Simple Magnetic Resonance Scores Associate With Outcomes of Patients With Primary Sclerosing Cholangitis

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BACKGROUND & AIMS: **Primary sclerosing cholangitis (PSC) has a variable, often progressive, course. Magnetic resonance cholangiography (MRC) is used in the diagnosis of PSC. Magnetic resonance risk scoring systems, called Anali without and with gadolinium, are used to predict disease progression, determined by radiologic factors. We aimed to assess the prognostic value of Anali scores in patients with PSC and validate our findings in a separate cohort.**

METHODS: **We performed a retrospective study of patients with large-duct PSC (internal cohort, 119 patients in France; external cohort, 119 patients in Canada, Italy, and the United Kingdom). All the first-available MRC results were reviewed by 2 radiologists and the Anali scores were calculated as follows: Anali without gadolinium = (1× dilatation of intrahepatic bile ducts) + (2× dysmorphy) + (1× portal hypertension); Anali with gadolinium = (1× dysmorphy) + (1× parenchymal enhancement heterogeneity). The primary end point was survival without liver transplantation or cirrhosis decompensation. The prognostic value of Anali scores was assessed by Cox regression modeling.**

RESULTS: **During a total of 549 patient-years for the internal cohort and 497 patient-years for the external cohort, we recorded 2 and 8 liver transplantations, 4 and 3 liver-related deaths, and 26 and 25 cirrhosis decompensations, respectively. In the univariate analysis, factors associated with survival without liver transplantation or cirrhosis decompensation in the internal cohort were as follows: serum levels of bilirubin, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase, alkaline phosphatase, albumin, and Anali scores. Anali scores without and with gadolinium identified patients' survival without liver transplantation or cirrhosis decompensation with a c-statistic of 0.89 (95% CI, 0.84–0.95) and 0.75 (95% CI, 0.64–0.87), respectively. Independent prognostic factors identified by multivariate analysis were Anali scores and bilirubinemia. The prognostic value of Anali scores was confirmed in the external cohort.**

CONCLUSIONS: **In internal and external cohorts, we found that Anali scores, determined from MRC, were associated with outcomes of patients with PSC. These scores might be used as prognostic factors.**

Keywords: Cholestatic Liver Disease; Radiology; Imaging; Biliary Tract; Prognosis.

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Abbreviations used in this paper: AUROC, area under the receiver operating characteristic curve; GBCA, gadolinium-based contrast agent; LS, liver stiffness; LT, liver transplantation; MR, magnetic resonance; MRC, magnetic resonance cholangiography; MRI, magnetic resonance imaging; PSC, primary sclerosing cholangitis.

Most current article

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2019.03.013

See editorial on 2654.

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease of unknown etiology characterized by inflammation and obliterative fibrosis of the biliary tree. Although the course is highly variable, PSC often is progressive, leading to biliary cirrhosis and its complications.[1] Overall, PSC is a severe disease and median transplant-free survival ranges from 13 years in patients seen at tertiary referral centers to 20 years in a population-based cohort.[2,3] Currently, there is no effective medical therapy and liver transplantation (LT) is the only life-extending therapeutic intervention for patients with end-stage liver disease. In the past 30 years, many potential prognostic factors including clinical, biochemical, histologic, elastographic, and radiologic features were examined.[1] Identification of prognostic factors is essential for tailoring the follow-up strategies and/or testing new therapeutic modalities in homogeneous groups of PSC patients. PSC-specific clinical scores combining different single prognostic factors have been proposed and validated.[1] Nevertheless, clinical scores have several limitations, and none of them is recommended in the clinical practice for a single patient.[4] Recently, a new prognostic model (Amsterdam–Oxford model) was proposed, but it showed a moderate prognostic value (c-statistic, 0.68) and was validated only in the first 3 years after the diagnosis of PSC.[5] Liver stiffness (LS) measurement appears to be another promising tool because it is correlated with fibrosis and histologic stage[6] and both its baseline value and the rate of LS progression have been reported as strong prognostic markers in PSC.[7] For these reasons, LS now is considered a potential end point for future clinical trials.[8] However, prospective data regarding the prognostic value of LS are lacking. PSC is primarily a bile duct disease, so that the prognostic value of cholangiographic features assessed by endoscopic retrograde cholangiography also has been evaluated.[9] However, because of its invasive nature, this technique is restricted to patients who need a therapeutic intervention.[10] Magnetic resonance cholangiography (MRC), which combines high diagnostic performance, cost effectiveness, and noninvasiveness, is currently the first recommended modality to diagnose PSC.[10] In a previous study performed by our group on a cohort of 64 PSC patients, we proposed and applied a standard model of interpretation of PSC lesions that quantified each intrahepatic and extrahepatic bile duct and parenchymal lesion.[11] We showed in this study that half of the patients displayed radiologic progression during a mean follow-up period of 4 years and that this progression was predicted independently by the presence, at baseline, of severe intrahepatic bile duct dilatation, dysmorphy, portal hypertension, and parenchymal enhancement heterogeneity after the injection of a gadolinium-based contrast agent (GBCA).[11] By using the combination of these features, we built 2 magnetic resonance (MR) risk scores (with and without GBCA administration), called Anali scores,[11,12] the purpose of which was not to participate to the diagnosis of PSC but to predict radiologic progression in PSC patients.[11] The aim of the present study was to assess the clinical prognostic value of the 2 Anali scores in an internal cohort of PSC patients and to validate the results in an external multicentric international cohort.

