Primary biliary cirrhosis (PBC) is a chronic progressive cholestatic liver disease of presumed autoimmune pathogenesis that usually affects middle-aged women and eventually leads to liver failure and the need for liver transplantation [1]. Probably the incidence and certainly the prevalence of PBC have increased in recent years [2–5], maybe because most of the patients are diagnosed in the early and asymptomatic phases of the disease, showing only abnormal liver biochemistry or antimitochondrial antibodies (AMA) during a routine checkup or a laboratory examination because of an associated disorder. The prevalence of asymptomatic forms has dramatically increased in the last two decades, as fewer than 20% of patients were asymptomatic in the earlier large series [6–8], whereas the prevalence of asymptomatic disease is as high as 61% in the latest series published [9].

PBC is characterized by the destruction of the small intrahepatic bile ducts, portal inflammation, and progressive fibrosis [10–12]. The disease was originally described as being associated with severe progressive cholestasis manifested by jaundice, xanthomata, pruritus, melanodermia, and clinical features of portal hypertension and liver failure [7,8,13,14]. The spectrum of the disease has changed markedly in the last few decades [15], and currently the typical patient with PBC is a middle-aged woman without symptoms or with only fatigue and itching [16–18]. The biochemical tests of the liver reveal a cholestatic pattern with elevated alkaline phosphatase and gamma-glutamyl transferase levels, and mild hypertransaminasemia without evidence of mechanical obstruction on abdominal ultrasonography. Most patients have normal bilirubin levels at diagnosis [9].

PBC may be present even in patients with normal biochemistry and showing only AMA [19]. It was reported that the majority of a cohort of AMA positive patients with normal liver biochemistry and no symptoms of liver disease had liver histology compatible or diagnostic of PBC. Moreover, most of these patients later developed liver biochemical abnormalities and symptoms attributable to PBC, including fatigue, pruritus, and right upper-abdominal discomfort [20]. The development of clinical and biochemical features of PBC thus indicates that a silent disease may be present even when only AMA and typical or compatible damage in the liver biopsy are present.

The course of the disease can be divided into three time periods: (1) an asymptomatic phase, probably lasting for up to 20 years; (2) a symptomatic phase, in which the patient remains anicteric or mildly jaundiced, lasting for up to 5 to 10 years; and (3) a short-lasting preterminal phase, characterized by a severe jaundice [13,21,22]. The asymptomatic phase also includes the silent form. This article focuses on the natural history of the different clinical
presentations of the disease, early or silent, asymptomatic and symptomatic, as well as the
course and the prognostic indicators of the disease.

**Silent primary biliary cirrhosis**

The hallmarks for the diagnosis of PBC are an elevation of the alkaline phosphatase
levels, high titers of AMA in serum, and a liver biopsy showing the typical chronic,
nonsuppurative, destructive cholangitis or changes compatible with PBC. This liver damage
can be observed in patients completely free of symptoms, and AMA may be the only
laboratory abnormality. In this respect, one study reported 29 patients who were AMA positive
with normal liver biochemistry and no symptoms of liver disease. The liver histology was
compatible or diagnostic of PBC in 22, thus indicating that the disease may be present in
patients with normal liver biochemical tests [19]. During the extensive follow-up of these
patients, 83% developed biochemical abnormalities, and 76% developed symptoms
attributable to PBC. The median follow-up time from the first positive AMA test to persistently
abnormal liver tests was 5.6 years, with a range between 0.9 to 19 years. The liver biopsy
repeated in 10 of the patients showed stage progression in four cases, although none of the
patients developed cirrhosis during the follow-up [20]. The rate of histologic progression of the
liver disease was very low and substantially slower than that reported in other series [17,22–
24]. No other series of patients with such features of normal liver tests and AMA has been
published, but there are individual cases with these characteristics, which indeed have
histological features diagnostic or compatible with PBC. Based on these data, patients with
AMA as the only abnormality should be considered as having definite PBC; however, there is
not sufficient information to sustain whether these patients may represent a particular subset
of a less aggressive form of the disease.

**Asymptomatic biliary cirrhosis**

Asymptomatic PBC was first described in 4 patients by Fox et al in 1973 [25]. Later the
same group reported a series of 20 asymptomatic patients, and showed that some of them
had not developed symptoms up to 10 years after initial presentation [26]. Other reports
during the following years indicated that asymptomatic PBC was not as unusual as expected
[7,27–31]. Asymptomatic patients tend to be first diagnosed at an older age than those with
symptomatic disease [32], thus suggesting that those who have asymptomatic disease are
not necessarily in a presymptomatic phase.

