The natural history of untreated primary biliary cirrhosis (PBC) is one of gradual progression through four phases: preclinical, asymptomatic, symptomatic (including systemic and portal hypertensive), and liver insufficiency. Box 1 describes the features of each of these phases. The preclinical phase is characterized by antimitochondrial reactivity in the serum immunoglobulins and on the surface of biliary epithelium. Patients then develop abnormal serum liver tests but remain asymptomatic for many years. Eventually, however, most untreated patients will develop symptoms, including systemic symptoms, such as fatigue and pruritus, and symptoms of portal hypertension, such as varices, ascites, and peripheral edema. A state of liver insufficiency follows, with progressive jaundice, hepatic encephalopathy, and liver failure.

The duration of each phase varies individually; in fact, rarely the two symptomatic phases may be skipped entirely [1]. However, in most patients, the phases are successive. Patients who are diagnosed in the symptomatic phases are sometimes younger than those who present in the asymptomatic phase [2,3], illustrating that some patients must have more rapid progression than others. Predicting the clinical course of a given patient is often difficult, if not impossible. Most so-called “natural history” studies combine both treated and untreated patients and also differ slightly in their own definition of symptomatic, particularly in whether they include the symptom of fatigue. However, the estimated average time from first appearance of AMA to death is approximately 20 to 22 years without treatment [4,5]. Prolonged follow-up of patient cohorts has shown that even those diagnosed in the asymptomatic phase will eventually develop fatigue, pruritus, and portal hypertension and have a decreased survival compared with the general population [3,6,7].
The earliest known manifestation of PBC is the appearance of antimitochondrial reactivity in the serum immunoglobulins and on the surface of biliary epithelial cells. Liver histology in patients who are positive for serum antimitochondrial antibodies (AMAs) through high titer indirect immunofluorescence, but who have neither elevation of serum liver tests nor symptoms of liver disease, is usually diagnostic of or compatible with early PBC [5,8]. A longitudinal follow-up study of 29 untreated preclinical patients assessed every year from first-detected AMA for a mean of 18 years showed that 24 (83%) developed cholestatic liver tests and 22 (76%) developed fatigue and/or pruritus. The median time to progression from AMA positivity to persistently abnormal liver enzymes was 5.6 years (range, 1–20 years) [5]. Whether all patients who test positive for AMA, particularly those who test positive by the more sensitive enzyme-linked immunosorbent assay (ELISA) technology, will eventually develop clinical disease is unknown because sufficient prospective follow-up is lacking. However, that they will all develop clinical manifestations of PBC seems unlikely because the prevalence of AMA in the general population is so high and some seem to be from other causes. In Italy, 0.5% of the population tested positive for AMAs using an MIT3-based ELISA, which detects specific antibodies to PDC-E2, BCOADC-2, or OGDC-2 [9]. In a recent survey performed at Mayo Clinic, 1% of healthy controls had anti–PDC-E2 antibodies [10]. Of patients who have recurrent urinary tract infections, 52% will test positive for anti–PDC-E2, which is probably because of cross-reactivity with Escherichia coli mitochondrial antigens [11]. In addition, 46% of patients who have acute liver failure from various non-PBC causes have transient reactivity to MIT3, which is likely produced during the immune-protective response to oxidative stress-induced liver damage [12].

### Box 1. Clinical phases of primary biliary cirrhosis

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Asymptomatic</th>
<th>Symptomatic</th>
</tr>
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<tbody>
<tr>
<td>AMA reactivity in serum and/or biliary epithelium</td>
<td>Elevated liver tests</td>
<td>Systemic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fatigue, pruritus</td>
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<tr>
<td></td>
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<td>Portal hypertensive</td>
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<tr>
<td></td>
<td></td>
<td>Varices, ascites, peripheral edema</td>
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<tr>
<td></td>
<td></td>
<td>Liver insufficiency</td>
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<tr>
<td></td>
<td></td>
<td>Progressive jaundice, hepatic encephalopathy, liver failure</td>
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</tbody>
</table>

