

**Review Article****Natural history of primary biliary cirrhosis**

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The natural history of primary biliary cirrhosis (PBC) has improved significantly over the last two decades. Most patients are diagnosed with asymptomatic PBC (a-PBC). The prognosis of a-PBC is usually better than that of symptomatic PBC (s-PBC). Among a-PBC patients, some remain asymptomatic, whereas others progress to s-PBC. The prognosis of s-PBC is still poor and the main cause of death in PBC is liver failure. Other complications, such as esophageal varices and

hepatocellular carcinoma, also affect the prognosis of PBC patients. Ursodeoxycholic acid treatment improves the prognosis of PBC patients in the early stage. There seems to be several types of PBC progression.

**Key words:** natural history, primary biliary cirrhosis, symptoms

**INTRODUCTION**

**P** RIMARY BILIARY CIRRHOSIS (PBC) is a chronic progressive cholestatic liver disease of presumed autoimmune pathogenesis usually affecting middle-aged women.<sup>1</sup> Histopathologically, PBC is characterized by chronic non-suppurative destructive cholangitis of the intralobular bile ducts and their extensive loss, resulting in the development of severe biliary cirrhosis along with its prolonged clinical course. Substantial variability in the prevalence rates in different countries has been documented.<sup>2,3</sup>

PBC was originally described as being associated with severe progressive cholestasis manifested by jaundice and pruritus, and clinical features of liver failure.<sup>4,5</sup> Over the last few decades, there has been an increased awareness of PBC and with the use of multiphasic biochemical screening as part of routine examination, more patients with asymptomatic PBC (a-PBC) are now diagnosed early and receive treatment at earlier stages.<sup>1</sup> Because of this, the prognosis of PBC has improved.

The natural history of PBC is extremely variable. This article focuses on the natural history, as well as the course and prognostic indicators of PBC.

**ANTIMITOCHONDRIAL ANTIBODY-POSITIVE PATIENTS WITH NORMAL LIVER BIOCHEMISTRY (“LATENT” OR “EARLY” PBC)**

**T** HERE IS ONE small study of liver pathology in 29 asymptomatic antimitochondrial antibody (AMA)-positive patients with normal liver biochemistry and no symptoms of the disease.<sup>6</sup> All but two had abnormal liver histology, and in 12, the findings were diagnostic, indicating that the disease may be present in patients with normal liver biochemistry.

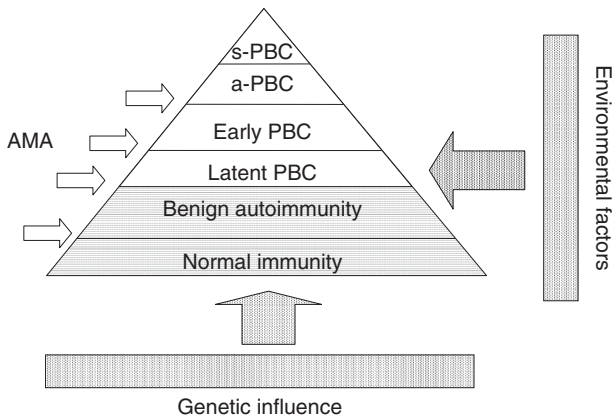
During the follow-up period of 17.8 years, 83% of these patients developed persistent abnormal liver biochemistry and 76% developed symptoms.<sup>7</sup> Liver biopsy repeated in 10 of these patients showed stage progression in four cases; however, no patient developed portal hypertension and cirrhosis. These data indicate that individuals positive for AMA without any clinical and biochemical indications should be considered as having slow progressing PBC.

The prevalence rate of AMA in the general population has been reported to range from 0.07% to 9.9%.<sup>8,9</sup> Shibata *et al.* have reported that 0.64% of Japanese corporate workers are positive for AMA.<sup>9</sup> Because the number of such individuals (estimated at 336 472 people in Japan from 30 to 59 years) seems very large, few people develop recognizable PBC even if they have AMA. This study indicates that genetic and/or environmental factors are also likely to be implicated in PBC etiology.