What You Need to Know

Background

Magnetic resonance risk scoring systems, called Anali without and with gadolinium, are used to predict radiologic progression of primary sclerosing cholangitis (PSC). We assessed the prognostic value of Anali scores in patients with PSC.

Findings

In internal and external cohorts, we found that Anali scores, determined from magnetic resonance cholangiography, are associated with survival without liver transplantation or cirrhosis decompensation of patients with PSC.

Implications for patient care

The Anali scoring system could be used to determine risk, select treatment, and design clinical trials for patients with PSC.

Patients and Methods

We designed a longitudinal retrospective study that conformed to the ethical guidelines of the 1975 Declaration of Helsinki and the protocol was approved by the ethical committee or institutional review board of all participating centers. Informed consent was obtained according to the local ethical committee policy.

Inclusion criteria were the following: age at inclusion of 18 years and older, diagnosis of large-duct PSC, and 1 baseline liver MR imaging (MRI) with MRC (including T1- and T2-weighted MR images and 3-dimensional MRC) available for review. Diagnosis of large-duct PSC was defined by the association of chronic cholestasis, typical features on MRC, and no cause of secondary sclerosing cholangitis.[4] The liver MRI, the closest MRI to the diagnosis of PSC, available for review, was considered the baseline MRI, and the date of this MRI was defined as the date of inclusion. Exclusion criteria were as follows: poor quality of MRI, absence of typical features of PSC on MRC, small-duct PSC, autoimmune hepatitis/PSC overlap syndrome, previous LT, previous choledocojejunostomy or hepatic comorbidities (viral hepatitis, alcoholic liver disease, or nonalcoholic fatty liver disease), secondary sclerosing cholangitis, cholangiocarcinoma, hepatocellular carcinoma, and cirrhosis decompensation at the time of inclusion.

Study Population

We investigated 2 cohorts of PSC patients: an internal cohort to assess the prognostic value of Anali scores and an external multicentric international independent cohort to validate the results. In each center, medical charts of patients with PSC or suspected PSC and with 1 MRI available were reviewed and selected according to the earlier-described criteria. Then, all MRIs from the internal and external cohorts were centrally reviewed by 2 expert radiologists together in conference (L.A. and S.E.M., with 25 and 12 years of experience in abdominal MRIs, respectively). Cases without typical radiologic features of large-duct PSCs were excluded (Supplementary Figure 1).

Internal Cohort

The internal cohort consisted of PSC patients regularly followed up at Saint-Antoine Hospital in the national Reference Center for Inflammatory Biliary Diseases and Autoimmune Hepatitis in Paris, France. Among the 268 screened patients, 119 were included after central radiologic reviewing and comprised the internal cohort (Supplementary Figure 1). It should be emphasized that the 64 patients who comprised the previous cohort used to build the aforementioned Anali scores[11] were not included.

External Cohort

The external cohort consisted of PSC patients regularly followed up in 3 reference centers for inflammatory biliary disease: the Liver Unit of the Queen Elizabeth Hospital in Birmingham, United Kingdom, the Center for Rare and Cholestatic Liver Disease of the University of Padova in Padova, Italy, and the Liver Unit of the McGill University Health Center in Montreal, Canada. Among the 202 patients screened in these centers, 119 were included after central radiologic reviewing and comprised the external cohort (Supplementary Figure 1). External cohort patients were not matched to internal cohort patients.

Magnetic Resonance Imaging Technique

MRI was performed according to the protocol for 3-dimensional MRC that was described previously[13] and in line with the recommendations provided by the International PSC Study Group.[14] According to inclusion criteria, T1- and T2-weighted MRI and 3-dimensional MRC were performed in all cases. When performed, a fat-suppressed, T1-weighted, ultrafast, gradient-echo acquisition was performed before and after intravenous administration of 20 mL of GBCA with hepatic arterial, portal venous, and equilibrium phase acquisition (30 s, 80 s, and 3 min, respectively). Administration of GBCA was performed at the radiologist's discretion, most often when disease seemed severe or when cholangiocarcinoma was suspected.

Image Analysis

The 2 expert radiologists, blinded to clinical information, reviewed all MRIs together in conference. MRIs from external centers were transmitted by compact disc. Native images and 3-dimensional maximum intensity projection reconstructions were analyzed on a Workstation, using the Carestream Picture Archiving and Communication System (version 11.32; Carestream Health, Rochester, NY). Maximum intensity projections were analyzed on thick slabs of 10 or 20 mm, oriented in the acquisition plane.

Image analysis was performed using a standard model described previously[11] and the 2 Anali scores, without and with gadolinium, were calculated as follows: Anali without gadolinium was calculated as (1 $\times$ dilatation of intrahepatic bile duct) + (2 $\times$ dysmorphy) + (1 $\times$ portal hypertension), with a possible score range of 0 to 5; and Anali with gadolinium was calculated as (1 $\times$ dysmorphy) + (1 $\times$ parenchymal enhancement heterogeneity), with a possible score range of 0 to 2.