In one of the first larger cohorts of patients with PBC, it was reported that the survival
of asymptomatic PBC was similar to that of the age and sex-matched population, thus the
authors concluded that experimental medical therapy was not indicated in these patients [33].
Later series including a longer follow-up, however, demonstrated that the mortality rate of
asymptomatic patients is higher than that of a general population matched by age, gender,
and race [34–39]. In this regard, in one study involving 37 asymptomatic patients, 89%
developed symptoms of liver disease after a median follow-up of 7.6 years. Moreover, 15
patients developed esophageal varices, and 67% of the precirrhotic patients developed
histological cirrhosis [33]. Other studies have also established that survival is lower in
asymptomatic patients with PBC than in the general population. In the study by Mahl et al
[36], the median survival of patients with asymptomatic PBC was 16 years, much longer than
the median survival for patients presenting with symptoms (7.5 years). Once symptoms
developed, the survival of both groups of patients were similar. More recently, the natural
history and the prognostic factors of asymptomatic PBC have been reported in a series of 99
asymptomatic PBC patients from Canada, with a median follow-up of over 5 years (range 7 to
206 months) [40]. During the observation period, 36% of the patients became symptomatic,
and the median time interval to the development of symptoms after presentation was 50.6
(3.5 to 156.8) months. Symptoms were mainly pruritus and jaundice, but some patients
developed ascites, edema, variceal bleeding, and hepatoma as the first clinical features of
the liver disease. There were no differences at diagnosis between patients who developed
symptoms and those who remained asymptomatic. The median estimated length of survival
of the entire study population from disease onset was 14 years. The overall survival was
shorter than for an age- and gender-matched control population (Fig. 1). Patients who
remained asymptomatic, however, had a survival equal to that of the general population (Fig.
2). There were 10 deaths or transplants observed in the cohort of patients during the follow-
up period, compared with 3.48 expected deaths, resulting in a standardized mortality ratio of
2.87. Nine of these deaths (or transplants), all liver-related, occurred in the patients who
became symptomatic. The median length of survival for those who became symptomatic was
7.5 years after the onset of symptoms.

![Fig. 1. Kaplan-Meier life table analysis of survival for the entire study population and an age and gender-matched control population (P<0.05). (From Springer J, Cauch-Dudek K, O'Rourke K, Wanless IR, Heathcote EJ. Asymptomatic primary biliary cirrhosis: a study of its natural history and prognosis. Am J Gastroenterol 1999;94:47–53; with permission.)](image1)

![Fig. 2. Kaplan-Meier life table analysis of survival for those patients who remained asymptomatic and those who developed symptoms, compared with an age and gender-matched control population. (From Springer J, Cauch-Dudek K, O'Rourke K, Wanless IR, Heathcote EJ. Asymptomatic primary biliary cirrhosis: a study of its natural history and prognosis. Am J Gastroenterol 1999;94:47–53; with permission.)](image2)

Univariate and multivariate analysis on a broad spectrum of clinical, biochemical, and
histological features at the time of initial presentation failed to reveal any prognostic variables
that would distinguish patients who would become symptomatic from those who would
remain symptom-free [40]. These data are in contrast with other studies, which observed that
histological stage, serum bilirubin, autoimmune disorders, hepatomegaly, and hepatic
granuloma are prognostic variables in asymptomatic PBC patients [31,32,34]. The
differences among series may be explained by the numbers of asymptomatic patients
included and the criteria for symptom-free disease used in the different studies. At present,
however, it should be considered that the length of survival for patients with asymptomatic
PBC is shorter than for the general population, but in patients who develop symptoms after
diagnosis, survival after the onset of symptoms is equal to that of patients who initially present with symptomatic disease [32,39]. It is important to consider that there may be a subgroup of asymptomatic patients with PBC who do not go on to develop symptoms. This group will probably have a survival similar to that of the general population. Unfortunately, there are no identifiable features that distinguish the asymptomatic population who will remain symptom-free from those who will develop symptoms. Therefore, the course of the disease cannot be predicted in an individual patient with asymptomatic PBC, because some of these patients may suddenly develop symptomatic progressive disease with severe cholestasis and liver failure, whereas others may remain asymptomatic for long periods of time [31].

