Clinical Roundtable Monograph

The Evolving Use of Biochemical Markers in the Management of Primary Biliary Cholangitis: A Clinical Perspective

Moderator

Kris V. Kowdley, MD
Director, Liver Institute Northwest
Clinical Professor
Elson S. Floyd College of Medicine
Washington State University
Seattle, Washington

Discussants

Gideon M. Hirschfield, MA, MB BChir, FRCP, PhD
Lily and Terry Horner Chair in Autoimmune Liver Disease Research
Division of Gastroenterology and Hepatology
Toronto Centre for Liver Disease
Toronto General Hospital
Toronto, Ontario

David E. Jones, BM, BCh, FRCP, PhD, OBE
Professor of Liver Immunology
Newcastle University
Honorary Consultant Hepatologist
Newcastle upon Tyne Hospitals
Newcastle upon Tyne, United Kingdom

Abstract: Primary biliary cholangitis is a chronic autoimmune liver disease characterized by immune-mediated damage to interlobular bile ducts within the liver that may lead to cholestasis, biliary cirrhosis, and end-stage liver disease. Although some patients with primary biliary cholangitis are asymptomatic, a substantial proportion may develop symptoms, such as pruritus and fatigue, which can have a profound effect on quality of life. Increased awareness of the disease has led to diagnosis of patients at an earlier stage. The availability of large, population-based databases has facilitated the development of prognostic models to predict long-term adverse liver-related outcomes using commonly available tests. Recent clinical trials of second-line therapies for primary biliary cholangitis have used changes in bilirubin and alkaline phosphatase as surrogate endpoints, and such measures might be used clinically to identify patients who may benefit from these new treatments once they are approved.

Primary Biliary Cholangitis: Clinical Insights Into Diagnosis and Staging

Gideon M. Hirschfield, MA, MB BChir, FRCP, PhD

Lily and Terry Horner Chair in Autoimmune Liver Disease Research
Division of Gastroenterology and Hepatology
Toronto Centre for Liver Disease
Toronto General Hospital
Toronto, Ontario

Introduction to Primary Biliary Cholangitis

Primary biliary cholangitis (PBC), previously referred to as primary biliary cirrhosis, is a chronic autoimmune disease of the liver associated with damage to the bile ducts.[1] The bile duct damage exhibits a specific pathology, with selective and progressive destruction of intrahepatic ducts. Untreated, PBC can lead to cholestasis and fibrosis of the liver, which triggers both intrahepatic and extrahepatic complications. Ultimately, PBC can result in end-stage liver disease, with potentially fatal results. The disease has a characteristic antimitochondrial antibody serologic signature.[2,3]

Many patients have a good quality of life. However, in a substantial proportion of patients, quality of life is reduced by symptoms that include pruritus, fatigue, joint aches, abdominal discomfort, and sicca complex (dry eyes/dry mouth).[2,4-7] Low bone mass is not infrequently encountered in this patient population, not only because a majority of the patients are postmenopausal women, but also because the disease—particularly when advanced—can be associated with osteoporosis.[8] Other symptoms associated with PBC include depression, anxiety, and sleep disturbance. Patients with PBC may coincidentally have other autoimmune conditions, such as primary Sjögren's syndrome, thyroid disease, celiac disease, and systemic sclerosis.

As a cholestatic disease, PBC can affect lipid metabolism, which may result in xanthoma, xanthelasma, and high cholesterol levels. Compared with low-density lipoprotein cholesterol levels, high-density lipoprotein cholesterol is disproportionately elevated, and therefore the patient's cardiovascular risk seems not to be increased.[9]

> It is key for clinicians to engage with patients regarding symptoms and to offer help.
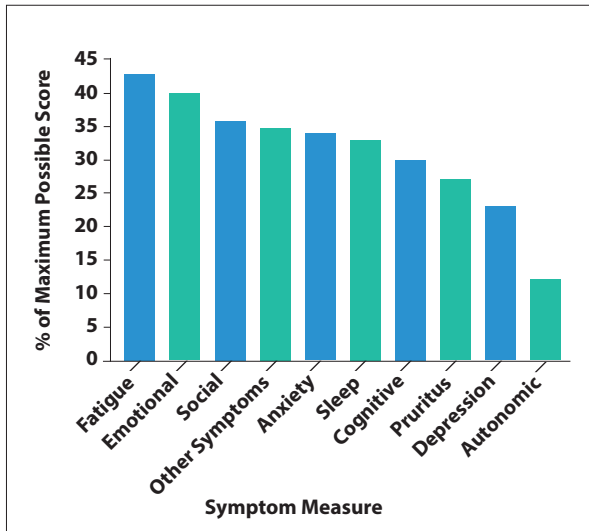
The first-line treatment of PBC consists of ursodeoxycholic acid (UDCA). Guidelines recommend treatment with oral UDCA administered at 13 to 15 mg/kg per day, either as a single daily dose or in divided doses if tolerability is a concern.[3] Second-line therapy consists of the farnesoid X receptor (FXR) agonist obeticholic acid,

Figure 1. Relative impact of different types of symptoms in patients with primary biliary cholangitis. Scores for the different symptom domains and measures were compared in the UK-PBC patient cohort. The symptom impact is shown. Adapted from Mells GF et al. *Hepatology*. 2013;58(1):273-283.[4]
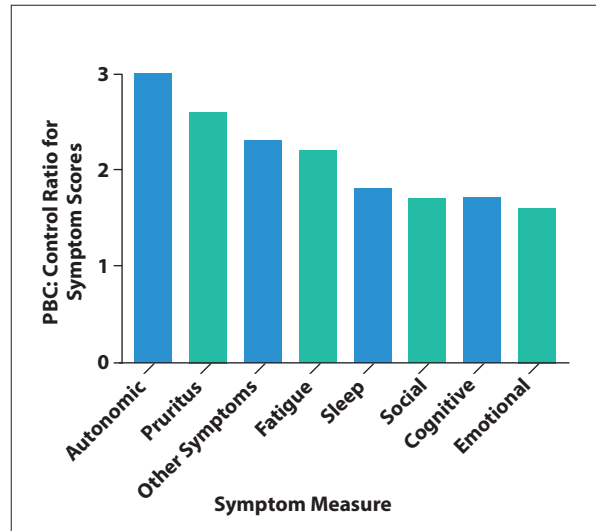
Figure 2. Relative impact of different types of symptoms in patients with primary biliary cholangitis. Scores for the different symptom domains and measures were compared in the UK-PBC patient cohort. The ratio of the symptom score is shown. Adapted from Mells GF et al. *Hepatology*. 2013;58(1):273-283.[4]

which is approved by the US Food and Drug Administration (FDA) for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA, or as monotherapy in adults who are unable to tolerate UDCA. Fibrates may be used in the second-line setting, based on their potential ability to decrease bile acid synthesis and bile acid–related hepatic inflammation.

Insights Into the Disease State

PBC is diagnosed by primary care physicians and specialists. Patients tend to be female.[10] The average age for disease onset is middle age, although the disease is diagnosed across all age groups.[11] Younger patients (<50 years) are less likely to adequately respond to treatment with UDCA. Patients usually present because results from their serum liver tests are cholestatic, and that includes elevations in alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT).[2] In most cases, patients are asymptomatic. In many patients, however, abnormal serum liver tests are accompanied by symptoms. These broad-ranging symptoms include fatigue, pruritus, bone aches, and dryness of the eyes and mouth (Figures 1 and 2).[2,4-7] Most primary care physicians and community doctors are able to exclude other causes of these signs and symptoms, such as biliary tree obstruction or drug-related adverse events. Persistent serum liver tests showing cholestasis will lead to tests of antimitochondrial antibodies and immunoglobulins (Ig); elevated levels of IgM are often seen in patients with PBC (Table 1).[2] Most patients receive a confirmed diagnosis of

PBC without a liver biopsy.

After a diagnosis of PBC, most clinicians and patients are eager to learn the disease stage, the cause of the disease, and whether treatments are available to manage both the disease and any associated symptom burden. As a starting point, it is helpful to understand whether fibrosis is already present. Fortunately, most patients with PBC now present with early-stage disease, which can be effectively treated to prevent end-stage liver disease. It is necessary to stage the patient, usually according to clinical measures. Hematologic values, particularly the platelet count, should be measured. Ultrasound results and spleen size are also considered. In most regions throughout the world, it is possible to administer some type of noninvasive fibrosis testing, such as elastography or serum fibrosis markers. This information is analyzed in combination to gauge the clinical stage of the patient at presentation. A further analysis is performed a year after the patient begins treatment.