Intrahepatic bile duct dilatation was scored 0 if it was 3 mm or smaller, scored as 1 if it was 4 mm, and scored as 2 if it was 5 mm or larger. Dysmorphy, portal hypertension, and parenchymal enhancement heterogeneity were scored as 0 if absent and as 1 if present. Portal hypertension was defined by the presence of portosystemic shunts with or without splenomegaly. Dysmorphy was defined by significant atrophy of either the right or left hepatic lobe and/or marked lobulations of liver surface and/or increase of the caudate/right lobe ratio.[11]

Clinical Data Collection

Clinical and biological data were collected retrospectively from patient records by local clinicians at each center. Data were anonymized, transmitted to the principal investigators of the study (NC and SL), and centrally reviewed. The following data were collected: data of PSC diagnosis, association with inflammatory bowel disease, the closest biochemical analysis to the date of inclusion ($\pm$3 mo), liver stiffness at inclusion ($\pm$6 mo), and clinical events that occurred after inclusion (LT, death and cause of death, and cirrhosis decompensation defined as the occurrence of variceal bleeding, ascites, hepatic encephalopathy, or hepatorenal syndrome).

Statistical Analysis

Patient characteristics were summarized either as medians and interquartile ranges, or as absolute numbers and percentages. Because assays may vary between hospitals and over time, biochemical variables were expressed as ratios of upper limits of normal.

Continuous variables were compared between the internal and external cohorts using the Mann–Whitney test. Qualitative variables were compared using the

chi-square test or the Fisher exact test, as appropriate. To assess the prognostic value of Anali scores, the end point was adverse, outcome-free survival. Data were censored at the date of last visit or at the time of adverse outcome, defined as liver-related death, LT, or cirrhosis decompensation. In the internal cohort, we performed univariate Cox regression analysis using continuous biochemical variables, inflammatory bowel disease status, and Anali scores to identify factors associated with the risk of adverse outcome. A logistic c-statistics analysis including the Youden index calculation then was applied to determine the optimal threshold of biochemical variables and Anali scores that best predicted the occurrence of adverse outcome. The prognostic variables and their respective weight on the rates of survival without adverse outcomes were determined in the internal cohort using Cox backward stepwise regression analysis and then tested in the external cohort. Two multivariate Cox regression models were constructed separately according to the presence of Anali score without gadolinium in the first model and Anali score with gadolinium in the second model because of the presence in both scores of the same parameter (dysmorphy). Survival rates were calculated based on the Kaplan–Meier estimates. Statistical analysis was performed using IBM SPSS Statistics for Macintosh, v 24.0 (IBM Corp, Armonk, NY).

Results

General Characteristics

We included 238 PSC patients, 119 patients in the internal cohort and 119 in the external cohort. The clinical characteristics of the patients from both cohorts are shown in Table 1. Details of the external cohort subpopulations are shown in Supplementary Table 1. The 2 cohorts were comparable except for an older age at inclusion and a higher serum concentration of total bilirubin in the external cohort. A similar percentage of patients were included at the time of PSC diagnosis in the internal and external cohorts (52% vs 45%, respectively, $P = .4$).

Table 1. Clinical and Biochemical Characteristics of PSC Patients in the 2 Cohorts

	Internal cohort (n = 119)	External cohort (n = 119)	*P*
Male sex, n (%)	80 (67)	76 (64)	0.5
	0 (0)	*0 (0)*	
Age at PSC diagnosis, *y*	34 (21–43)	36 (25–51)	.05
	0 (0)	*0 (0)*	
Age at inclusion, *y*	36 (25–50)	40 (30–56)	.01
	0 (0)	*0 (0)*	
Interval time between diagnosis and inclusion, *y*	1 (0–4)	2 (0–7)	0.2
	0 (0)	*0 (0)*	
Localization at diagnosis			0.8
Intrahepatic only	32 (27)	30 (27)	
Intrahepatic + extrahepatic	87 (73)	89 (75)	
Extrahepatic only	0	0	
	0 (0)	*0 (0)*	
IBD	86 (72)	85 (71)	0.7
Ulcerative colitis	51 (79)	59 (69)	
Crohn's disease	29 (34)	19 (23)	
Indeterminate	6 (7)	7 (8)	
	0 (0)	*0 (0)*	
Liver stiffness, *kPa*	9.10 (6.60–12.20)	10.10 (6.00–14.20)	0.9
	50 (42)	*81 (68)*	
Total bilirubin level, *μmol/L*	15 (10–23)	20 (12–33)	.02
	29 (24)	*20 (17)*	
AST, ×ULN	1.31 (0.74–2.67)	1.70 (1.00–2.55)	0.1
	21 (18)	*23 (19)*	
ALT, ×ULN	1.67 (0.80–3.20)	1.80 (1.10–2.80)	0.7
	21 (18)	*21 (18)*	
γGT, ×ULN	4.20 (1.80–9.88)	4.15 (2.45–8.05)	0.9
	19 (16)	*26 (22)*	
ALP, ×ULN	1.57 (0.96–3.00)	1.86 (1.10–3.39)	0.3
	19 (16)	*24 (20)*	
Albumin, *g/L*	41 (36–44)	36 (40–44)	0.6
	40 (34)	*21 (18)*	
Platelet count, $\times 10^9$/L	291 (199–359)	244 (187–290)	.001
	23 (19)	*21 (18)*	

NOTE. Quantitative variables are expressed as the median (interquartile range). Nominal variables are expressed as an absolute number (percentage). Missing data are indicated in italics and are expressed as an absolute number (percentage).
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γGT, γ-glutamyl transpeptidase; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis; ULN, upper limit of normal.