**Symptomatic biliary cirrhosis**

Patients with symptomatic PBC show a more rapid progression to end-stage liver disease and they have a worse prognosis than that observed in asymptomatic patients. The symptomatic disease usually progresses slowly, however, and the clinical and biochemical manifestations of cholestasis may remain unchanged over several years [13,22,33]. In the late phase of the disease, serum bilirubin levels usually increase and clinical features of liver failure and portal hypertension may develop, particularly ascites and hepatic encephalopathy [21,22]. Hypoalbuminemia and prolonged prothrombin time also appear at the late phase of the disease, as does a fall in serum lipid and cholesterol levels. The other biochemical and immunological tests tend to remain stable or with minor changes. Xanthomas and pruritus may disappear or diminish in the final phases of PBC [13,22]. The histological stage also tends to advance slowly, but some patients who die with liver failure or who are transplanted may have no evidence of established cirrhosis. In this respect, Vleggaar et al have recently observed that there is a subgroup of PBC patients with profound cholestasis and jaundice with no evidence of substantial fibrosis or cirrhosis [41]. These patients are mainly ductopenic, they develop severe jaundice a few years after diagnosis of the disease without signs of portal hypertension, and the liver biochemistry reflects intact protein synthesis. Liver transplantation for treating progressive weight loss and the consequences of malabsorption should be considered in this premature ductopenic variant of PBC.

The mean survival time after diagnosis varies between 6 to 10 years in most series [9,13,22,23], and is longer in the latest series published, probably because the authors included larger number of patients diagnosed in earlier stages of the disease. Several clinical, biochemical, and histological features have prognostic significance in PBC (Table 1), although bilirubin level is the best predictor of survival [21], as this biochemical parameter enters in all the mathematical models that have been developed to find prognostic factors in PBC [9,35,38,42–47]. Advanced age, low serum albumin, prolonged prothrombin time, elevated alkaline phosphatase and immunoglobulin levels [22], hepatomegaly, edema, ascites, encephalopathy, and centrilobular cholestasis or cirrhosis on liver biopsy are features that have also been associated with poor prognosis of PBC. These variables are included in different prognostic models of survival in PBC. In advanced cases, the development of ascites and hepatic encephalopathy as manifestations of liver failure indicates a very poor prognosis [38]. Patients usually die within a short period of time, particularly if they develop encephalopathy. Male gender probably also represents bad prognosis, because males are diagnosed in advanced stages of the disease [38], although in some studies the actuarial survival probability was not significantly different between men and women [9]. Increased serum procollagen type III peptide [48,49] and serum levels of hyaluronate [50] also have
prognostic significance in PBC, as does the presence of granulomas in the liver [51]. The former parameters, as markers of liver fibrosis or fibrogenesis, are associated with bad prognosis, whereas granulomas correlate with good prognosis, probably because this particular lesion is more frequently seen in early stages of PBC.

As expected, and because patients with late stages of PBC (stages III and IV) experience portal hypertension, the advanced histological stage is associated with poor prognosis, and indeed histological stage is an independent predictor of survival in a number of natural history models [22,33,42]. In a recently published paper, aimed to assess the incidence of cirrhosis in patients treated with ursodeoxycholic acid (UDCA) and to determine the predictive factors of cirrhosis development under this treatment, Coperchot et al found that the independent factors of cirrhosis development were serum bilirubin greater than 17 ?M, serum albumin less than 38 g/L, and moderate to severe lymphocytic piecemeal necrosis in the liver biopsy [52]. Because this liver lesion is common in autoimmune hepatitis and chronic viral hepatitis, the authors suggest that the PBC patients with this specific damage may in fact have autoimmune hepatitis or an overlap syndrome. Other studies, however, have shown similar survival in patients with PBC and a possible overlap syndrome and in those with only features of PBC [53]. Other indices of overall hepatic function such as galactose elimination capacity [54] and indocyanine green clearance [55] have also been pointed out as a prognostic indices in patients with PBC.