Symptom Management

Symptoms can be prevalent in PBC and are important to patients. Apart from pruritus, these symptoms are not specific to PBC, but nevertheless they should be addressed as part of the overall management plan. In very–late-stage disease, the overall symptom burden corresponds with disease severity. For the majority of patients, however, there is a disconnect between symptom severity and disease stage/risk (other than for pruritus). The impact of symptoms

Table 1. Broad Clinical Utility of Diagnostic and Prognostic Testing in Primary Biliary Cholangitis

	Result	Suspicion	Diagnosis	Prognosis
Serum Liver Tests				
ALP	Increased	Yes	Yes	Yes
GGT	Increased	Yes	No	Yes
AST (AspAT) or ALT	Increased	Yes	No	Yes
Serum Autoantibody Profile				
Antimitochondrial antibodies (>1 in 40)	Positive	Yes	Yes	No
IgM	Increased	Yes	No	No
Anti-gp210	Positive	No	Yes	Yes
Anti-sp100	Positive	No	Yes	No
Anti-centromere	Positive	Yes	No	Yes
Liver Function				
Bilirubin	Increased	No	No	Yes
Albumin	Decreased	No	No	Yes
International normalized ratio	Increased	No	No	Yes
Platelets	Decreased	No	No	Yes
Imaging				
Ultrasound	NA	No	No	Yes
Transient elastography	NA	No	No	Yes
Histology				
Liver biopsy	Descriptive	Yes	Yes	Yes

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AspAT, aspartate aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; IgM, immunoglobulin M; NA, not applicable.

Adapted from Lleo A et al. *Lancet.* 2020;396(10266):1915-1926.[2]

is dependent on other non–liver-related factors, such as young age and social isolation. Inevitable confounders such as polypharmacy, sleep apnea, fibromyalgia, depression, and thyroid disease impact symptom burden. It is key for clinicians to engage with patients regarding symptoms and to offer help. Successful interventions for pruritus are available, but remain underused. Patient support groups and regular exercise can be helpful.

The TRACE algorithm offers practical ways to help patients with PBC manage fatigue.[12] The components of this strategy are:

- Treat the treatable: All symptoms that negatively affect the patient should be addressed.
- Ameliorate the ameliorable: Depression is common in patients with PBC and can exacerbate fatigue.

Patients who develop depression should be offered appropriate therapy.
- Cope: Strategies for coping with fatigue include pacing and planning activities throughout the day, as well as lifestyle adaptation.
- Empathize: Symptoms should be managed with a clear approach tailored to each patient.

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An Examination of the Evidence Behind Biochemical Markers in Primary Biliary Cholangitis

Kris V. Kowdley, MD

Director, Liver Institute Northwest
Clinical Professor, Elson S. Floyd College of Medicine
Washington State University
Seattle, Washington

The Evolving Use of Prognostic Scores and the Role of Biochemical Markers in PBC

The role of biochemical markers in the management of PBC has evolved a great deal over the past several years. A variety of prognostic models have been relied on to optimize management of patients with PBC.[1] The Mayo score had been considered the classic prognostic model for patients with untreated disease, and it could be used to describe the natural history of PBC.[2] The Mayo score incorporates factors such as the patient's age; their levels of bilirubin, aspartate transaminase (AST), and albumin; and the presence of variceal bleeding. Previously, this score and others were useful for the patients presenting for treatment in the clinic, who had later stages of disease. The increasing ability to diagnose PBC earlier in the disease course has made these prognostic models less relevant. The older models are most applicable to patients with more advanced disease.

The earlier diagnosis of PBC led to the realization that there is a difference between disease stage and prognostic risk category. This difference is highlighted by the use of the Rotterdam criteria, which combine bilirubin and albumin measurements to categorize patients into groups with different prognostic and survival outcomes.[3]

> As more patients are diagnosed earlier in the course of the disease—when their liver function is less compromised—there has been an effort to utilize biochemical markers as potential predictors of outcome in PBC.

In this way, the Rotterdam criteria are focused on disease stage and the associated liver function.

Primary Biochemical Markers

As more patients are diagnosed earlier in the course of the disease—when their liver function is less compromised—there has been an effort to utilize biochemical markers as potential predictors of outcome in PBC. Thus far, the

At Baseline[a]

At 1-Year Follow-Up[a]

At 5-Year Follow-Up[b]
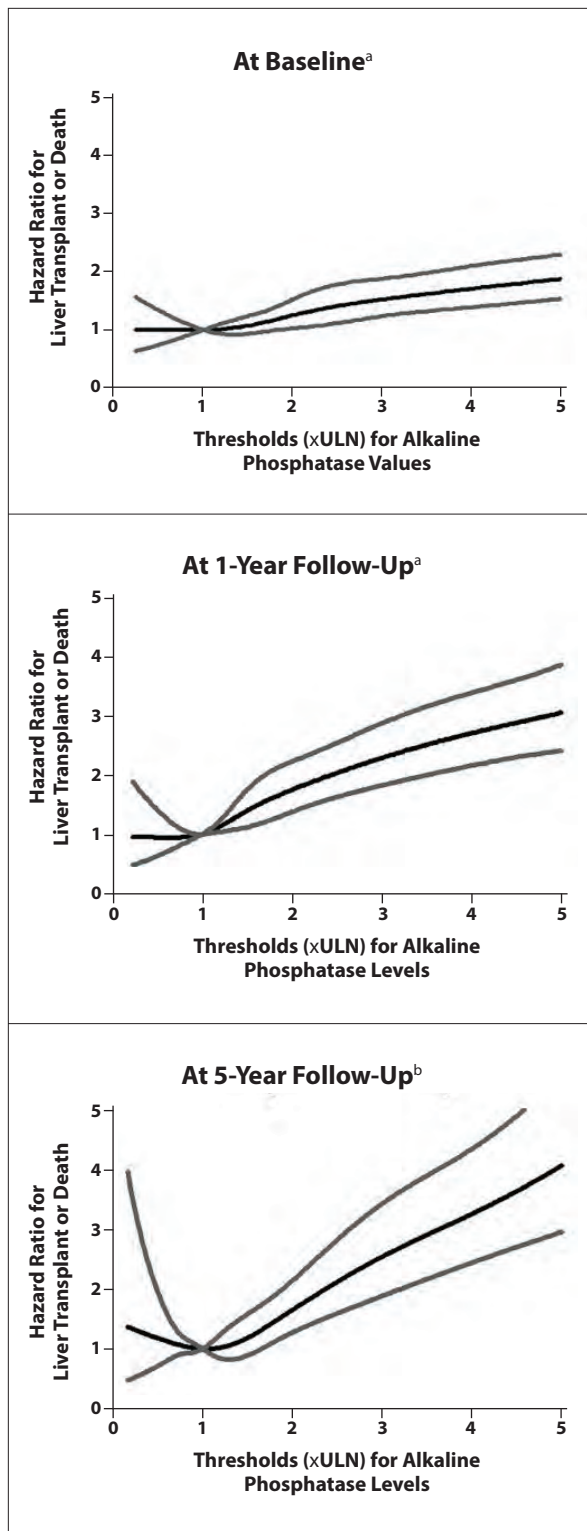
Figure 3. The hazard for liver transplant or death according to alkaline phosphatase levels at different time points estimated with cubic spline function in the Global PBC Study. ULN, upper limit of normal. [a]Among 4635 patients, 3710 were included in this analysis. [b]Among 3161 patients, 2203 were included in this analysis. Adapted from Lammers WJ et al. *Gastroenterology*. 2014;147(6):1338-1349.e5.[10]

primary biochemical markers used in patients with PBC include bilirubin and ALP. Between these, it has become evident that bilirubin is a signifier of more advanced disease stages, whereas ALP might better predict long-term outcome and the risk for future events.

Serum bilirubin is well defined as an independent predictor of prognosis and the natural course of PBC, and this marker is incorporated into the Mayo PBC score.[4-7] Despite the established prognostic utility of bilirubin, its application is limited to patients with relatively advanced disease, who are most likely to show meaningful changes in bilirubin levels. In contrast, the isoenzyme ALP appears to be more broadly applicable across the spectrum of PBC disease severity.[8,9] Elevated levels of ALP are a marker of cholestasis.