Magnetic Resonance Descriptive Data

MRC with GBCA injection were available for 150 patients: 77 (66%) and 73 (61%) in the internal and external cohorts, respectively. The median Anali scores without gadolinium were 1 (interquartile range, 0–4) and 3 (interquartile range, 1–4) in the internal and external cohorts, respectively ($P = .01$). The median Anali scores with gadolinium were 1 (interquartile range, 0–2) and 2 (interquartile range, 0–2) in the internal and external cohorts, respectively ($P = .5$). The distribution of Anali scores is illustrated in Supplementary Figure 2. The distribution of Anali scores did not differ according to the inflammatory bowel disease status, in both cohorts (data not shown). In the internal cohort, patients who received GBCA injection had a higher concentration of serum bilirubin (31 vs 17 μmol/L; $P = .048$) and more often a high Anali score without gadolinium (3–5) than the group of patients who did not receive GBCA injection (59% vs 25%, respectively; $P = .01$). In the external cohort, no differences were observed between subgroups of patients, according to the GBCA injection (data not shown).

Follow-Up Evaluation and Clinical Events

A total of 549 and 497 patient-years were available in the internal and external cohorts, respectively. An

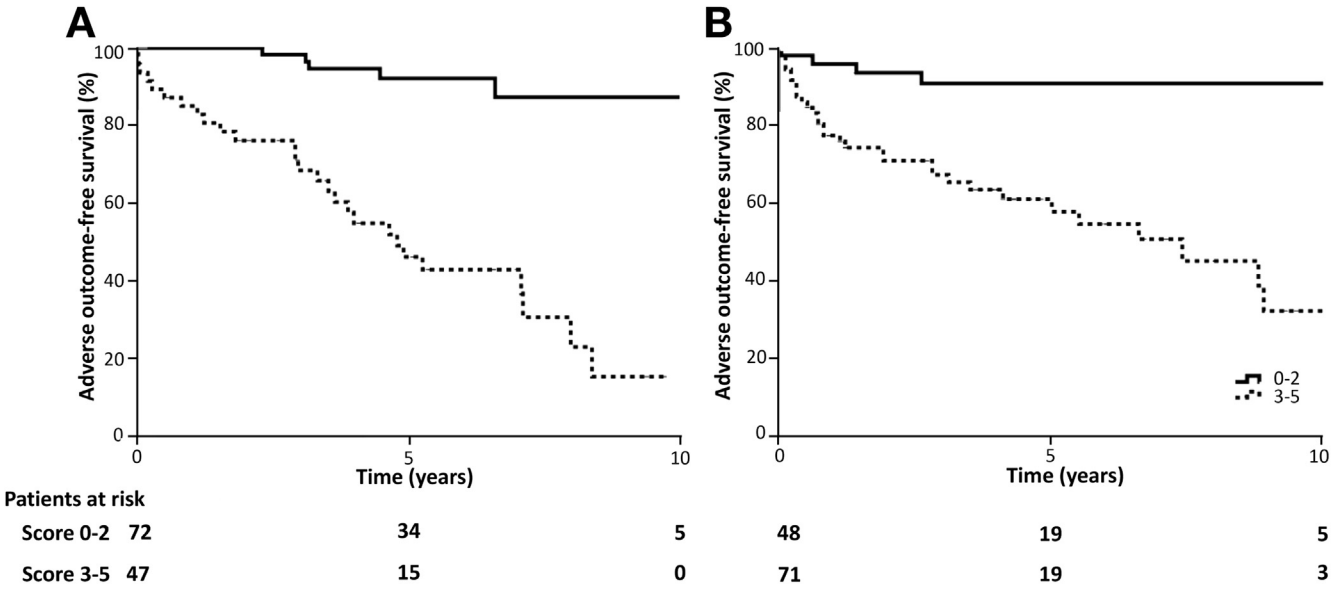

Figure 1. Adverse-outcome–free survival according to Anali score without gadolinium. Kaplan–Meier curves for adverse-outcome–free survival in (*A*) internal and (*B*) external cohorts, according to Anali score without gadolinium. The *solid line* and the *dashed line* represent patients with an Anali score without gadolinium of ≤2 and >2, respectively.

adverse outcome occurred in 32 patients (2 LT, 4 liver-related deaths, and 26 cirrhosis decompensation) and in 36 patients (8 LT, 3 liver-related deaths, and 25 cirrhosis decompensation) in the internal and external cohorts, respectively. The causes of death were cholangiocarcinoma in 6 patients and septic shock of biliary origin in 1 patient. The reasons for LT were end-stage liver disease in 7 patients, recurrent cholangitis in 2 patients, and cholangiocarcinoma in 1 patient. Overall, the 4-year adverse-outcome–free survival was 78% ± 4% and 73% ± 5% in the internal and external cohorts, respectively (.5) (Supplementary Figure 3).