Development of esophageal varices occurs approximately in one third of the patients with PBC during their follow-up [56,57]. They can be found in some patients with moderate to severe inflammation in the liver biopsy and without cirrhosis, because portal hypertension may be present in early stages of PBC [58–60]. The clinical course of these patients with PBC developing esophageal bleeding, however, seems to be better than that observed in patients with liver cirrhosis due to other etiologies, particularly alcoholic cirrhosis [61]. The rate of development of esophageal varices in patients with PBC has been reported in one study from the Mayo Clinic. During a median period of 5.6 years, 83 of the 256 PBC patients developed esophageal varices [57]. Histological stage of the disease was the most significant predictor of variceal development, followed by serum bilirubin level. Two thirds of the patients who developed esophageal varices had upper gastrointestinal bleeding, and 48% had a proven episode of variceal bleeding. The estimated 1- and 3-year survival rates after the

| Table 1. Prognostic variables in primary biliary cirrhosis |
|-----------------|----------------|----------------|
| **Clinical**    | **Analytical** | **Histological** |
| Age             | Bilirubin      | Fibrosis       |
| Hepatomegaly    | Albunin        | Cirrhosis      |
| Ascites/edema   | Prothrombin    | Histological stage |
| Hepatic encephalopathy | Alkaline phosphatase | Cholestasis |
| Gender          | Immunoglobulin | Granuloma     |
| Variceal bleeding | Procollagen type III | Lymphocytic piecemeal necrosis |
|                 | Hyaluronate    |                |
|                 | Indocyanine clearance |                |
|                 | Galactose elimination |                |
|                 | Hemoglobin     |                |

Variables in italics entered in most studies.
development of esophageal varices were 83% and 59%, respectively. The prognosis is less favorable once variceal bleeding occurs, as survival rates were estimated to be 65% and 46% at 1 and 3 years, respectively.

Other complications such as liver cancer can also adversely affect the survival of patients with PBC. For many years PBC was considered a chronic liver disease not associated with the development of primary liver cancer [62,63]. In the last decade, however, some reports have found that patients with PBC also develop hepatocellular carcinoma as seen in other chronic liver diseases, particularly those associated with ethanol abuse and HCV-related cirrhosis [64–68]. In this respect, it has been observed that the incidence of hepatocellular carcinoma is as high as that observed in patients with cirrhosis of other etiologies, particularly HCV-related cirrhosis [68]. This complication exclusively develops in the patients with advanced stages of the disease [62–66,68]. Recent data, however, have suggested that liver cancer can also be diagnosed in patients with early stages, and that the factors independently associated with the development of hepatoma are age at the time of diagnosis, male gender, and history of blood transfusion. Moreover, age, male gender, and advanced-stage, but not the development of, hepatocellular carcinoma, are associated with survival in PBC [69].

Prognosis of primary biliary cirrhosis based on mathematical models

During the last two decades, several investigations have identified prognostic variables for PBC patients and have developed survival models based mainly on clinical and biochemical variables, although some models also include histological features. The first observation that PBC usually has a long stable course followed by a preterminal phase was described in 1979. This study proposed that PBC patients with serum bilirubin levels higher than 10 mg/dl have a mean survival of 1.4 years [21]. Similar results were published first in a European study [13], and also in a small cohort of PBC patients from Spain [22]. In these two studies, age, hepatomegaly, advanced histological stage, the presence of clinical features resulting from portal hypertension such as ascites, and hepatic encephalopathy, along with bilirubin levels, were associated with poor prognosis.

From these reports, many studies have been performed to find a mathematical model able to define the probability of survival in patients with PBC, based on the natural history of the disease, Cox regression analysis, and patient follow-up as part of controlled clinical trials. On the basis of a retrospective follow-up of 280 patients with PBC, Roll et al established that the clinical variables of age, hepatomegaly, serum bilirubin levels greater than 5 mg/dl, and the presence of fibrosis on liver biopsy were correlated with a decreased survival time [33]. The survival function, however, was not established in this former study. A similar analysis was performed using the data collected during a randomized European trial on azathioprine in the treatment of PBC [42]. A PBC survival model was created using the variables that independently predicted an overall poor prognosis in a Cox multiple regression analysis. These variables were age, serum levels of bilirubin and albumin, and the presence of cirrhosis or centrilobular cholestasis on liver biopsy (Table 2).
Most of the former studies included histological features, and therefore indicated that an invasive procedure such as liver biopsy should be performed to determine prognosis. To overcome the limitations of liver biopsy, a new model was developed in the Mayo Clinic using only clinical and biochemical variables. This model was based on a study of 312 patients, using 45 clinical and biochemical variables. These patients were part of a randomized, double blind, placebo-controlled trial evaluating the use of penicillamine in the treatment of PBC, with negative results in terms of survival. The model was cross-validated with data from an independent group of 106 PBC patients who were eligible for the trial but declined to participate. The original [43] and the updated [70] Mayo models included five independent variables predicting survival: age, serum levels of bilirubin and albumin, prothrombin time, and presence or absence of peripheral edema, including response to diuretic therapy (see Table 2). These five variables were used to determine a risk score that can be translated into a survival function to estimate survival for the individual patient with PBC. The estimated survival decreases as the risk score progressively increases. This model has been cross-validated with the European model and with other intramural and extramural independent data sets and has been found to be generalizable and applicable to a broad spectrum of patients with PBC [71–73].

