EDITORIAL

Is Magnetic Resonance Cholangiopancreatography Worth a Thousand Words in Determining Prognoses of Patients With Primary Sclerosing Cholangitis?

For many patients, their diagnosis of primary sclerosing cholangitis (PSC) was one of the first times they had to confront their own mortality. Those patients who searched the Internet typically found troubling results, with early natural history studies from tertiary referral centers reporting the median survival from diagnosis to death or liver transplantation of approximately 10 years. The next difficult moment was learning that there is no therapy available to treat PSC. For these patients with a recent diagnosis, some of our goals are to help them understand the heterogeneous nature of PSC and their current position along the disease course.

Previous experience with natural history models in PSC has yielded mixed results, and none of these models has been widely incorporated into routine clinical practice. The initial attempt was the Mayo risk score that included age, fibrosis stage from liver biopsy, the presence of inflammatory bowel disease, serum bilirubin, and hemoglobin. Other early approaches also included liver biopsy staging, but the variable pattern of fibrosis and risk of sampling led to the exclusion of fibrosis stage in time. The revised Mayo risk score includes age, serum albumin, aspartate aminotransferase, serum bilirubin, and history of variceal hemorrhage to predict survival out to 4 years. The Mayo risk score has seen limited adoption with its 4-year time frame and limited ability to guide patients in early phases of disease. The Model for End-Stage Liver Disease is commonly used in liver transplant allocation but is appropriate with advanced liver disease and only predicts survival at 90 days. The Amsterdam-Oxford model was recently developed to predict liver-related mortality and liver transplantation. This model uses PSC subtype, age at diagnosis, albumin, platelets, aspartate aminotransferase, alkaline phosphatase, and bilirubin. The Amsterdam-Oxford model has moderate test characteristics that will limit its use in clinical practice. Alkaline phosphatase has frequently been noted to predict outcomes in PSC, but its use is also limited by the natural fluctuations in otherwise clinically stable patients. The most recent attempt for this type of score has emerged from the United Kingdom (UK), with 2 UK-PSC risk scores to predict 2-year and 10-year outcomes of liver transplantation or death. The components of these scores are age, bilirubin, alkaline phosphatase, albumin, platelets, extrahepatic biliary disease, and variceal hemorrhage. These scores demonstrated good discrimination in the recent study, and it will be important to see their performance in other cohorts.

With ongoing challenges in developing prognostic scores for PSC, recent studies have considered magnetic resonance cholangiopancreatography (MRCP) findings as a potential biomarker in these models. A systematic review and meta-analysis of 6 studies with 456 patients reported that the sensitivity and specificity of MRCP for diagnosing PSC were 86% and 94%, respectively. The widespread adoption of MRCP as a diagnostic tool has led to considerations of other uses and applications including prognostication.

In this issue of Clinical Gastroenterology and Hepatology, Lemoine and Cazzagon are the co-first authors on an article that examined the validity of scoring systems derived from MRCP-based criteria to predict clinical outcomes in patients with PSC. The Anali scores were named with a combination of the first names of 2 of the authors in their initial article that described the development of the scores. That initial study included the development of standardized radiologic criteria from MRCP studies and then a cohort study with multivariate analysis to develop scores to predict radiologic progression. Studies with and without gadolinium were included, and 2 separate scores emerged to predict radiologic progression. The score for studies without gadolinium includes dilation of intrahepatic bile ducts, hepatic dysmorphism, and portal hypertension. The score for studies with gadolinium included dysmorphic- and parenchymal enhancement heterogeneity. The current study takes these scores developed to predict radiologic progression to see whether they could also predict the clinical outcomes of survival without liver transplantation or cirrhosis decompensation. The study was well-designed and included an internal cohort and then a multicenter international cohort for validation, although a significant limitation of this study is the retrospective design. Two expert radiologists were blinded to clinical information and reviewed the studies together in conference. The approach means that the study cannot comment on interobserver agreement, which could be a major issue because of the subjective nature of some of the components in the Anali scores. The study found that the Anali scores performed fairly well in predicting survival without liver transplantation or cirrhosis decompensation. The Anali score without gadolinium had an area under the receiver operating characteristic curve (AUROC) of 0.89 in the internal cohort and 0.76 in the external cohort. The score with gadolinium had an AUROC of 0.76 in the internal cohort and 0.73 in the external cohort. Cox regression modeling found that both Anali scores were associated with survival. With the exception of high serum bilirubin in the
model for the Anali score without gadolinium, all other laboratory results were not statistically significant in the multivariate analysis.