Prognostic Performance of Anali Scores

The Anali score without gadolinium was strongly associated with the occurrence of adverse outcome in the internal and external cohorts ($P < .001$ for both) (Figure 1). In the internal cohort, the area under the receiver operating characteristic curve (AUROC) of Anali score without gadolinium was 0.89 (95% CI, 0.84–0.95). The cut-off value with the highest total sensitivity and specificity was 2 (sensitivity, 84%; specificity, 77%). The Anali score with gadolinium also was strongly associated with the occurrence of adverse outcome in both cohorts ($P = .001$ and $P = .003$, respectively) (Figure 2). In the internal cohort, the AUROC of Anali score with gadolinium was 0.76 (95% CI, 0.64–0.87). The cut-off value with the highest total sensitivity and specificity was 1 (sensitivity, 85%; specificity, 68%).

Likewise, in the external cohort, the AUROCs of Anali scores without and with gadolinium were 0.76 (95% CI, 0.67–0.85) and 0.73 (95% CI, 0.61–0.85), respectively.

In the internal cohort, the prognostic values of Anali scores were analyzed with those of variables significantly associated with adverse-outcome–free survival in univariate analysis (Table 2). In the first Cox regression model, including Anali score without gadolinium, independent predictors of adverse-outcome–free survival were high Anali score without gadolinium and high serum bilirubin level (Table 3). In the second Cox regression model, including Anali score with gadolinium, the radiologic score was the only independent predictor of adverse-outcome–free survival; a trend toward significance also was observed for alkaline phosphatase (Table 4). In this model, total bilirubin was excluded because the model did not converge owing to the presence of a significant correlation between total bilirubin and Anali score with gadolinium ($r = 0.467$; $P < .001$). In the external cohort, the Cox regression model confirmed that Anali score without gadolinium was associated independently with adverse-outcome–free survival (hazard ratio, 3.56; 95% CI, 1.21–10.48; $P = .02$). A trend also was observed for total bilirubin in the same model (hazard ratio, 2.36; 95% CI, 0.94–5.97; $P = .06$). Likewise, the Anali score with gadolinium was associated independently with adverse-outcome–free survival in the external cohort (hazard ratio, 5.27; 95% CI, 1.54–18.01; $P = .01$).

Discussion

The aim of this study was to assess the clinical prognostic value of 2 simple MR risk scores that we previously designed and showed were able to predict radiologic progression in PSC patients.[11] MRC is the recommended modality for the diagnosis of PSC.[10] Moreover, recent data have suggested that hepatobiliary cancer surveillance (including by MRI) improved the outcome and survival of patients,[15] possibly expanding the clinical utility of adding a

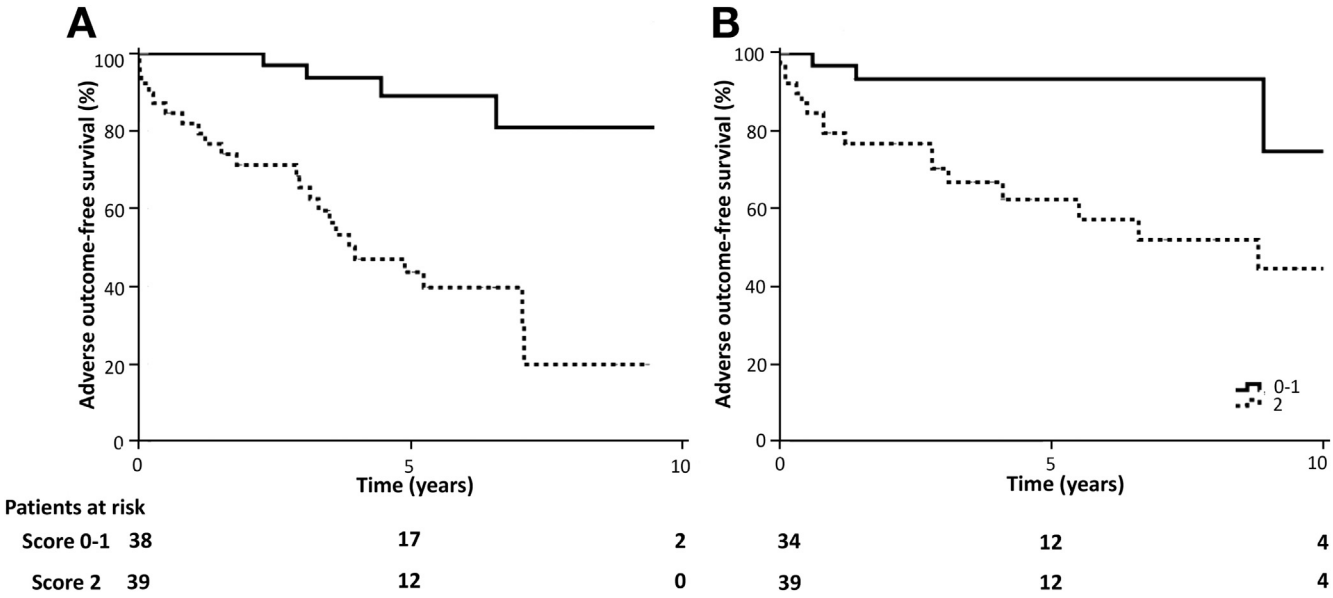

Figure 2. Adverse-outcome–free survival according to Anali score with gadolinium. Kaplan–Meier curves for adverse-outcome–free survival in (*A*) internal and (*B*) external cohorts, according to Anali score with gadolinium. The *solid line* and the *dashed line* represent patients with an Anali score with gadolinium of $\leq$1 and >1, respectively.