**Preclinical phase**

The earliest known manifestation of PBC is the appearance of antimitochondrial reactivity in the serum immunoglobulins and on the surface of biliary epithelial cells. Liver histology in patients who are positive for serum antimitochondrial antibodies (AMAs) through high titer indirect immunofluorescence, but who have neither elevation of serum liver tests nor symptoms of liver disease, is usually diagnostic of or compatible with early PBC [5,8]. A longitudinal follow-up study of 29 untreated preclinical patients assessed every year from first-detected AMA for a mean of 18 years showed that 24 (83%) developed cholestatic liver tests and 22 (76%) developed fatigue and/or pruritus. The median time to progression from AMA positivity to persistently abnormal liver enzymes was 5.6 years (range, 1–20 years) [5]. Whether all patients who test positive for AMA, particularly those who test positive by the more sensitive enzyme-linked immunosorbent assay (ELISA) technology, will eventually develop clinical disease is unknown because sufficient prospective follow-up is lacking. However, that they will all develop clinical manifestations of PBC seems unlikely because the prevalence of AMA in the general population is so high and some seem to be from other causes. In Italy, 0.5% of the population tested positive for AMAs using an MIT3-based ELISA, which detects specific antibodies to PDC-E2, BCOADC-2, or OGDC-2 [9]. In a recent survey performed at Mayo Clinic, 1% of healthy controls had anti–PDC-E2 antibodies [10]. Of patients who have recurrent urinary tract infections, 52% will test positive for anti–PDC-E2, which is probably because of cross-reactivity with Escherichia coli mitochondrial antigens [11]. In addition, 46% of patients who have acute liver failure from various non-PBC causes have transient reactivity to MIT3, which is likely produced during the immune-protective response to oxidative stress-induced liver damage [12]. Serial assessments of
more of the “AMA-positive-only” individuals over a span of 10 to 20 years are needed to determine the specificity of AMA as a predictor of clinical PBC.

**Asymptomatic phase**

The asymptomatic phase is characterized by persistently abnormal liver enzymes in the absence of any symptoms. The earliest laboratory abnormalities may be very mild elevations in aspartate aminotransferase or alanine aminotransferase, but this progresses rather quickly to a cholestatic pattern of predominantly elevated alkaline phosphatase and gamma glutaryl transferase. A transient and slight eosinophilia may also be seen. With the widespread use of multichannel automated chemistry, an incidental elevated alkaline phosphatase is often the modern stimulus for a workup that leads to a diagnosis of PBC. Most patients who have PBC are now diagnosed in the asymptomatic phase. In a large geographic cohort of 770 patients who had PBC diagnosed between 1987 and 1994 in the United Kingdom, 61% presented in the asymptomatic phase [13].

A longitudinal study of 37 untreated patients in the asymptomatic phase found that 89% developed symptoms (eg, fatigue, pruritus, portal hypertension, jaundice) within 2 to 4 years and that their survival was shorter than a control population in the United States [14]. Other studies have reported longer asymptomatic periods but have still found that asymptomatic patients have shorter overall survival than control populations. At Yale University, 36 asymptomatic patients who had primary biliary cirrhosis were followed up for a median of 12.1 years. Over this period, 67% developed signs or symptoms of progressive disease (eg, fatigue, pruritus, ascites, encephalopathy, variceal bleeding, jaundice), but 33% remained without symptoms [6,15].

A larger, more recent retrospective review from University of Toronto of 91 asymptomatic patients, 24% of whom were treated with ursodeoxycholic acid (UDCA), found that 36% became symptomatic and 11% died or underwent liver transplantation over a median follow-up of 5 years. Survival of this entire group was still less than that predicted for an age- and gender-matched control population. However, only patients who developed symptoms had shortened survival; those who remained asymptomatic survived as long as the matched control population (Fig. 1). Unfortunately, the univariate and multivariate analysis on various clinical, biochemical, and histologic features failed to identify any prognostic variables that could distinguish those who would become symptomatic from those who would remain symptom-free [3]. This study indicated that the presence of cirrhosis at baseline was not associated with the symptomatic stage, and did not predict the development of symptoms in those who had cirrhosis and no symptoms for the duration of this study (15 years).
Symptomatic phase

The symptomatic phase can be subdivided into symptoms that are systemic and those that are caused by portal hypertension. Typically the systemic symptoms of fatigue and pruritus begin years before evidence of portal hypertension appears, although this rule certainly has exceptions.

Systemic symptoms

Fatigue

Although fatigue is the most commonly reported symptom of PBC, it has only recently begun to be studied in a careful manner, and its natural history is still not well understood. The severity of fatigue in a 4-year longitudinal study was very stable overall; only transplant recipients experienced a significant improvement in fatigue [12]. Fatigue in that study was also found to be an independent predictor of mortality in multivariate analysis, particularly cardiac death [16].