Other models have been developed more recently. Comparable clinical variables have been identified as significant predictors of prognosis [9,35,36,42,74] using the Cox regression hazard model. Four of these studies have developed a prognostic index formula based upon

<table>
<thead>
<tr>
<th>Model</th>
<th>Formula</th>
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<tbody>
<tr>
<td>European</td>
<td>$R = 1.03 \times \log_2 (\text{bilirubin in mg}) + 0.0009 \times \exp(\text{age in years})/10 - 2 - 0.05 \times \log_2 (\text{albumin in g/dl}) + 0.85 \times (\text{if cirrhosis}) + 0.65 \times (\text{if central cholestasis}) + 0.62 \times (\text{no azathioprine}) + 3.09$</td>
</tr>
<tr>
<td>Mayo</td>
<td>$R = 0.051 \times (\text{age}) + 1.209 \times \log_2 (\text{bilirubin}) + 3.304 \times \log_2 (\text{albumin}) + 2.784 \times \log_2 (\text{prothrombin time}) + 0.075 \times (\text{edema}^2)$</td>
</tr>
<tr>
<td>Oslo</td>
<td>$R = 2.077 \times \log (\text{bilirubin}) + 1.6812 \times \log (\text{serum creatinine}) - 0.25 + 5.75$</td>
</tr>
<tr>
<td>Barcelona</td>
<td>$R = 0.051 \times (\text{bilirubin in mg/dl}) + 1.221 \times (\text{hepatomegaly}) - 0.297 \times (\text{hemoglobin in g/dl})$</td>
</tr>
<tr>
<td>Newcastle</td>
<td>$R = \exp (0.0742 \times \text{age}) + (0.193 \times \log_2 (\text{bilirubin ratio}) - (-0.7079 \times \text{albumin ratio}) + (0.2610 \times \log_2 (\text{alkaline phosphatase ratio}))$</td>
</tr>
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[a] 0 = no edema without diuretic therapy; 0.5 = edema without diuretic therapy or edema resolved with diuretic therapy; 1 = edema despite diuretic therapy.
these independent predictors of prognosis [9,35,38,42] (see Table 2). The most consistent variables incorporated in these models are serum bilirubin levels and age, although other models put emphasis on liver biopsy findings, esophageal variceal bleeding, and low hemoglobin levels [38] as essential predictors of a more unfavorable outcome (see Table 2). One prognostic study on PBC was performed at the Hospital Clinic in Barcelona, based on 122 patients (113 female), and assessing 41 clinical, biochemical, hematological, and histologic variables [38]. Male gender, enlargement of the liver and spleen pruritus, jaundice, ascites, encephalopathy, advanced histological stage, and high circulating bilirubin and low cholesterol levels resulted in shorter survival. Low hemoglobin was also associated with poor prognosis. The independent variables entering in the final model predicting survival were bilirubin, hemoglobin, and liver enlargement. The expected survival calculated from the prognostic index fit well with the actual survival, although the model failed to accurately predict the individual short-term survival. By contrast, development of severe jaundice with bilirubin over 15 mg/dl, and the development of ascites or encephalopathy were associated with poor short-term survival (Figs. 3–5)[38]. In patients with PBC, however, serum bilirubin level is the most heavily weighted variable in all the models and could be used as a simplistic prognostic index.

