:10.1007/s10620-020-06498-7, PMID:32743773.
[77] Rong G, Wang H, Bowlus CL, Wang C, Lu Y, Zeng Z, *et al*. Incidence and risk factors for hepatocellular carcinoma in primary biliary cirrhosis. Clin Rev Allergy Immunol 2015;48(2-3):132–141. doi:10.1007/s12016-015-8483-x, PMID:25762349.
[78] Tzartzeva K, Obi J, Rich NE, Parikh ND, Marrero JA, Yopp A, *et al*. Surveillance Imaging and Alpha Fetoprotein for Early Detection of Hepatocellular Carcinoma in Patients with Cirrhosis: A Meta-analysis. Gastroenterology 2018;154(6):1706–1718. doi:10.1053/j.gastro.2018.01.064, PMID:29425931.
[79] Trivedi PJ, Lammers WJ, van Buuren HR, Parés A, Floreani A, Janssen HL, *et al*. Stratification of hepatocellular carcinoma risk in primary biliary cirrhosis: a multicentre international study. Gut 2016;65(2):321–329. doi:10.1136/gutjnl-2014-308351, PMID:25567117.
[80] Carbone M, Neuberger J. Liver transplantation in PBC and PSC: indications and disease recurrence. Clin Res Hepatol Gastroenterol 2011;35(6-7):446–454. doi:10.1016/j.clinre.2011.02.007, PMID:21459072.
[81] Imam MH, Silveira MG, Sinakos E, Gossard AA, Jorgensen R, Keach J, *et al*. Long-term outcomes of patients with primary biliary cirrhosis and hepatocellular carcinoma. Clin Gastroenterol Hepatol 2012;10(2):182–185. doi:10.1016/j.cgh.2011.09.013, PMID:21963959.
[82] Siddique O, Yoo ER, Perumpail RB, Perumpail BJ, Liu A, Cholankeril G, *et al*. The importance of a multidisciplinary approach to hepatocellular carcinoma. J Multidiscip Healthc 2017;10:95–100. doi:10.2147/JMDH.S128629, PMID:28360525.