Pruritus

In a population-based study of 770 patients from England who had PBC, the cumulative risk for developing pruritus was 19%, 45%, and 57% at 1, 5, and 10 years, respectively [13], and was 13%, 31%, and 47% in the subset of previously asymptomatic patients [17]. Once present, pruritus follows a daily circadian rhythm, being more intense in the evenings [18]. Although the severity and presence of pruritus fluctuates from day to day, it does not usually disappear permanently unless effective therapy is started or, paradoxically, severe liver insufficiency develops [19]. UDCA seems to have little
effect on established pruritus, although trends toward lower incidence rates in patients treated with UDCA have been noted in clinical trials [20].

Abdominal pain is another symptom reported by approximately 17% of patients who have PBC, but it does not seem to be a symptom related to disease progression. The origin and natural history of abdominal pain was described in 31 patients enrolled in a randomized trial of UDCA. The causes found included asymptomatic cholelithiasis in four patients, esophageal erosions in one, gastric erosions in four, a gastric ulcer in one, and duodenal erosions in two. No apparent cause was found in 14 patients, and age, histologic stage, gender, and liver biochemistries was similar among patients who had pain and those who did not. Pain usually resolves gradually: 33% of patients had pain persisting at 1 year and only 20% had pain persisting after 2 years [21]. Hepatomegaly, although technically a sign rather than a symptom, has also been included in some studies as a marker of the symptomatic phase.

**Portal hypertensive symptoms**

In the 2002 report of symptom development in 770 patients who had PBC, ascites was present in 20% and bleeding varices in 10.5% after 10 years of follow-up [13]. The outlook of patients who develop these complications is abridged. Occasionally, varices have been reported to develop in PBC before histologic cirrhosis can be documented. This occurrence is believed to be caused by either nodular regenerative hyperplasia or intense periportal inflammation and carries a better prognosis. However, it is uncommon, and new portal hypertension in most patients who have PBC is an ominous sign. In 143 patients who first developed ascites (n = 111) or peripheral edema (n = 32), the mean time to death was 3.1 years [22].

**Liver insufficiency phase**

The liver insufficiency phase is characterized by worsening jaundice and is a preterminal phase, lasting up to 4 years [23]. Mean survival once the bilirubin is 2.0 mg/dL is 4 years, and when the bilirubin reaches 6.0 mg/dL, mean survival is only 2 years [24]. Encephalopathy, when it occurs, is usually during this phase. Pruritus, alkaline phosphatase, and cholesterol may all paradoxically improve in the preterminal stage. The risk for hepatocellular carcinoma in patients who have PBC is also increased compared with healthy individuals [25]. This risk is almost exclusively limited to patients with advanced disease and is higher for men, in whom incidences as high as 20% have been reported [26].

**Histologic progression**

Histologic progression occurs concurrently with clinical progression, but not necessarily at the same rate. For example, asymptomatic patients may
be cirrhotic, and some patients who have a rapid ductopenic form of disease develop marked jaundice and a need for transplantation without cirrhosis. The chronologic continuum of histologic changes is illustrated in Fig. 2. Early changes consist of portal inflammation with nonsuppurative destructive cholangitis. The inflammation is predominantly lymphocytic, but significant numbers of plasma cells and eosinophils may also be seen. Portal granulomas may also be seen in early disease and are called a florid duct lesions when a bile duct is involved. This signature lesion of PBC, however, is sometimes hard to capture on a biopsy specimen particularly if the specimen contains fewer than 10 portal tracts. Interface hepatitis, traditionally believed to be a prominent feature of autoimmune hepatitis, is also characteristic of the middle stages of PBC and, in fact, is associated with more aggressive disease [27]. With the ongoing destruction of native bile ducts, other cells at the edge of the portal tracts begin to undergo ductular proliferation to create new “pseudoducts,” which are often associated with scattered polymorphonuclear cells. These pseudoducts may also undergo epithelial–mesenchymal transition and contribute to fibrogenesis. Pseudoducts, however, are not as effective as native ducts at draining bile from the liver, and liver damage continues. Affected hepatocytes may appear foamy, called cholate stasis. Fibrosis extends progressively in an arborizing pattern: first periportal, then branching out of the portal tracts, then bridging adjacent portal tracts, and finally surrounding irregular jigsaw-shaped nodules of hepatocytes. Eventually the inflammation subsides and a cirrhotic liver remains, with variable degrees of ductopenia and dysfunction.