![Fig. 3. Actuarial survival for the patients with PBC who developed bilirubin above 15 mg/dl.](image)

![Fig. 4. Actuarial survival for the patients with PBC who developed ascites.](image)

![Fig. 5. Actuarial survival for the patients with PBC who developed hepatic encephalopathy.](image)

One of the limitations of these models is the fact that all rely on measurements obtained at a single point in time during the illness. New models based on serial measurements of the independent predictors of poor prognosis have been reported [46,47,75]. In a study by Klion et al, the risk score in patients with PBC increased by a mean of 0.23 per year [75]. The gradual increase in the risk score was considered to present the natural progression of PBC, and an abrupt increase in the slope of the value was associated with a poor prognosis and the imminent need for liver transplantation. A prognostic model based on serial measurements of independent predictors along with other clinical variables during the course of the disease will probably lead to a more accurate prediction of disease progression and survival. Although these models are helpful in the clinical decision-making process, they do not replace clinical judgment.
**Consequences of ursodeoxycholic acid treatment on the mathematical models**

The effects of UDCA on the course and the consequences on survival, as well as in preventing histological progression of the disease, are commented upon in another article. Because UDCA treatment significantly decreases serum bilirubin levels [16,17,76–81], the leading variable for calculating the risk score, the mathematical models for predicting survival in patients with PBC have been questioned. Concerns have been raised as to whether the reduction in the risk score attributed to a decrease in serum bilirubin accurately reflects the observed improvement in survival in patients treated with UDCA. Different independent studies, however, have indicated that the Mayo risk score retains its power for predicting survival, even in patients under UDCA [71,73].

One study applied the Mayo natural history model in 222 patients with PBC enrolled in the Canadian placebo-controlled trial of UDCA [71]. Following completion of the study period of 24 months, more than half of the study subjects initially randomized to UDCA or placebo were continued or started on UDCA and were followed for a mean period of 4 years. The risk score for each patient was calculated at entry and at 6 months of therapy. Patients were classified into three categories according to the risk score: low, intermediate, and high, and survival of patients in the treatment and placebo groups was analyzed considering liver transplantation or death as a failure. After treatment with UDCA for 6 months the serum bilirubin levels fell in all three UDCA groups, whereas in the placebo groups, the bilirubin levels rose. The Mayo model effectively divided the placebo- and UDCA-treated patients at baseline into three groups with distinct survival curves, and most important, the predicted curves showed a good match with the actual survival curves after 6 months of treatment with UDCA, thus supporting the usefulness of the Mayo model in patients under UDCA.

Another study of 180 patients with PBC enrolled in a randomized controlled trial of UDCA at the Mayo Clinic and followed for up to 7 years while on UDCA also indicated that the Mayo survival model, recalculated after 6 months on UDCA therapy, accurately predicted patient survival. When the model calculated at entry was applied, patients on UDCA therapy had approximately half as many deaths or transplants as predicted by the Mayo model. In contrast, when the Mayo risk score was calculated at 6 months of UDCA therapy, the model's prediction was very similar to the actual occurrence of events. Actually the observed and calculated expected survival for the UDCA group after 6 months of treatment were closely matched by the changes in the risk score [73]. Therefore, when the biochemical parameters stabilize following the institution of UDCA (usually between 3 to 6 months), the model can be recalculated to provide a more accurate survival estimate during continued treatment with UDCA.

**Summary**

The natural history of PBC is characterized by slowly progressive cholestasis with liver damage, development of cirrhosis and its complications, and death, unless the patient undergoes liver transplantation. The disease has at least three clinical presentations, each with a different course and prognosis: the silent and usually less aggressive form, the asymptomatic form, and the symptomatic form. There are no identifiable features that
distinguish the asymptomatic population who will remain symptom-free from those patients who will develop symptoms. As expected, the survival is longer in asymptomatic than in symptomatic patients. Overall survival of asymptomatic PBC is shorter than for an age- and gender-matched control population, but the patients remaining asymptomatic had a survival equal to that of the general population.

Natural history studies have identified several variables associated with survival, particularly age, bilirubin, albumin, prothrombin time, ascites, encephalopathy, and advanced histological stage. Development of esophageal varices and hepatocellular carcinoma can also affect survival. Serum bilirubin level is, however, the most heavily weighted prognostic variable and can be used as a simplistic prognostic index for patients with PBC. In the last two decades, natural history models have been developed that include clinical, biochemical, and histological variables, the most popular being the Mayo model. It has the advantage of avoiding histological variables, and therefore can be applicable to a broad spectrum of patients with PBC. The models may also be used to evaluate the efficacy of different new treatments. Prognostic models based on serial measurements of the independent predictors of poor prognosis would lead to a more accurate prediction of survival; however, they probably will not replace clinical outlook.

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