The Global PBC Study

The correlation of serum ALP and bilirubin levels—either individually or in combination—with transplant-free survival was evaluated by Lammers and colleagues in the Global PBC Study.[10] This large, international, observational PBC database was powered to permit an individual patient-level meta-analysis to determine the prognostic significance of these biochemical markers. Data from the Global PBC Study Group collaboration represented 15 liver centers in 8 North American and European countries, each of which contributed sets of patient data from major long-term follow-up cohorts. The majority of follow-up data were collected from patients initiating UDCA therapy.

A total of 4845 patients were included in the analysis.[10] Patients had been diagnosed with PBC between 1959 and 2012; 79% had received their diagnosis after 1990. Patients were followed for a median of 7.3 years (interquartile range [IQR], 3.6-11.5). The histologic disease stage was reported for the patients who had undergone a liver biopsy (76%); most of these patients had stage I or II disease. According to the Rotterdam criteria, the biochemical disease stage was early in 42%, moderately advanced in 15%, and advanced in 5% (the stage was not available in 38%). At baseline, the median serum ALP level was 2.10 (IQR, 1.31-3.72; the level was not available in 24%). The median serum bilirubin level was 0.67 (IQR, 0.45-1.06; the level was not available in 23%).

In the total cohort, the transplant-free survival rate was 88% at 5 years, 77% at 10 years, and 63% at 15 years.[10] A total of 85% of patients were treated with UDCA. Among these patients, the rates of transplant-free survival were 90% at 5 years, 78% at 10 years, and 66% at 15 years. These rates were significantly higher than those reported in untreated patients (79%, 59%, and 32%, respectively; *P*<.0001).

The levels of both ALP and bilirubin at baseline and each year over 5 years were associated with the risk for liver transplant and death (Figures 3 and 4).[10] Higher levels were associated with worse clinical outcomes. A threshold of 2.0 × the upper limit of normal (ULN) for serum ALP was found to predict clinical outcomes. For patients with ALP levels at or less than 2.0 × ULN, the rates of transplant-free survival were 94% at 5 years, 84% at 10 years, and 73% at 15 years. In comparison, for patients with ALP levels higher than 2.0 × ULN, these rates were 81%, 62%, and 50%, respectively (P<.0001). Similarly, the 5-year, 10-year, and 15-year transplant-free survival rates were higher in patients with normal bilirubin levels after 1 year of follow-up (95%, 86%, and 74%, respectively) vs those with abnormal bilirubin levels (65%, 41%, and 30%, respectively). These differences in transplant-free survival associated with the bilirubin level were also statistically significant (P<.0001). The association between elevated ALP levels and worse transplant-free survival was significantly higher in patients with both normal and abnormal bilirubin levels.[10]

The Global PBC database meta-analysis demonstrated a strong association between abnormally increased serum ALP and bilirubin levels with reduced transplant-free survival in patients with PBC. Furthermore, this analysis confirmed that a combination of both variables improves prognostic prediction in these patients, regardless of whether they received UDCA.[10]

Evidence for Prognostic Scores to Determine Response to First-Line UDCA Therapy

UDCA is a frequent first-line treatment in patients with PBC, and it improves survival. The biochemical response to treatment with UDCA, referred to as the treatment response, is a strong predictor of long-term outcomes in patients with PBC.[11] This knowledge led to the development of several prognostic models based on biochemical response. Several of these prognostic scores have been validated as highly accurate in this setting, and they are widely used to risk-stratify patients with PBC. There are now a number of different response criteria prognostic models that are based on the concept of how the patient is doing after 1 or 2 years of UDCA therapy. These models, which initially used varying combinations of bilirubin and ALP levels to determine response, have since incorporated other biochemical markers to predict long-term outcomes with regard to the risk for liver transplant or death.

GLOBE PBC Score
The Global PBC Study Group aimed to identify UDCA-treated patients with an insufficient response to treatment.[12] The investigators compared a dataset of PBC
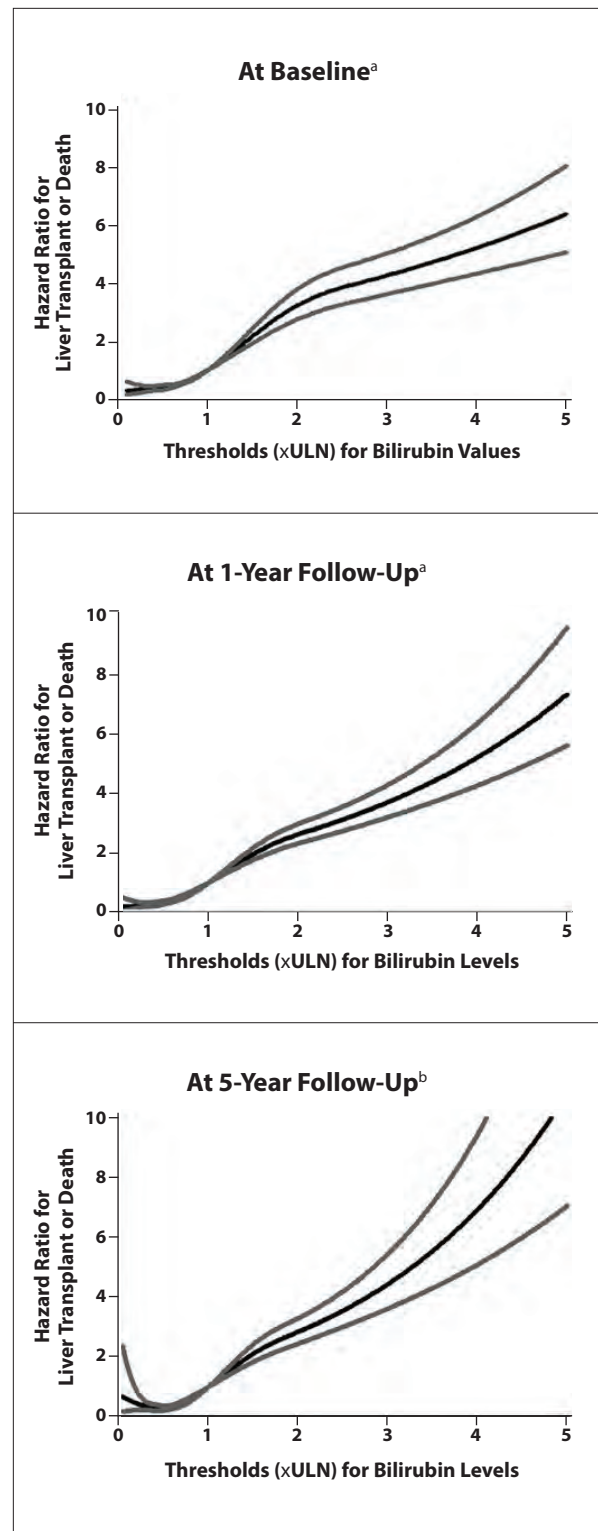
Figure 4. The hazard for liver transplant or death according to bilirubin levels at different time points estimated with cubic spline function in the Global PBC Study. [a]Among 4635 patients, 3681 were included in this analysis. [b]Among 3161 patients, 2109 were included in this analysis. Adapted from Lammers WJ et al. *Gastroenterology*. 2014;147(6):1338-1349.e5[10]
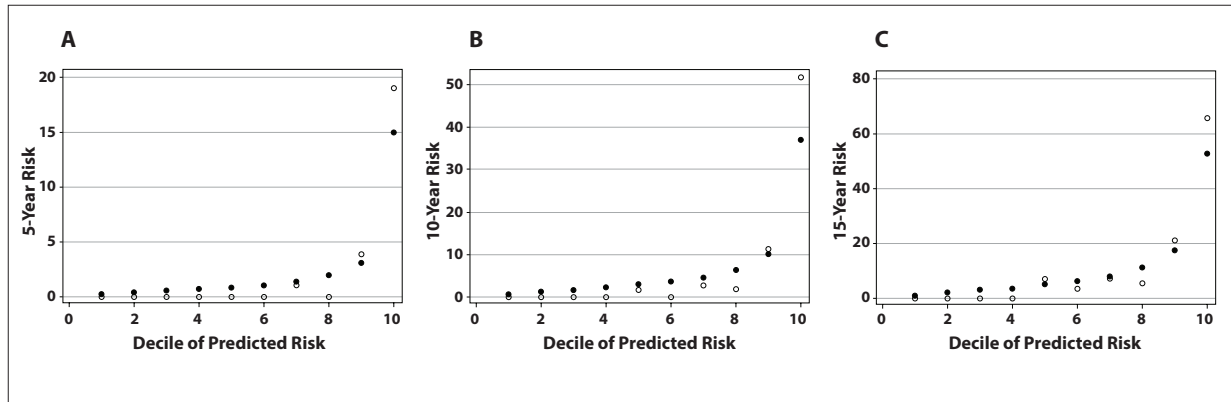
Figure 5. The predicted vs observed risk for an event across each decile of the UK-PBC risk score at 5 years (A), 10 years (B) and 15 years (C). Adapted from Carbone M et al. *Hepatology.* 2016;63(3):930-950.[13]

patients against a representative healthy population to develop the GLOBE PBC score. The score was developed based on data from the patients treated with UDCA. Among these 2488 patients, the 5-year, 10-year, and 15-year transplant-free survival rates were 90.0%, 77.5%, and 65.6% respectively.[12]