The results from this study suggest the Anali scores may be helpful in prognostication, and future studies will be important to gain more insight and perhaps determine their role in clinical practice. The 2 Anali scores with and without gadolinium have different components and different thresholds to be classified as an abnormal score. Although this reflects the variable use of contrast in MRCP studies with PSC patients, the awkwardness of the different scores might affect their acceptance in clinical practice. Their test characteristics in the external cohort suggest that the accuracy for the Anali scores is fair, and perhaps the accuracy would improve if the scores were combined with other scoring systems or other modalities. MRCP is likely to remain a common test for patients with PSC, and incorporation of the findings into this type of score is very logical. This study only looked at baseline MRCP, and perhaps 2 studies over the course of 1- to 2-year period would be more predictive. The authors mention transient elastography, which has limited data in PSC to this point but might also be an important component for consideration. In addition to these questions, more research is needed for the Anali scores. The components have a subjective portion in the assessment, and the current study design had the 2 expert radiologists work together in conference for the readings. Performance by radiologists outside the study team and interobserver agreement will be important to understand with the Anali scores.

When progress is made in a challenging area as with the Anali scores, it becomes easier to see the gaps in knowledge. When considering a patient with a new diagnosis of PSC, patients and their clinicians would want to be able to comment on prognosis all along the disease course, including those with early stage PSC. The approach with the UK-PSC score to predict 2-year and 10-year outcomes comes closer to that need for short-term and longer-term prognostication. Patients and clinicians want to understand mortality risk and the need for transplantation but also predict the full range of major complications, including ascending cholangitis, cholangiocarcinoma, and complications of portal hypertension. Surveillance and treatment strategies could be targeted to those at the greatest risk, and those with lower risk would be offered some reassurance. This study did not evaluate the risk of ascending cholangitis or cholangiocarcinoma. The authors appropriately believed that the retrospective nature of their study would affect their ability to assess for ascending cholangitis, and this question would be best evaluated in a prospective study. When considering the risk of ascending cholangitis, it is curious that only one direct measure of bile ducts (dilation of intrahepatic bile ducts) made one of the Anali scores. The biliary nature of injury in PSC is perhaps accounted for by the hepatic dysmorph and the parenchymal enhancement heterogeneity.

Further research is needed to understand the development of ascending cholangitis, with an ultimate goal of prevention.

Although the Anali scores warrant further research before they can be considered for use in routine clinical practice, their development has been important for the field of PSC research. The standardized radiologic criteria developed early in the process have been an advance for the field. The Simtuzumab program used these specific criteria in an analysis of patients in their prospective trial and developed a score to predict clinical outcomes and progression to cirrhosis.1,17 The score from the Simtuzumab program had similar components to the Anali scores and included hepatic dysmorph, portal hypertension, and the presence of perihepatic lymph nodes. The most common clinical event in the phase 2 Simtuzumab study was ascending cholangitis, which would suggest that the Anali scores might also be able to predict this outcome.

The field of hepatology has seen numerous major advances in the last 3 decades, and so the lack of progress for treatment of PSC is disappointing for patients and their clinicians. After multiple failed attempts in the past, there is new energy with multiple drugs in development for PSC. As we look toward the day that these treatments are available to patients, these current prognosis studies are critical. With a heterogeneous course that plays out over multiple decades, it will be helpful to understand which patients are at risk for the different types of complications in the short-term and long-term. Therapies with different mechanisms of action might be more appropriate at different points in the disease course. Perhaps identifying patients at risk for complications will teach us more about the pathophysiology of PSC and guide development of therapies. There is reason to be hopeful that we are close to a major breakthrough for the treatment of PSC, and this research to understand the prognosis is a vital component that needs to continue.

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References


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