PBC has been reported in 4–6% of first-degree relatives of PBC patients.<sup>10–13</sup> Recently, Lazaridis *et al.*<sup>14</sup>

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**Figure 1** Proposed model of the evolution of primary biliary cirrhosis (PBC) and the importance of antimitochondrial antibody (AMA). AMA might be useful in clarifying the pathogenic process of PBC, especially in the early stages (marked by unfilled arrows). a-PBC, asymptomatic PBC; s-PBC, symptomatic PBC.

investigated the prevalence of AMA in first-degree relatives of PBC patients in the USA and reported that the prevalence rates of AMA in first-degree relatives and controls were 13.1% and 1%, respectively. Most donors for living-donor liver transplantation (LDLT) are family members, and LDLT has been reported to be associated with a higher rate of recurrent disease than cadaveric donor transplantation.<sup>15,16</sup> The precise importance of serum AMA during the pathogenesis of PBC needs to be ascertained. If serum AMA is a marker of pathogenic autoimmunity, a survey of serum AMA would be helpful in detecting latent or early PBC, especially among family members of PBC patients (Fig. 1).<sup>17</sup>

## ASYMPTOMATIC PBC

WHEN PBC WAS first recognized, all patients were symptomatic. Fox *et al.* first described a-PBC patients in 1973.<sup>18</sup> The same group reported that some a-PBC patients did not develop symptoms until 10 years after their initial presentation.<sup>19</sup> A subsequent study reported that the survival rate of a-PBC patients was similar to that of a normal US population matched for age and sex.<sup>20</sup> A later series, including a longer follow up, however, demonstrated that the mortality rate of a-PBC patients was higher than that of the general population matched by age, sex, and race.<sup>21–23</sup>

In a study of 279 patients observed for up to 24 years by Mahl *et al.*,<sup>22</sup> the median survival time of a-PBC

patients was 16 years, much longer than that of symptomatic PBC (s-PBC) patients (7.5 years). With a median follow-up period of 12.1 years, 33% of a-PBC patients remained symptom free. However, once symptoms developed, the survival rates of both groups were similar. Additional studies confirmed that a-PBC patients had longer survival time than s-PBC patients. More recently, the natural history of a-PBC has been reported in a series of 91 a-PBC patients in Canada.<sup>23</sup> During the observation period, 36% of patients became symptomatic, and the median time interval to the development of symptoms after presentation was 50.6 months. They also confirmed the finding that the survival time was shorter than that of an age- and sex-matched control population.

However, the results of one recent study are not in agreement with those of the studies cited earlier. In a large, community-based study, 469 initially a-PBC patients were observed for up to 28 years in north-east England.<sup>24</sup> The median survival time was similar in the asymptomatic and symptomatic groups. The probability of developing symptoms was estimated to be 50% at 5 years and 95% at 20 years using the Kaplan–Meier analysis.

It is important to consider that there may be a subgroup of a-PBC patients who do not develop symptoms. This group will probably have a survival rate similar to that of the general population. Several groups have tried to identify the factors affecting progression from a-PBC to s-PBC. Nyberg *et al.* studied 56 Swedish patients<sup>25</sup> and suggested that the presence of hepatomegaly or advanced histological stage was predictive of the subsequent development of PBC symptoms. In a study of 37 patients in the USA, the presence of associated autoimmune disorders showed a correlation with decreased survival time.<sup>26</sup> More recently, Springer *et al.*<sup>23</sup> investigated 91 a-PBC patients, but were unable to identify any progressive variables, including associated autoimmune disorders, hepatomegaly, or histological stage, that would distinguish those who would become symptomatic (defined as pruritus, jaundice, hepatic encephalopathy, bleeding varices, edema, or ascites) from those who would remain symptom free. In a national survey in Japan, the serum levels of bilirubin, albumin, and total cholesterol, and histological stage and ursodeoxycholic acid (UDCA) administration were considered useful for predicting the progression to s-PBC (defined as jaundice).<sup>27</sup> By using imaging methods, we have found that the ratio of liver and spleen volumes is one of the important factors for predicting the progression to s-PBC.