Using this patient dataset, the GLOBE score incorporated age, bilirubin, albumin, ALP, and platelet count as independent predictors of liver transplant or death. This score was then applied to a validation cohort of 1631 patients who had overall characteristics and transplant-free survival rates that were similar to the derivation cohort.[12]

Patients with a GLOBE score above 0.30 (considered nonresponders; approximately 40% of patients) had a significantly diminished survival compared with a matched general population (hazard ratio [HR], 5.51; 95% CI, 4.52-6.72; *P*<.0001).[12] The 5-year, 10-year, and 15-year transplant-free survival rates in this group of patients were 79.7%, 57.4%, and 42.5%, respectively. In comparison, patients with a GLOBE score of 0.30 or less (responders) had a life-expectancy comparable with that of a matched general population. The 5-year, 10-year, and 15-year transplant-free survival rates were 98.0%, 92.0%, and 82.3%, respectively (*P*<.0001). Nonresponsive patients were also significantly more likely to present with a late stage of disease at baseline than responding patients. The investigators concluded that the GLOBE score could reliably determine the prognosis of patients with PBC who have been treated with UDCA for 1 year, regardless of their disease stage.[12]

The UK-PBC Risk Score
The UK-PBC risk score was designed to estimate the absolute risk for developing end-stage liver disease among patients with PBC treated with UDCA.[13] To develop the model, 1916 patients treated with UDCA were selected from the UK-PBC Research Cohort.

At baseline, approximately 10% of these patients had advanced disease at diagnosis (defined by splenomegaly or ascites), and approximately 20% of participants were antinuclear antibody–positive. The UK-PBC risk score was developed using this derivation cohort to include 5 variables: albumin level, platelet level, level of bilirubin after 12 months of UDCA, levels of transaminases after 12 months of treatment, and level of ALP after 12 months of treatment.[13]

The model was applied to a validation cohort of 1249 patients treated with UDCA.[13] Within the validation cohort, the area under the receiver operating characteristic curves (AUROCs) were 0.96 (95% CI, 0.93-0.99) for the 5-year risk score, 0.95 (95% CI, 0.93-0.98) for the 10-year risk score, and 0.94 (95% CI, 0.91-0.97) for the 15-year risk score (Figure 5).

The authors from this study concluded that in clinical practice, the UK-PBC scoring system could be useful to identify those patients at highest risk for developing end-stage liver disease and thus who would obtain the greatest benefit from further risk reduction using second-line therapy.[13]

The Paris-I/II Criteria
It is widely considered that serum ALP and bilirubin are the 2 most important parameters in evaluating response to UDCA.[14] The Paris-I criteria were developed to discriminate between low- and high-risk patients treated with UDCA. The Paris-I criteria are generally considered to be a strong predictor of transplant-free survival in patients with PBC, and have been validated in large studies.[15] The Paris-I criteria were defined as serum bilirubin at or less than 1 mg/dL, ALP at or below 3 ULN, and AST at or below 2 ULN, all assessed at 1 year after initiation of UDCA therapy. Death or liver transplant were determined to be 2.5-times more likely to occur in patients who

showed either ALP exceeding 3 × ULN, AST exceeding × 2 ULN, or serum bilirubin higher than 1 mg/dL at 1 year of treatment. This patient subgroup—with a high risk for liver transplant or death—accounts for nearly 40% of all patients and has a 10-year transplant-free survival rate of approximately 50%. In contrast, survival rates among patients without these elevated biochemical markers were similar to those of a control population.[15]

Additionally, as disease stage is known to affect the biochemical response to UDCA, stage-specific thresholds were incorporated into the Paris-II criteria to better fit early-stage patients, an increasingly large proportion of patients with PBC. It was shown that patients meeting the Paris-II criteria, defined as patients with both ALP and AST at or less than 1.5 × ULN and normal total bilirubin after 1 year of UDCA therapy, had no evidence of progressive disease over an average of 7 years. Using the Paris-II criteria, adverse outcomes were observed only in nonresponding patients. The survival rates without adverse outcome at 5, 10, and 15 years of follow-up were 100% in responders. In nonresponders, these survival rates were 93%, 87%, and 74%, respectively.[9]

The Paris-II criteria were also evaluated to determine if they could be applicable to a population of patients with disease at a late histologic stage.[9] However, the only criteria that were able to significantly discriminate among these patients with advanced PBC were the Paris-I criteria (HR in nonresponders, 1.39; 95% CI, 1.05-1.84; *P*<.05). In contrast, the Paris-II criteria did not reach statistical significance. This observation led the study authors to conclude that the Paris-II criteria should be limited to patients with early stages of the disease. Although the Paris-I criteria seemed more broadly applicable across PBC disease stages, they were found to be less accurate and reliable than the Paris-II criteria for early stages.[9]

Toronto Criteria

The Toronto criteria can predict histologic progression in patients with PBC.[16] Using 10-year histologic progression of disease in paired biopsies from the same patient, combined with biochemical response to UDCA and baseline histology, the Toronto criteria were developed to predict the disease course in a cohort of patients with predominantly early disease. The Toronto criteria define biochemical response to UDCA as ALP less than 184 IU/L (1.67 × ULN) after 2 years of treatment. In paired liver biopsies, more than 80% of patients who did not respond to UDCA according to the Toronto criteria showed histologic progression after 10 years (odds ratio, 12.14; 95% CI, 2.69-54.74).[16] Since its development in 2010, the Toronto criteria have become a platform for the design and conduct of clinical trials for the second-line treatment of PBC.

APRI

The AST to platelet ratio index (APRI) also predicts outcomes in PBC, and was shown to be independent of UDCA response.[17] The clinical utility of APRI was suggested by a derivation cohort of 386 patients with PBC (AUROC, 0.781; 95% CI, 0.721-0.840). Here, an APRI higher than 0.54 at baseline was predictive of liver transplant or death (adjusted HR, 2.40; 95% CI, 1.32-4.36; *P*<.01). Importantly, the APRI continued to be statistically significantly predictive of liver transplant or death when applied at 1 year (adjusted HR, 2.75; 95% CI, 1.49-5.08; *P*<.01), despite controlling for UDCA-response (AUROC, 0.806; 95% CI, 0.756-0.857).[17]

A higher APRI at baseline (>0.54) was confirmed to predict adverse outcome (liver transplant or death) in the validation series, with sensitivity and specificity comparable with that observed in the derivation cohort (adjusted HR, 3.04; 95% CI, 1.66-5.55; *P*<.001). In the validation cohort of 629 patients, the AUROC for the APRI was 0.741 (95% CI, 0.662-0.820). The association of higher (>0.54) APRI with liver transplant or death in the validation cohort at 1 year was also significant (adjusted HR, 4.66; 95% CI, 2.39-9.12; *P*<.00001). At 1 year, the AUROC for the APRI in the validation cohort was 0.783 (95% CI, 0.709-0.857).[17]

By using a combination of APRI at 1 year and UDCA-response criteria, the investigators were able to classify patients as low, intermediate, or high risk. Patients with PBC defined as low risk had a biochemical response and an APRI at 1 year of 0.54 or less. Those defined as intermediate risk had either a biochemical response and an APRI at 1 year exceeding 0.54 or a biochemical nonresponse and an APRI at 1 year of 0.54 or less. Patients defined as high risk had a biochemical nonresponse and an APRI at 1 year of greater than 0.54.[17]

Transplant-free survival was significantly longer in low-risk patients compared with intermediate-risk patients. Additionally, high-risk patients had the poorest transplant-free survival. Ten-year transplant-free survival rates across the low-, intermediate-, and high-risk groups from the derivation cohort were 86%, 59%, and 13%, respectively. This correlation was confirmed in the validation series.[17] The authors of this APRI model concluded that APRI at diagnosis and/or after 1 year could be used to independently predict liver transplant or death in patients with PBC.