regular MRI to follow-up evaluation. Therefore, this is the right time to test the prognostic value of imaging features. Besides the noninvasive nature of MRC, another advantage of these 2 MR risk scores is that they combine both cholangiographic changes and the consequences of biliary disease on the liver parenchyma, thus allowing a global evaluation of the impact of the disease on the liver. In particular, Anali score without gadolinium includes not only dysmorphy, but also signs of portal hypertension, which faithfully reflects advanced liver disease, whereas dysmorphy can be caused by focal atrophy of the liver parenchyma secondary to a biliary obstruction, and therefore is not an unequivocal feature of cirrhosis in PSC.[12,16] Thus, we might hypothesize that Anali score without gadolinium potentially may be able to identify different stages of the disease rather than only distinguishing patients with and without advanced disease.

By using 2 large internal and external cohorts including 238 patients with large-duct PSC, we could show that these 2 scores were associated independently with the occurrence of adverse outcome. Indeed, in the internal cohort, the risk of developing an adverse outcome in patients with high Anali scores without and with gadolinium was 25- and 13-fold higher, respectively, than in patients with low Anali scores. Moreover, the prognostic performance of the 2 scores exceeded those of validated biochemical markers (alkaline phosphatase, bilirubin). Importantly, the prognostic value of these 2 scores has been confirmed in the external cohort.

Reports on the prognostic value of MR features in PSC patients are scarce. In a retrospective study including 53 patients, Kitzing et al[17] found that progressive hepatic morphologic changes on serial MRI were associated with adverse clinical outcome but the investigators did not report on biliary abnormalities. Other studies conducted in 62 and 47 PSC patients, respectively, have reported that arterial[18] and delayed[19] peribiliary enhancement were associated with a higher Mayo risk score, whereas yet another study including 48 patients found only a weak correlation between MRC score for extrahepatic bile ducts and hard end points (death and LT).[20] Taking advantage of the large phase 2 simtuzumab trial (NCT01672853) including 234 patients, Muir et al[21]

Table 2. Features Associated With Adverse-Outcome–Free Survival in the Univariate Analysis in the Internal Cohort

Parameter	HR	95% CI	*P*
Total serum bilirubin	1.01	1.01–1.02	<.01
AST	1.64	1.34–2.01	<.01
ALT	1.23	1.09–1.36	<.01
γGT	1.11	1.06–1.17	<.01
ALP	1.14	1.00–1.31	.05
Albumin	0.08	0.078–0.90	<.01
Anali without gadolinium	2.53	1.84–3.44	<.01
Anali with gadolinium	2.88	1.59–5.21	<.01

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γGT, γ-glutamyl transpeptidase; HR, hazard ratio.

Table 3. Features Associated With Adverse-Outcome–Free Survival in the Multivariate Analysis (Cox Regression Model 1 Including Anali Without Gadolinium) in the Internal Cohort

Parameter	HR	95% CI	*P*
Anali without gadolinium >2	24.95	3.25–191.75	<.01
Total bilirubin level >17 μmol/L	3.82	1.26–11.62	.02

HR, hazard ratio.

Table 4. Features Associated With Adverse-Outcome–Free Survival in the Multivariate Analysis (Cox Regression Model 2 Including Anali With Gadolinium) in the Internal Cohort

Parameter	HR	95% CI	*P*
Anali with gadolinium >1	13.72	1.76–107.03	.01
ALP >2 × ULN	3.068	0.85–11.02	.08

ALP, alkaline phosphatase; HR, hazard ratio; ULN, upper limit of normal.

proposed a MRI risk score based on MRC findings at baseline (portal hypertension, dysmorphy, and enlarged perihepatic nodes), which was associated with the development of clinical events that were mostly ascending cholangitis and jaundice. In a recent study of 111 PSC patients, Schulze et al[22] found a significant correlation between the relative enhancement in the hepatobiliary phase of liver parenchyma after hepatocyte-specific contrast agent injection on the one hand, and both hepatic function and hard clinical outcomes on the other hand.

Nevertheless, radiologic interpretation of MRI remains a challenge in PSC patients.[23] To decrease the subjectivity of MRC interpretation, we herein applied a standard model of interpretation.[11] Several patients from the different groups were excluded because the radiologists did not find any typical features of PSC on MRC. Although this exclusion could be considered as a bias, we assume that it represents a strength of our results because, by nature, inclusion of patients with normal MRC, which is very unlikely to progress, could falsely increase the performance of any severity score.

The Anali score without gadolinium is calculated with features assessed using standard series, whereas the Anali score with gadolinium needs an acquisition after GBCA injection. In PSC patients, there is no evidence to recommend contrast media injection during routine MRI unless a hepatobiliary cancer is suspected,[14] and thus the policy was to perform GBCA injection according to the radiologist's judgment of disease severity. This explains why injected patients in the internal cohort presented with more severe disease as confirmed by higher bilirubin levels and a higher Anali score without gadolinium compared with noninjected patients. This, together with the smaller sample size, could explain the lower prognostic performance of Anali score with gadolinium compared with Anali score without gadolinium.

We chose to assess the prognostic value of Anali scores using survival without LT and cirrhosis decompensation, which is a major event impacting the natural history of PSC and is related directly to the progression of fibrosis contrary to the occurrence of other complications such as acute cholangitis, cholangiocarcinoma, or colorectal cancer.