This sequence of events is conveniently divided into 4 histologic stages (see Fig. 2), and the transition rates between histologic stages have been

![Histological Progression of Primary Biliary Cirrhosis](image-url)

Fig. 2. Progression of histologic changes in primary biliary cirrhosis.
calculated using Markov modeling [27,28]. In a large randomized trial of D-penicillamine, which was found to have no effect on histologic progression, the mean increase in histologic stage was one stage every 1.5 years. After 4 years, 31% of patients whose initial biopsy showed stage 1 had progressed to cirrhosis, and 50% of patients who started in stage 2 had progressed to cirrhosis [28].

Markers of progression

Because some patients will have a relatively slow, benign clinical course and others will progress more rapidly to portal hypertension and liver insufficiency, the ability to identify surrogate markers of disease progression is extremely important. A broad spectrum of clinical, serologic, histologic, and genetic markers have been proposed, as listed in Box 2.

<table>
<thead>
<tr>
<th>Box 2. Prognostic markers of disease progression</th>
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<tbody>
<tr>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td>Varices(^a)</td>
</tr>
<tr>
<td>Ascites(^a)</td>
</tr>
<tr>
<td>Peripheral edema(^a)</td>
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<tr>
<td>Age(^a)</td>
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<tr>
<td>Encephalopathy</td>
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<tr>
<td>Hepatomegaly</td>
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<tr>
<td><strong>Serologic</strong></td>
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<tr>
<td>Bilirubin(^a)</td>
</tr>
<tr>
<td>Low albumin(^a)</td>
</tr>
<tr>
<td>Prothrombin time(^a)</td>
</tr>
<tr>
<td>Hyaluronic Acid</td>
</tr>
<tr>
<td>Procollagen II</td>
</tr>
<tr>
<td>Tissue Inhibitor of metalloproteinase 1</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
</tr>
<tr>
<td>Low platelet count</td>
</tr>
<tr>
<td>AST</td>
</tr>
<tr>
<td>Anti-PML</td>
</tr>
<tr>
<td>Anti- SP100</td>
</tr>
<tr>
<td><strong>Histologic</strong></td>
</tr>
<tr>
<td>Piecemeal necrosis</td>
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<tr>
<td>Fibrosis(^a)</td>
</tr>
<tr>
<td><strong>Genetic</strong></td>
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<tr>
<td>Apolipoprotein A(^3)(^4)</td>
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<td>TNF-(^{a}) promoter 2</td>
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</tbody>
</table>

\(^a\) Independent predictors of survival.
Unsurprisingly, clinical evidence show that portal hypertension and liver insufficiency are linked to poorer survival. The degree of histologic fibrosis is an independent predictor of survival, although some physicians and patients hesitate to undertake the risks of a liver biopsy performed for prognostic purposes. Of the serum tests widely available, serum bilirubin is the single most useful predictor of clinical outcome, although it does not become elevated until later in the disease process. Serum fibrosis markers, including hyaluronic acid, procollagen III, and tissue inhibitor of metalloproteinase, have the advantage of being noninvasive and rising earlier in the disease process. Liver stiffness also predicts the presence of histologic fibrosis with good accuracy (AUROC of 0.92) but has not yet been evaluated independently as a predictor of PBC progression [29].

Presence of antinuclear antibodies, specifically anti-SP100 and anti-PML, is associated with more advanced disease [30,31], and piecemeal necrosis on biopsy has also been linked to a more aggressive course. Antinuclear antibodies through indirect immunofluorescence and piecemeal necrosis are diagnostic criteria for autoimmune hepatitis, suggesting that patients who have features of PBC and autoimmune hepatitis may be in at higher risk for progression. In fact, over 6 years of follow-up, 26 patients who had PBC who also met International Autoimmune Hepatitis Group (IAHG) criteria for autoimmune hepatitis showed a higher rate of portal hypertension, esophageal varices, gastrointestinal bleeding, ascites, and death and/or liver transplantation compared with 109 patients who did not meet IAHG criteria [32].

Recent investigations have begun to identify genetic polymorphisms that may be associated with more severe disease, including apolipoprotein ε4 and TNF-α promoter 2 [33,34]. Each of these associations is weak, indicating that multiple individual polymorphisms probably make up the genetic profile of individuals susceptible to more aggressive disease.