New Data From the Global PBC Study Group

There have been 2 other more recent observations from the Global PBC Study Group. First is the recognition that a bilirubin threshold of 0.6 mg/dL may be a cutoff point at which the risk for liver transplant or death begins to

increase. A recent publication from the Global PBC Study Group reported that a bilirubin threshold of 0.6 × ULN had the highest ability to predict liver transplant or death at 1 year (HR, 2.12; 95% CI, 1.69-2.66; *P*<.001).[18] The 10-year survival rates of patients with a bilirubin level at or below 0.6 × ULN was 91.3%, whereas it was significantly lower for patients with a bilirubin level above the threshold of 0.6 × ULN (79.2%; *P*<.001). Furthermore, UDCA-induced reduction in bilirubin below this threshold was associated with an 11% improvement in 10-year survival.[18]

The second observation is that there may not be a dichotomous relationship between ALP and patient outcomes. Any ALP elevation exceeding 1 × ULN may indicate that the patient has an ascending linear risk with regard to long-term outcomes. Indeed, normalization of ALP levels appears to be the optimal goal, with 10-year survival rates of 93.2% in patients with ALP at or less than 1 × ULN and 86.1% in those with ALP between 1.0 to 1.67 × ULN.[18]

Physicians are starting to approach the treatment of PBC in a similar manner to that of autoimmune hepatitis. For example, the goal of treatment should be to achieve a complete biochemical remission, if possible. Of course, this goal has not been a possibility during treatment with FXR agonists because ALP normalization is not commonly observed with this mechanism of action. However, as the patient progresses to treatment with second-line and third-line therapies, as well as combination therapies, it is no longer acceptable to settle for an ALP of less than 1.67 × ULN, particularly in light of these latest data from the Global PBC Study Group. Instead, it may be better to strive for an ALP level as close to normal as possible, or at least below 1.5 × ULN.

Biochemical Markers Beyond ALP and Bilirubin

Additional data from the Global PBC Study Group suggest that GGT, a serum marker of cholestasis, may provide a further level of granularity.[19] In a group of 2129 patients with PBC, there was a correlation between serum levels of GGT and ALP. Higher serum GGT levels were associated with a lower hazard for transplant-free survival. A threshold of GGT higher than 3.2 × ULN at 12 months after treatment identified those patients who required liver transplant or died from a liver-related cause at 10 years (AUROC, 0.70). The association between the risk for liver transplant or liver-related death and elevated serum GGT persisted even in patients with ALP levels below 1.5 × ULN. These data suggest that a serum GGT below 3.2 × ULN may be associated with additional prognostic value compared with ALP alone. Inclusion of information regarding the level of GGT increased the prognostic value of the GLOBE score.[19]

Liver stiffness, as assessed by transient elastography and magnetic resonance elastography, has also been explored for its prognostic ability. In a group of 538 patients with PBC, liver stiffness measurements by transient elastography (n=286) or magnetic resonance elastography (n=332) were reviewed.[20] Liver stiffness cutoffs for predicting fibrosis stages were then determined using AUROC among those patients who underwent a liver biopsy. The optimal thresholds of liver stiffness for predicting advanced histologic stage (F4) were 14.40 kPa for transient elastography and 4.60 kPa for magnetic resonance elastography. Intriguingly, both measurements of liver stiffness were better able to predict histologic advanced fibrosis compared with biochemical markers. The ability of liver stiffness to predict hepatic decompensation remained even after adjustment for UDCA responsiveness (HR, 1.14; 95% CI, 1.05-1.24 for transient elastography and HR, 1.68; 95% CI, 1.28-2.19 for magnetic resonance elastography). Liver stiffness was also able to predict hepatic decompensation after adjusting for the GLOBE score (HR, 1.13; 95% CI, 1.07-1.19 for transient elastography and HR, 2.09; 95% CI, 1.57-2.78 for magnetic resonance elastography).[20]

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Practical Applications of Biochemistry Results in Primary Biliary Cholangitis

David E. Jones, BM, BCh, FRCP, PhD, OBE

Professor of Liver Immunology
Newcastle University
Honorary Consultant Hepatologist
Newcastle upon Tyne Hospitals
Newcastle upon Tyne, United Kingdom

The UDCA Response Score

An important and new clinical tool that has emerged from the UK-PBC cohort is the UDCA Response Score (URS), which uses pretreatment clinical parameters to predict a patient's response to first-line UDCA treatment.[1] Among 2703 patients with PBC, the pretreatment parameters that were associated with a lower likelihood of achieving a response to UDCA were higher ALP concentration ($P<.0001$), higher total bilirubin concentration ($P=.0003$), lower aminotransferase concentration ($P=.0012$), younger age ($P<.0001$), longer time from diagnosis to the start of UDCA treatment (treatment time lag, $P<.0001$), and worsening of ALP concentration from diagnosis ($P<.0001$). By incorporating these pretreatment variables, a predictive score of UDCA response was developed, which was validated with an AUROC of 0.87 (95% CI, 0.86-0.89; Figure 6) in the derivation cohort and 0.83 (95% CI, 0.79-0.87) in the external validation cohort (Figure 7).

The URS provides a tool for evaluating patients when they first present with PBC.[1] Even more important than the actual score is the insight it provides into how the patient
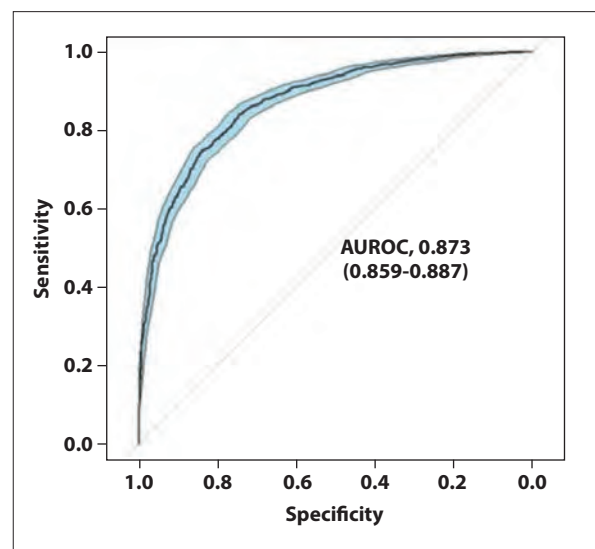
Figure 6. The AUROC curve for the prediction of response to UDCA as calculated by the UDCA Response Score in the derivation cohort, using stratified bootstrapping to estimate the confidence interval (AUROC, 0.87; 95% CI 0.86-0.89), in an analysis from the Italian PBC Study Group and the UK-PBC Consortium. AUROC, area under the receiver operating characteristic curve; UDCA, ursodeoxycholic acid. Adapted from Carbone M et al. *Lancet Gastroenterol Hepatol*. 2018;3(9):626-634.[1]
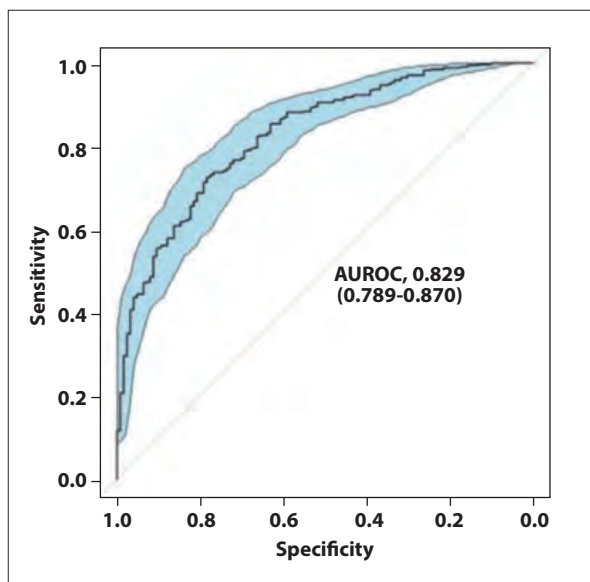
Figure 7. The AUROC curve for the prediction of response to UDCA as calculated by the UDCA Response Score in the external validation cohort (AUROC, 0.83; 95% CI, 0.79-0.87) in an analysis from the Italian PBC Study Group and the UK-PBC Consortium. AUROC, area under the receiver operating characteristic curve; UDCA, ursodeoxycholic acid. Adapted from Carbone M et al. *Lancet Gastroenterol Hepatol.* 2018;3(9):626-634.[1]

will respond to treatment. In the future, this information might be used to treat patients better from the beginning, instead of waiting until the disease has progressed.