There are some discrepancies among previous studies regarding the natural history of a-PBC. One of the possible reasons regarding this is that sample size and observation period were different in these studies. In addition, standardized definitions of a-PBC and s-PBC are yet to be established internationally. For example, pruritus is considered a liver-related symptom of PBC; however, it is a subjective symptom. The exact cause of pruritus is elusive, but this does not seem to be a liver-specific phenomenon in PBC patients. Therefore, the definition of a-PBC varied among the studies.

The condition becomes more confusing in the context of fatigue. Fatigue is one of the major debilitating symptoms in patients with PBC and it compromises the quality of life of the patients with PBC considerably.<sup>28,29</sup> However, fatigue has not been incorporated as a liver-related symptom in the diagnostic criteria of PBC in Japan.

## SYMPTOMATIC PBC

**P**ATIENTS WITH S-PBC show more rapid progression to end-stage liver disease and they have a more severe prognosis than those with a-PBC. The mean survival time after diagnosis varies between 6 and 10 years in most series, and is longer in the latest series published.<sup>30–32</sup> Several clinical, biochemical, and histological features have prognostic significance in PBC, although the serum bilirubin level is the best predictor of survival.<sup>33</sup> After a relatively stable phase, the serum bilirubin level increases rapidly in the month preceding death. Advanced age, a low serum albumin level, prolonged prothrombin time, and the presence of hepatomegaly or cirrhosis have also been reported as factors associated with the poor prognosis of PBC.<sup>34</sup> In addition, the significance of autoantibodies has been proposed by several groups. Among them, the anti-gp210 antibody, which recognizes an integral glycoprotein of the nuclear pore membrane, is highly specific for PBC and is associated with disease severity, and therefore is a marker of poor prognosis.<sup>35–37</sup> Recently, Nakamura *et al.*<sup>38</sup> reported that the presence of anti-gp210 antibody is a significant risk factor for hepatic failure type progression of PBC. In addition, Yang *et al.*<sup>39</sup> reported that antinuclear antibodies in general, and anticentromere antibodies are associated with hepatic failure in PBC. However, other groups did not obtain such data.<sup>40,41</sup>

Several investigators have developed survival models based mainly on clinical, biochemical, and histological features using the Cox proportional hazards regression

model. The Mayo survival model for predicting the survival rate for PBC is one of the most commonly used internationally.<sup>42,43</sup> This model was based on a study of 312 patients using 45 clinical and biochemical variables, and was cross-validated with data from an independent group of 106 patients. The advantage of the Mayo model is that it does not require liver biopsy. The original<sup>42</sup> and updated<sup>43</sup> Mayo model uses five independent prognostic variables: age, serum levels of bilirubin and albumin, prothrombin time, and presence or absence of peripheral edema, including response to diuretic therapy. Based on the results of national surveys of PBC in Japan, four variables were identified as significant independent prognostic factors: age and serum levels of bilirubin, albumin, and cholesterol.<sup>3</sup>

## DEVELOPMENT OF ESOPHAGEAL VARICES

**I**N ADDITION TO the above-mentioned parameters, portal hypertension, particularly esophageal varices, has been regarded as one of the risk factors causing death in patients with PBC. Gores *et al.*<sup>44</sup> reported in 1989 that approximately one-third of patients with PBC developed esophageal varices during follow up (median, 5.6 years), and half of these had episodes of variceal bleeding. They reported that histological stage and serum bilirubin level were predictors of the development of varices. After the development of varices, the 1- and 3-year survival rates were 83% and 59%, respectively. Prognosis became poor once variceal bleeding occurred, with survival rates estimated to be 65% and 46% at 1 and 3 years, respectively.