This study had some limitations. This was a retrospective study with an intrinsic bias and missing data. Intraobserver and interobserver variabilities of the 2 MR scores were not assessed. However, the 2 MR prognostic scores were calculated using binomial variables and a categoric variable (intrahepatic biliary dilatation), resulting in 2 simple and easy-to-calculate scores. However, the interobserver variability of Anali scores has to be addressed specifically in future studies with nonexpert radiologists. The Anali scores were evaluated only at a single time point, precluding determination of the prognostic value of dynamic changes of the scores in subsequent MRIs. Moreover, comparison with other validated prognostic scores or LS was not performed. Therefore, future studies should address these issues and especially assess the prognostic performance of Anali scores in combination with LS.

However, this work also had major strengths, including the study of 2 wide cohorts of well-characterized PSC patients with pure large-duct PSC, excluding overlap syndrome and hepatic comorbidities that would have modified both radiologic features and outcome. Additional strengths were the adequate follow-up period, the inclusion of both patients at the time of the PSC diagnosis and after the PSC diagnosis, the choice of hard and objective end points, and, finally, the central radiologic review by 2 expert radiologists.

In conclusion, this multicentric international study showed the prognostic value of 2 simple MR scores in PSC patients, strengthening the role of MRI in the management of PSC patients. These 2 simple scores can be used at different stages of PSC and could be applied to select patients for future clinical trials.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2019.03.013.

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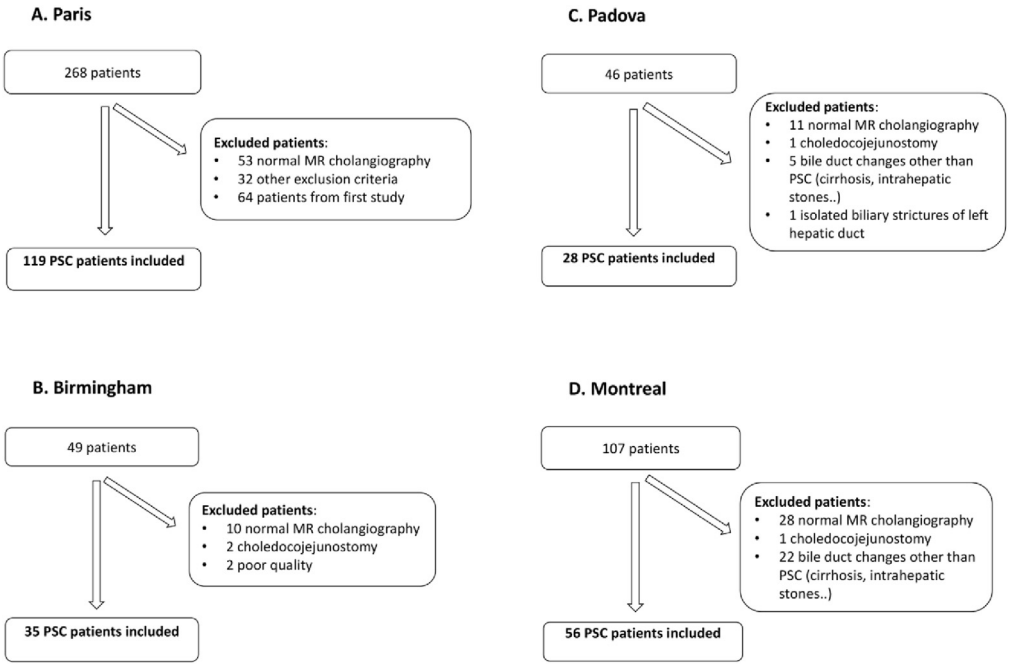
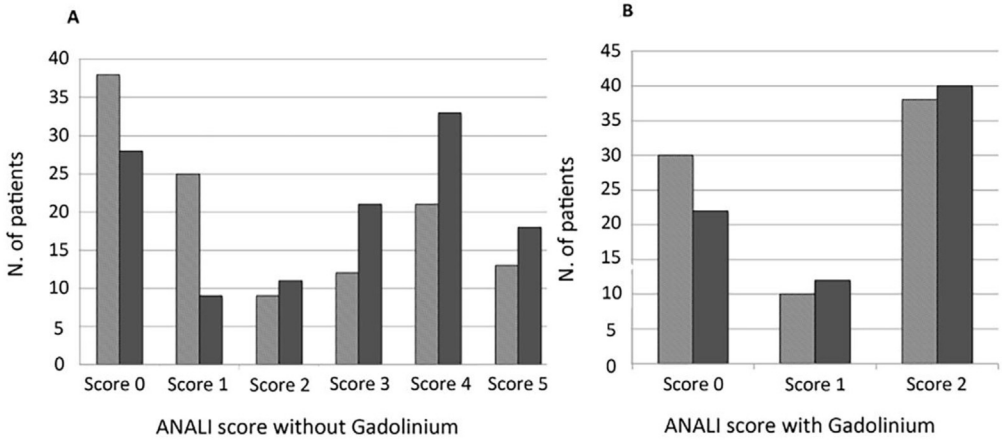
Conflicts of interest
The authors disclose no conflicts.