Applying the Data in Clinical Practice

The PBC community has now developed a robust evidence base. Large cohorts have enabled clinicians to both validate previous data and move treatment forward. There are now several valid methods to measure patient prognosis. However, the practical clinical applications of these data are complicated. There are many competing methods to assess patients, and clear guidance regarding their best use is lacking. This can create confusion among clinicians (and patients).

As an example, at my institution, a 55-year-old patient with PBC died from complications of end-stage liver disease. This patient had presented 10 years earlier with PBC at a nearby hospital. At no point during those 10 years had she received any form of treatment; she was an untreated PBC patient. It was interesting to review the records and see the reasons why she did not receive any therapy. She was not symptomatic. She appeared to be at an early stage of disease, although she in fact had more advanced disease. Many rationalizations were made by people who did not understand the optimal clinical management of PBC. Eventually, the patient presented at our

unit with a bilirubin of 600 μMol/L. The day she arrived, she had a variceal bleed, was intubated, and was admitted to the intensive care unit, where she died. This was particularly poignant as it occurred against the backdrop of the COVID-19 pandemic. However, an especially notable aspect to this case is that the patient had an entirely treatable disease that had never been appropriately treated.

The enormous amount of data available can generate confusion. Clinicians struggle with the concept that a patient can be considered a responder to UDCA according to one set of criteria, but not another. It is understandable that clinicians then question whether any of the criteria are meaningful. Of course, the problem is that these criteria are validated in large populations of patients. When applying them to an individual patient, the interpretation becomes less clear.

Therefore, it is necessary to provide simple messages to help clinicians make informed decisions regarding management. It is important to know the treatments the patient received before and after the diagnosis. The impact of these treatments should be considered. The clinician must gauge the amount of scarring in the liver, as well as the degree of fibrosis (particularly because the degree of fibrosis at onset is a prognostic factor). Vibration-controlled transient elastography can help determine the extent of liver damage. However, these scans occasionally produce rogue results, regardless of the technician's skill. Biopsy is no longer a preferred method to stage patients. Tools such as the APRI score[2] and even simple platelet counts can be useful. It is essential to determine the disease stage—regardless of the method used—because it will dictate the patient's course.

The most important consideration in the management of PBC is how the patient responded to previous treatment. Whether a clinician uses the Paris-I criteria, the Paris-II criteria, or the Toronto criteria to stage a patient with PBC is less important than ensuring that at least one of them is used.[3-5] My advice to treatment centers is to choose a measure that the clinicians are comfortable with and then stick with it. An audit can, in retrospect, indicate whether the measure was optimal. Although these scores can provide information, they can also create anomalies. For example, a patient with an ALP that decreases from 250 IU/L to 200 IU/L would be considered a responder according to the Toronto criteria. However, a patient whose ALP decreases from 1000 IU/L to 250 IU/L would not be considered a responder, despite greater absolute and relative improvements in ALP. This is paradoxical, and can be extremely confusing for clinicians.

There is no clear answer as to which score is the most useful. Instead, perhaps clinicians should consider how to best move a patient toward normal levels. By considering where the patient is currently—how much fibrotic scarring

there is, and how well the disease has been treated or might be treated—the clinician then has information to act on.

Managing patients with the goal of moving them toward normal values has 2 advantages. First, it will lead to better treatment, particularly of the subgroup of patients with residual disease. Second, this concept is far easier

> There is a short-term direction to move toward normalization of liver function as a target, both to simplify the messaging and to improve control.

to understand, and it also becomes a very clear message for patients (whereas multiples of the ULN can be quite confusing for patients and clinicians). Achieving normal values is something that all people can understand. This shift, however, will lead to a reassessment of the severity of disease in some patients. Patients who thought their disease was well managed may learn that it was not. I explain this concept to patients by using the analogy of cholesterol. Previously, a cholesterol level of 6.5 mmol/L was consid-

ered healthy. More recent research, however, suggests that even a level of 5 mmol/L is problematic. The number has not changed, but our appreciation of its meaning has.

The UK-PBC score and the GLOBE score have greatly contributed to the quality of research in PBC.[6,7] However, these scores have, in many ways, further complicated the clinical understanding of this disease. Indeed, I encourage many clinicians in the United Kingdom to not use these scores. These scores are, of course, useful in a more advanced therapeutic setting.

When managing patients with PBC, it is necessary to consider their stage of disease upfront. Clinicians should not wait to see if a patient will do poorly. Instead, they should closely evaluate the patients from the first presentation, in order to gauge their likely disease trajectory. Mechanistic biomarkers might be a component of this evaluation. This type of evaluation will allow contemplation regarding the treatments that are administered early in the course of the disease. Perhaps the reason why second-line therapy seems to be of limited efficacy is that patients are not treated until they are in very advanced stages of disease. Some preclinical data are now emerging that suggest that the bile duct injury that occurs is reversible, but only if FXR agonists are used early when the damage begins.[8]

Unmet Needs

Mechanistic biomarkers are needed to better manage patients with PBC. There were regulatory discussions sur-
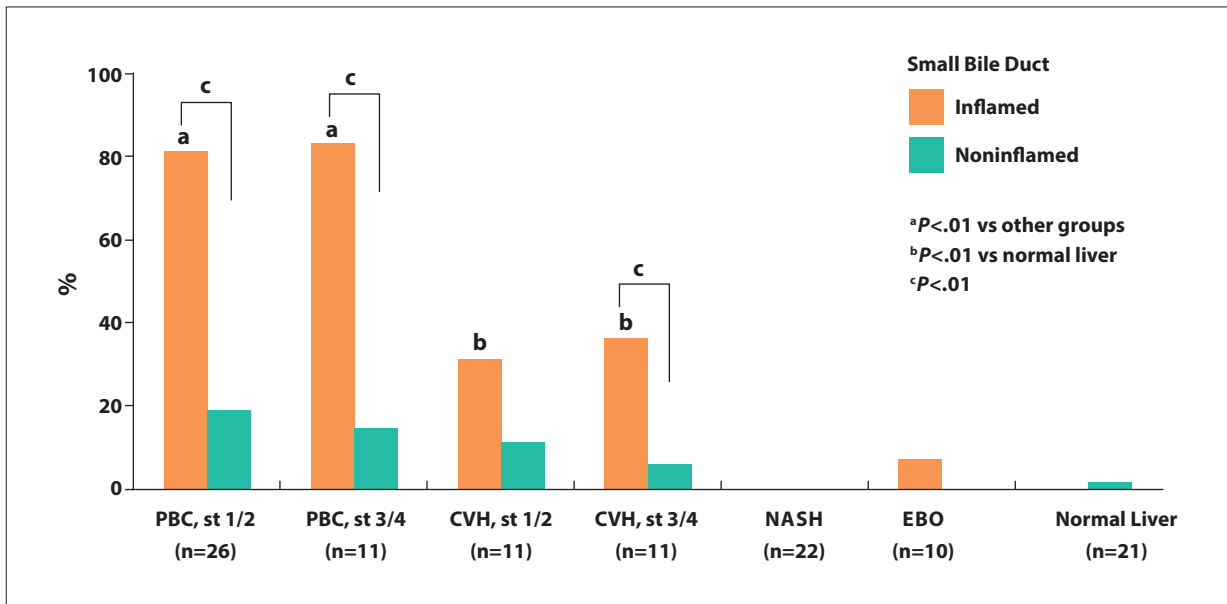
Figure 8. In a study of cellular senescence, the expression of CCL2 was significantly more frequent and intense in inflamed small bile ducts in PBC when compared with noninflamed small bile ducts in PBC and small bile ducts in control livers ($P<.01$). CVH, chronic viral hepatitis; EBO, extrahepatic biliary obstruction; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cholangitis; st, stage. Adapted from Sasaki M, Nakanuma Y. *Int J Hepatol.* 2012;2012:452143.[9]

rounding ALP cutoffs, but this approach did not turn out to be particularly helpful. Markers that are more closely linked to the process of the disease would allow an easier determination of a patient's prognostic risk. The biology of senescence is one area that is particularly interesting. Senescence of the bile duct cells is a strongly negative feature (Figure 8).[9] Peripheral circulating factors released by senescent cells are quantifiable and may be a marker for the actual mechanism of the disease.