The need to apply these markers to appropriately time liver transplantation, analyze clinical trial outcomes, and provide patient counseling has led to the development of several mathematical models that combine these markers to estimate survival, including the Mayo, Newcastle, European, Oslo, and Barcelona risk scores [35–37]. Of these, the Mayo Risk Score is the most popular because it has been extensively validated in external populations, including patients on UDCA and patients awaiting transplantation [38,39]. The Mayo Risk Score incorporates serum bilirubin, age, albumin, prothrombin time, and presence of ascites or edema but does not require liver histology. Time-independent Cox models have several limitations, including selection bias of the population used to derive the model, selection bias of the time at which the patients are evaluated, reduced accuracy in individuals as opposed to large groups, and the fact that they use variables derived at only one time point [40]. However, the original Mayo Risk Model has been updated to use serial data in a time-dependent Cox model, with improved prediction of survival in individual patients who have PBC.
awaiting liver transplantation [39]. In other populations, the use of bilirubin alone or ascites alone [22,41] is as useful as using the complete Mayo Risk formula. A reliable prognostic marker of progression from asymptomatic to symptomatic disease is still needed.

**Impact of ursodeoxycholic acid on natural history**

The prognosis of patients diagnosed with PBC has improved significantly over the past 2 decades. This improvement has two simultaneous potential reasons, and the relative contribution of these factors has not been elucidated. First, more patients are being diagnosed earlier in the disease process (lead-time bias). Second, more patients are being treated with UDCA, and indirect evidence shows that UDCA slows the disease progression from early to late disease. The evidence is indirect because the therapeutic effect of UDCA can only be measured when patients are started on medication in the early phases (histologic stages I and II) and treated long enough to document lack of progression to portal hypertension, liver insufficiency, or death. Unfortunately, no randomized trials have continued the placebo arm long enough with sufficient numbers of patients who have early phase disease to allow a direct comparison of mortality rates between patients who had undergone long-term treated and those who were untreated. However, patients started on UDCA in early-phase disease are less likely to develop varices [42] or ascites [43], and also live longer than would be predicted by the Mayo prognostic R score model [41–45]. Pares and colleagues [46] showed that the subgroup of patients who had PBC who had a biochemical response to UDCA (decrease to $\leq 40\%$ of baseline or to normal range) had a survival rate that was higher than predicted by the Mayo model and similar to a historical control population. Although the limitations of prognostic models and historical placebo cohorts are well known and should be considered, class I (ie, large, randomized trial) evidence is unlikely to ever be collected given the ethical dilemma and expense of continuing a placebo arm in a large cohort of patients who have early disease for 10 to 15 years. Current available data indicate that UDCA, when started early, slows the natural history of clinical and histologic disease progression. The Spanish trial of 192 patients randomized to UDCA or placebo showed that UDCA prevented histologic progression [47]. Combined results of four large randomized UDCA trials ($N = 367$) also showed that significantly less histologic progression occurred from stages 1 and 2 to 3 and 4 in patients treated with UDCA compared with placebo [48]. No effect was measurable in patients already in stage 3 and 4. Likewise, patients in the liver insufficiency phase do not experience benefit from UDCA and should be considered for transplantation.

After transplantation, PBC may recur in the allograft. Few data are available on the natural history of recurrent PBC, but data suggest that the course is slowly progressive, just like PBC in the native liver. In one
study, 2 of 17 patients who had recurrent PBC posttransplantation progressed to septal fibrosis (stage 3) during 5 years of follow-up [49]. In another study, 12 of 13 patients were still stage 1 or 2 after 5 years, but one had developed early cirrhosis [50]. Despite these reported cases of histologic fibrosis in posttransplantation PBC, progression to the symptomatic and portal hypertension phases is extremely rare. Thus, retransplantation for recurrent PBC is an anomaly.

Summary

Primary biliary cirrhosis is an insidious disease that progresses through the clinical phases: preclinical, asymptomatic, symptomatic, and liver insufficiency. The preclinical phase is characterized by AMA reactivity only. Then patients develop biochemical abnormalities but remain asymptomatic, followed by the development of symptoms, usually fatigue and pruritus and later varices, edema, or ascites. Liver insufficiency is characterized by accelerated jaundice and has a poor prognosis. The outlook of patients diagnosed with PBC has improved significantly over the past 2 decades because more patients are being diagnosed earlier in the disease process and being treated with UDCA. Indirect evidence shows that UDCA slows disease progression when given early. PBC may recur in a transplanted liver but it is characterized by slow progression and retransplantation is hardly necessary. A need remains to better define and predict the course of symptomatic and asymptomatic patients on and off UDCA to better evaluate outcomes of clinical trials.

References