Although esophageal varices have been regarded as a late complication of PBC, accumulating evidence indicates that portal hypertension is in fact a common consequence of PBC, developing early during the course of the disease. Several pathogeneses of portal hypertension have been suggested, including granulomatous inflammation, resulting in presinusoidal portal hypertension, presinusoidal fibrosis, and nodular regenerative hyperplasia.<sup>45–47</sup> We have recently reported that PBC patients with complications of esophageal varices without other symptoms, such as pruritus or jaundice (defined as a-PBC in Japan when this data was published in 2003), had a poorer prognosis than a-PBC patients.<sup>48,49</sup> We proposed that these patients should be classified under s-PBC; thereafter, the diagnostic criteria of PBC in Japan were revised accordingly in 2004.

Since prognosis becomes poor once variceal bleeding occurs<sup>44</sup> and treating esophageal varices is difficult,<sup>50</sup> several groups have attempted to define non-invasive

predictors of esophageal varices in PBC patients.<sup>51,52</sup> Blessler *et al.*<sup>51</sup> examined 86 PBC patients and reported that platelet count  $<200,000/\text{mm}^3$ , albumin level  $<4.0 \text{ g/dL}$ , and a bilirubin level  $>20 \mu\text{mol/L}$  ( $1.16 \text{ mg/dL}$ ) were independent predictors of the development of esophageal varices. Recently, Levy *et al.*<sup>52</sup> reported that a Mayo risk score (4.5 or greater) and platelet count ( $<140,000/\text{mm}^3$ ) were independent risk factors for the development of esophageal varices in PBC patients. Such PBC patients should be routinely screened for esophageal varices.

## DEVELOPMENT OF HEPATOCELLULAR CARCINOMA

CLASSICALLY, PBC PATIENTS were considered at low risk for developing hepatocellular carcinoma (HCC). However, recent reports have found that PBC is associated with increased risk of HCC. The incidence of HCC in PBC patients was reported to be within 0.7–3.6%.<sup>53–55</sup>

The reported risk factors for HCC in PBC patients were inconsistent; however, age at diagnosis, male sex, and a more advanced histological stage were associated with the development of HCC.<sup>53,55</sup> Recently, several groups have shown that portal hypertension is associated with the development of HCC in PBC patients.<sup>56,57</sup> The precise mechanisms of hepatocarcinogenesis in PBC patients have not yet been clarified, and further studies in larger patient cohorts are required. However, these data indicate that PBC patients who have risk factors should be systemically screened for HCC.

Two groups reported that HCC development in PBC patients was not associated with survival time,<sup>55,56</sup> possibly because its development occurred at an older age in these studies.

## EFFECT OF UDCA TREATMENT ON SURVIVAL TIME

UDCA IS CURRENTLY the only drug approved for treating PBC patients. Many randomized trials, combined analyses of randomized trials, and long-term observational studies have shown that UDCA improves liver function tests<sup>58–60</sup> and delays histological progression<sup>61–63</sup> in PBC patients.

UDCA has also been shown to prolong survival time without liver transplantation.<sup>64–68</sup> Poupon *et al.*<sup>64</sup> reported that UDCA significantly reduced the number of liver transplantations or death in a combined analysis of three randomized trials of 548 patients. The long-term

effect of UDCA has recently been reported in a study of 262 PBC patients.<sup>65</sup> The survival rate without liver transplantation, estimated using a multistate Markov model, was slightly lower than that of an age- and sex-matched control population, but better than that predicted by the updated Mayo model. In this study, they also showed that the survival rate of patients with stages I and II was similar to that of the control population, whereas UDCA did not improve the survival rate in PBC patients with stages III and IV. Recently, Pares *et al.*<sup>66</sup> reported that the biochemical response to UDCA after 1 year is associated with the survival rate in a study of 192 PBC patients. They demonstrated that the survival rate of responders (defined by a decrease in the concentration of alkaline phosphatase to more than 40% of pretreatment or normal levels after 1 year of treatment with UDCA) was significantly higher than that predicted by the Mayo model and similar to that estimated for the control population. By contrast, the survival rate of patients without a biochemical response was lower than that estimated for the control population.