Currently, the goal should be to simplify management directives and better guide clinicians. There is a short-term direction to move toward normalization of liver function as a target, both to simplify the messaging and to improve control. In the future, better markers that provide insight into the biology of the disease will allow individualized risk assessments. This information could be used to incorporate more effective treatments in higher-risk patients earlier in their disease course. We can learn from our colleagues in inflammatory bowel disease and rheumatology, who have already embraced disease-modifying therapy. The PBC community also needs to do so.

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The Evolving Use of Biochemical Markers in the Management of Primary Biliary Cholangitis: Discussion

Kris V. Kowdley, MD, Gideon M. Hirschfield, MA, MB BChir, FRCP, PhD, and David E. Jones, BM, BCh, FRCP, PhD, OBE

Dr Kris V. Kowdley How do you counsel your patients regarding symptoms, and do you consider symptoms a measure of prognosis?

Dr Gideon M. Hirschfield Patients who start off asymptomatic will not necessarily stay asymptomatic, and thus we need to avoid labeling patients as such. PBC is not a static disease, but rather a slowly progressing one.

Dr David E. Jones I have been monitoring the literature on PBC for many years. In the United Kingdom, a fallacy surrounding UDCA in the early days was that only symptomatic patients required treatment. Some clinicians still believe this. In fact, administering effective treatment to patients before they are symptomatic allows the best chance of management. It is far easier to prevent patients from becoming fatigued than to break that cycle of symptoms once it is established. It is a persistent fallacy that patients do not require treatment until they develop symptoms.

For me, the implication to patient management is similar to what was done in autoimmune hepatitis, with

the suggestion that any degree of abnormality has some additional risk. There was previously a time in which 2 × ULN for alanine transaminase (ALT) was regarded as a good response. It is now clear, however, that these patients likely progressed to end-stage liver disease. Autoimmune hepatitis and PBC are different diseases that follow different processes, but normal values are there for a reason. It is important to remember the history of the management of autoimmune hepatitis, in particular where the community got it wrong. Of course, we are now part of a community of physicians who aim for much better control in the management of patients with PBC.

We have recently reported data from a UK-PBC proteomics study, which evaluated the nature of the disease process in different groups and people.[1] What we found was that every group of patients with abnormal liver function tests also showed abnormalities in the PBC proteome. In other words, the only group of patients who appear normal in terms of the disease course are those with normal liver function tests. This association is linear and reminiscent of the Global PBC study, which showed a linear relationship between higher serum ALP and bilirubin and worse disease stage.[2]

At some point, the question then will be what degree of risk is sufficient to warrant either expensive treatment or treatment with side effects? This is an interesting question, and it is important to know there is a trade-off. A change in the target goals may reveal that some therapies are less effective than previously thought.

Dr Gideon M. Hirschfield I would add the question of whether PBC can remain patient-centered. One of the by-products of the success of all these risk scores is that there are too many and they are too sophisticated. The important message is to choose a risk score, and use it. That message is now becoming even more simple: target lower and better liver function tests. Regardless, it is important to evaluate each patient individually and to select among the different therapies to achieve this target.

My colleagues and I developed a score we called "ABA."[3] This score can be assessed at baseline and after 1 year of UDCA treatment. We developed this mainly because I wanted to express in a paper what I do in clinical practice, which is to look at the patient's age, whether the bilirubin is elevated, and whether the ALP is above 3 × ULN. These characteristics provide a great deal of information regarding the general risk for the patient, and whether he or she requires a high-intensity follow-up vs the more typical follow-up strategies.

We did not develop this score as a means to further complicate the picture, or just to provide a competing prognostic model. It was simply meant to provide clinicians a tool to do what so many of us just do on our own.

We need good scores, but we need good clinicians to synthesize the scores into practice.

Dr David E. Jones I agree completely. Another interesting development is the implementation of audit standards in both the European and UK treatment guidelines.[4,5] They were to an extent empirically formed, and based on reasonable observations at the time. The logic behind this was that an audit is a tool to improve management. Clinicians are not as good as we think we are, and the steps we take in actual clinical practice may differ from our intentions and even our perceptions. In the United Kingdom, all trainees have to do an audit, which is always performed on colonoscopy cecal intubation rates. It is extraordinary that colonoscopy cecal intubation rates are the only aspect of care that is audited. My colleagues and I realized that an easy approach to auditing PBC might provide insight into practice. An audit requires a target. For example, administering UDCA and recording the response is an auditable procedure that provides a good benchmark. When deciding on a measure to audit, it is necessary to identify a measurement that provides sharp insight into an important aspect of the disease, so that it will act as a bellwether. In the management of PBC, if a clinician administers UDCA and records a response to it, the chances are that he or she is probably approaching other aspects of management equally well. In the United Kingdom, this auditing criteria showed that the use of UDCA was slightly less complete than might be hoped for, and dosing was low.[6] There was a reasonable rate of recording of response. This is owing to the legacy of treatment; in most patients, dosing is below 13 to 15 mg/kg. The majority of undertreated patients were still UDCA responders; in fact, frequently they have normal liver function tests. We are advising clinicians who have performed audits to not increase the dose of UDCA in an 80-year-old patient with normal liver function tests just because they are defined as being underdosed. If they have responded as you want them to, then that is good enough. Audit is useful and sheds light on management, but the results should not be used dogmatically.

Dr Kris V. Kowdley The theme that we are all converging on is that it is great to use population-based data, but it must be individualized to the patient, particularly in light of his or her current symptoms (whether they are related to liver disease or not). It is necessary to look at the individual patient's disease trajectory when deciding whether second-line therapies might be an option.

Dr David E. Jones In addition, we are not implying that a particular biomarker level should automatically trigger initiation of second-line therapy. Instead, these

levels should be recorded and conveyed to the patient. The decision regarding second-line treatment should be made together with the patient. Second-line therapy is not appropriate in all cases, but it must always be considered. The patient's views must be incorporated into the management plan. Data from our audit study suggest that clinicians are not involving the patient in this decision.

Dr Kris V. Kowdley Use of auditing in patients with PBC should be advocated. Electronic medical records can be scanned to check whether a patient's ALP level is abnormal. A clinician may choose not to take any action based on this information. However, it can be helpful to know.

Dr Gideon M. Hirschfield It is all about graded risk. It is highlighting the risk to all of the clinicians who manage patients with PBC—not just those who specialize in PBC—so that they can be sure to maintain that dialogue with the patient. There are several treatment options. Obeticholic acid is FDA-approved for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. Other options included off-label therapy with fibrates, as well as clinical trials. The clinician should guide, but not direct, the conversation with the patient about treatment.

Dr Kris V. Kowdley What are your thoughts, from Canadian and UK perspectives, regarding the current roles of vibration-controlled transient elastography and liver biopsy?

Dr David E. Jones Vibration-controlled transient elastography has gone prime time. It is universally available in the United Kingdom. In most centers, it is the chosen way to screen for progression of disease in all patients. Unlike a computed tomography scan, it provides a real-time observation. Rogue results can occur, even with good operators. That just means there needs to be a level of caution with its use. The more times a clinician uses this technique, the more they get a feel for it. It is a very useful tool.

Biopsy is no longer routinely performed for diagnosis. An exception would be a truly autoantibody-negative patient, in whom a biopsy is required to diagnose PBC. We perform biopsies in approximately 10% of patients, in nearly all cases to investigate why the patient did not respond as predicted to therapy. In this way, biopsy is used in a targeted way, again reflecting the individualization of therapy. If selection of the next treatment is unclear, then biopsy can be a useful tool. As we develop better molecular tools to interrogate the tissue, biopsy may become less relevant.