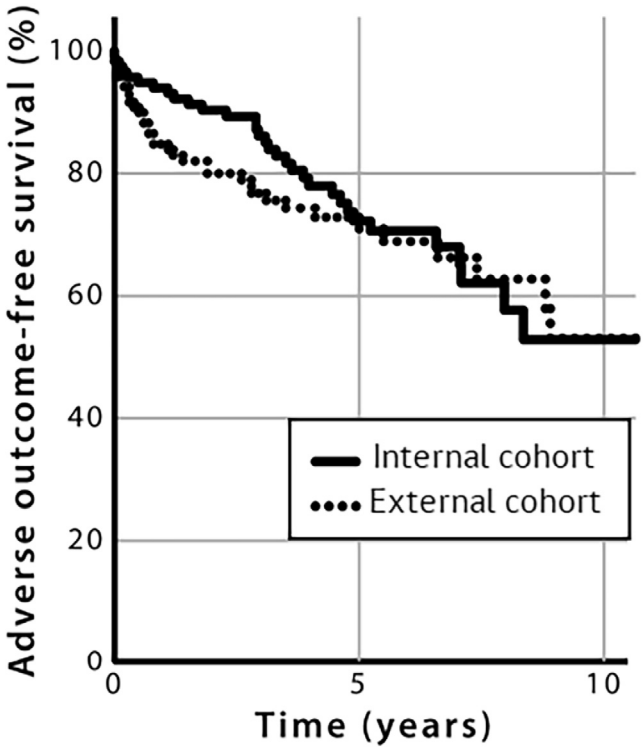
Funding
Supported by a European Association for the Study of the Liver Entry Level Sheila Sherlock fellowship for 2017 and 2018 for this project (N.C.). This work also was funded by the Microbiome Foundation.



Supplementary Figure 1. Flow chart of included patients in the internal and external cohorts. Inclusion of patients in the (*A*) internal cohort and in (*B–D*) subgroups of the external cohort. MR, magnetic resonance; PSC, primary sclerosing cholangitis.



Supplementary Figure 2. Distribution of patients according to the Anali scores. Distribution of patients according to (*A*) Anali score without gadolinium and (*B*) Anali score with gadolinium in the internal (*light grey bars*) and the external (*dark grey bars*) cohorts.



Supplementary Figure 3. Adverse-outcome–free survival in the internal and external cohorts. Kaplan–Meier curves for adverse-outcome–free survival in the internal (*solid line*) and external (*dashed line*) cohorts. Adverse outcome was defined by the occurrence of liver-related death, liver transplantation, or cirrhosis decompensation.

Supplementary Table 1. Characteristics of the External Cohort Subpopulations

	Padova cohort (n = 28)	Birmingham cohort (n = 35)	Montreal cohort (n = 56)
Male sex, n (%)	19 (68)	21 (60)	35 (63)
	0 (0)	*0 (0)*	*0 (0)*
Age at PSC diagnosis, *y*	29 (20–35)	38 (24–55)	41 (27–54)
	0 (0)	*0 (0)*	*0 (0)*
Age at inclusion, *y*	36 (30–43)	46 (30–62)	42 (28–54)
	0 (0)	*0 (0)*	*0 (0)*
Localization at diagnosis			
Intrahepatic	5 (18)	17 (49)	8 (14)
Intrahepatic + extrahepatic	23 (82)	18 (51)	48 (86)
Extrahepatic	-	-	-
	0 (0)	*0 (0)*	*0 (0)*
IBD	21 (75)	26 (74)	38 (68)
Ulcerative colitis	17 (81)	23 (89)	19 (50)
Crohn's disease	4 (19)	2 (8)	13 (34)
Indeterminate	-	1 (3)	6 (16)
	0 (0)	*0 (0)*	*0 (0)*
Liver stiffness, *kPa*	8.3 (5.4–12.1)	10.9 (6.1–16.6)	Not available
	12 (43)	*13 (37)*	
Total bilirubin, *μmol/L*	17 (8.7–25.5)	20 (13–36)	21 (13–47)
	0 (0)	*0 (0)*	*20 (36)*
AST, ×ULN	1.2 (0.8–2.0)	1.9 (1.1–2.6)	2.2 (1.3–3.6)
	1 (4)	*0 (0)*	*22 (39)*
ALT, ×ULN	1.5 (0.7–2.6)	1.8 (0.9–2.7)	1.9 (1.2–3.5)
	1 (4)	*0 (0)*	*20 (36)*
γGT, ×ULN	2.8 (0.8–6.7)	4.6 (2.8–9.3)	5.1 (2.9–8.3)
	2 (7)	*0 (0)*	*21 (38)*
ALP, ×ULN	1.4 (0.7–2.1)	3.1 (1.6–3.7)	1.9 (1.2–3-3)
	1 (4)	*3 (9)*	*20 (36)*
Albumin, *g/L*	41 (40–46)	43 (38–47)	35 (29–40)
	0 (0)	*0 (0)*	*21 (37)*
Platelet count, $\times 10^9$/L	250 (227–334)	206 (143–273)	262 (197–304)
	1 (4)	*0 (0)*	*20 (36)*

NOTE. Quantitative variables are expressed as the median (interquartile range). Nominal variables are expressed as an absolute number (percentage). Missing data are indicated in italics and expressed as an absolute number (percentage).

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γGT, γ-glutamyl transpeptidase; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis; ULN, upper limit of normal.