There are some studies questioning the efficacy of UDCA on survival.<sup>69</sup> This discrepancy may be explained by the difference in sample size, histological stage of patients, and observation periods among the studies.

The effect of UDCA treatment on the development of esophageal varices was investigated in a prospective study of 180 PBC patients.<sup>70</sup> They reported that the risk of developing varices was 16% for UDCA-treated patients and 58% for those receiving placebo during the observation period.

## PORTAL HYPERTENSIVE PROGRESSION OF PBC

THE MAIN CAUSE of death in PBC patients is liver failure. However, some groups have recently proposed that some PBC patients show “portal hypertensive type progression”.<sup>38,56</sup>

Nakamura *et al.*<sup>38</sup> reported in 2007 that portal hypertension-type progression was defined as the clinical progression leading to the development of HCC or complications of portal hypertension, including esophageal varices, without developing jaundice (serum bilirubin level  $<1.5 \text{ mg/dL}$ ). They showed that positivity for anti-gp210 antibodies was a significant risk factor for hepatic failure type progression, whereas positivity for anticentromere antibodies was a significant risk factor for portal hypertension-type progression. Unconditional logistic regression analyses showed that positivity for anticentromere antibodies and age were indepen-

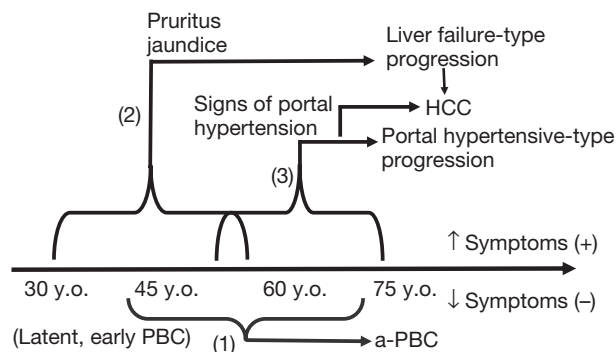
dent risk factors for portal hypertension-type progression. This study indicates that the progression pattern of PBC patients might be predicted by these two types of autoantibody in the early stages (Scheuer's stages 1 and 2). However, positivity for these antibodies is low (26.1%<sup>38</sup>) and some patients show negativity for anti-gp210 antibodies during treatment.<sup>37</sup> Therefore, observation of clinical course is necessary. In addition, the association between the development of esophageal varices and HCC was not evaluated in this study.

In 2006, we<sup>56</sup> defined "portal hypertensive PBC" as the clinical presentation which initially developed esophageal varices without other symptoms. We showed that the incidence of HCC was significantly higher in portal hypertensive PBC patients.

As the definition of portal hypertensive type progression is different between two groups, and the sample size of these studies is small, further studies are necessary to clarify whether this progression type constitutes a subgroup of PBC.

## CONCLUSION

FROM THE REPORTED data, we propose that there are at least three types of progression of PBC (Fig. 2).



**Figure 2** Proposed main progression type of primary biliary cirrhosis (PBC) according to symptoms. (1) Among asymptomatic PBC (a-PBC) patients, some remain asymptomatic. (2) Some patients progress to the symptomatic phase initially developing symptoms, such as pruritus and jaundice, and then liver failure in their 40s–50s (liver failure-type progression). (3) There are some patients whose progression is slow and who initially develop signs of portal hypertension, such as esophageal varices (portal hypertensive-type progression). Some develop hepatocellular carcinoma (HCC) in their 60s–70s.

- 1 Among a-PBC patients (including "latent" or "early" PBC patients), some remain asymptomatic and have a survival rate equal to that of the general population.
- 2 Some patients progress to the symptomatic phase (s-PBC patients); their prognosis becomes poor and they do not respond well to therapy. Most of them develop liver failure in their 40s–50s.
- 3 There are some patients who slowly progress to s-PBC in their 60s–70s, and develop symptoms of portal hypertension, with some finally developing HCC.

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