Dr Gideon M. Hirschfield I agree. In Canada, there are geographic issues, similar to the United States. Vibration-controlled transient elastography is the standard-of-care in the larger centers, but there are still access issues for patients who live further away from these centers. In my practice, patients undergo vibration-controlled transient elastography every 1 or 2 years. This frequency might be high, but I find it helpful. What I do not find helpful about vibration-controlled transient elastography is its standardized reporting. Vibration-controlled transient elastography should not be used to provide standard values in cholestatic liver disease. It should be used to provide broad information over time.

Additionally, it is important to avoid false reassurance. Just because the vibration-controlled transient elastography result stays the same for a few years, this would not be a sufficient reason to ignore a very high ALP. The nature of the disease is very slow, and the nature of decompensation in cholestasis liver disease is very fast.

Liver biopsy continues to have a role. I primarily perform biopsies in the context of clinical trials, and also I use biopsies selectively. I do not use biopsies for staging. I do use biopsies when there might be an overlap disease. The most common overlap of PBC is with nonalcoholic steatohepatitis (NASH), not autoimmune hepatitis! I think that is an important issue in the United States and in Canada, and it is evolving. Histology is a helpful way to distinguish between PBC and NASH. Patients tend to agree to undergo biopsies when the reasons are made clear.

It is necessary to provide input to pathologists. When I request a liver biopsy in a patient with autoimmune liver disease, I inform the pathologist of the type of information needed. Otherwise, there is the risk that the pathologist will provide a standardized assessment that may not be optimal for these more complex diseases.

Dr Kris V. Kowdley The comment about the pathologist is critical. Often, a pathologist will make an offhanded comment, such as that interface hepatitis is present. This comment can lead the general gastroenterologist to initiate treatment with immunosuppression based on a diagnosis of overlap syndrome, which ultimately muddies the waters a great deal.

In the United States, the availability of vibration-controlled transient elastography is limited. The challenge is, again, based on the practice. In our practice, we have many patients with PBC, and they are engaged and proactive. Thus, we keep up with current advances and implement leading-edge treatment strategies. In the United States, the largest number of patients with PBC are treated in gastrointestinal practices. Most of these practices will have only a handful of PBC patients. It

is these practices that likely are not utilizing vibration-controlled transient elastography. This challenge underlies the importance of performing an audit to confirm the number of patients with PBC in your practice and to track their ALP levels.

Dr Gideon M. Hirschfield In North America, there is an opportunity for patients with PBC to access virtual medicine, as well as other health care providers, such as nurse practitioners and physician assistants. These health care professionals can be a key member of the health care team, particularly in the United States. In Canada, there are fewer people championing the complexity of PBC and the precision needed to care for this rare disease, even in the gastrointestinal community.

Dr Kris V. Kowdley How would you manage a patient who has PBC on biopsy, but has more ALT/AST elevation compared with ALP elevation, and who has no overlap or autoimmune features on biopsy?

Dr Gideon M. Hirschfield My hypothesis is that overlap disease will disappear with better PBC-focused treatments. Ultimately, there will be a very small number of patients who have true overlap. Better treatment of PBC will lead to improvements in liver function tests, including transaminases. Maybe the answer in the future will be novel combinations of drugs.

Dr David E. Jones I agree. Although having said that, occasionally a patient will respond to corticosteroids. Clearly, other treatments are needed in addition to UDCA. The balance of evidence now suggests that second-line PBC therapy should be a consideration.

If second-line treatments do not achieve an adequate response—and the patient is showing ongoing disease activity—then corticosteroids, such as budesonide, might be an option. However, second-line PBC therapy should always be considered before a corticosteroid.

Disclosures

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Slide Library

Primary Biliary Cholangitis

- PBC is a chronic autoimmune disease of the liver associated with damage to the bile ducts
- The bile duct damage exhibits a specific pathology, with selective and progressive destruction of intrahepatic ducts
- Untreated, PBC can lead to cholestasis and fibrosis of the liver, which triggers both intrahepatic and extrahepatic complications
- Ultimately, PBC can result in end-stage liver disease, with potentially fatal results

PBC, primary biliary cholangitis.

Primary Biliary Cholangitis: Biochemical Markers

- As more patients are diagnosed earlier in the course of disease—when their liver function is less compromised—there has been an effort to utilize biochemical markers as potential predictors of outcome in PBC
- The primary biochemical markers include bilirubin and alkaline phosphatase
- Bilirubin is a signifier of more advanced disease stages, whereas alkaline phosphatase might better predict long-term outcome and the risk for future events

Primary Biliary Cholangitis: Early Diagnosis

- Patients usually present because results from their serum liver tests are cholestatic, including elevations in ALP and gamma-glutamyltransferase
- Most patients are asymptomatic
- Persistent serum liver tests showing cholestasis will lead to tests of antimitochondrial antibodies and immunoglobulins
- Elevated levels of IgM are common
- Most patients receive a confirmed diagnosis without a liver biopsy

ALP, alkaline phosphatase; IgM, immunoglobulin M.

The Global PBC Study

- The correlation of serum ALP and bilirubin levels, either individually or in combination, with transplant-free survival was evaluated in the Global PBC Study
- A total of 4845 patients were included in the analysis
- This meta-analysis demonstrated a strong association between abnormally increased serum ALP and bilirubin levels with reduced transplant-free survival in patients with PBC
- The study confirmed that a combination of both variables improves prognostic prediction in these patients, regardless of whether they received UDCA

1. Lammers WJ et al. Gastroenterology. 2014;147(6):1338-1349.

Primary Biliary Cholangitis: Symptoms

When symptoms do occur, they can include:

- Pruritus
- Fatigue
- Joint aches
- Abdominal discomfort
- Sicca complex (dry eyes/dry mouth)
- Low bone mass
- Depression
- Anxiety
- Sleep disturbance

New Data From the Global PBC Study Group

- In 2020, data from the Global PBC Study Group showed that[1]:
  − A bilirubin threshold of 0.6 mg/dL may be a cutoff point at which the risk for liver transplant or death begins to increase
  − Any ALP elevation exceeding 1 × ULN may indicate that the patient has an ascending linear risk with regard to long-term outcomes
- As the patient progresses into second- and third-line therapies, as well as combination therapies, it is no longer acceptable to settle for an ALP of less than 1.67 × ULN. Instead, it may be better to strive for an ALP level as close to normal as possible, or at least below 1.5 × ULN

UDCA, ursodeoxycholic acid.
1. Lammers WJ et al. Gastroenterology. 2014;147(6):1338-1349.

Primary Biliary Cholangitis: Prognostic Scores

- UDCA is a frequent first-line treatment in patients with PBC, and it improves survival. The biochemical response to treatment with UDCA is a strong predictor of long-term outcomes in patients with PBC.[1] Several prognostic models are based on the biochemical response:
  - The GLOBE PBC score
  - The UK-PBC risk score
  - The Paris I and II criteria
  - The Toronto criteria
- The APRI index also predicts outcomes in PBC, and it was shown to be independent of the UDCA response[2]

APRI, aspartate transaminase to platelet ratio index.
1. Pares A et al. Gastroenterology. 2006;130:715-720. 2. Trivedi PJ et al. J Hepatol. 2014;60(5):1249-1258.

The UDCA Response Score

- The UDCA Response Score (URS) uses pretreatment clinical parameters to predict a patient's response to first-line UDCA treatment
- The URS provides a tool for evaluating patients when they first present with PBC
- Even more important than the actual score is the insight it provides into how the patient will respond to treatment
- In the future, this information might be used to treat patients better from the beginning

Management Goals: Normal Levels

- There is no clear consensus regarding which prognostic score is the most useful. It is more important to ensure that at least one of the scores is used
- Another approach would be to move the patient toward normal levels. By considering where the patient is currently—how much fibrotic scarring there is, and how well the disease has been treated or might be treated—the clinician then has information to act on
- Managing patients with the goal of moving them toward normal values has 2 advantages: it will lead to better treatment (particularly for patients with residual disease) and the concept is easier to understand

Management Considerations

- The most important consideration in the management of PBC is how the patient responded to previous treatment
- The clinician must gauge the amount of scarring in the liver, as well as the degree of fibrosis
- Vibration-controlled transient elastography can help determine the extent of liver damage. However, these scans occasionally produce rogue results
- Biopsy is no longer a preferred method to stage patients. Tools such as the APRI score and even simple platelet counts can be useful
- It is essential to determine the disease stage—regardless of the method used—because it will dictate the patient's course

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