Predictors of Jaundice Resolution and Survival After Endoscopic Treatment of Primary Sclerosing Cholangitis

John E. Eaton,[1] Abdul Haseeb,[1] Christian Rupp,[2] Leonardo H. Eusebi,[3] Kim van Munster,[4] Robert Voitl,[2] Douglas Thorburn,[3] Cyriel Y. Ponsioen,[4] Felicity T. Enders,[5] Bret T. Petersen,[1] Barham K. Abu Dayyeh,[1] Todd H. Baron,[1] Vinay Chandrasekhara,[1] Christopher J. Gostout,[1] Michael J. Levy,[1] John Martin,[1] Andrew C. Storm,[1] Ross Dierkhising,[5] Patrick S. Kamath,[1] Gregory J. Gores,[1] and Mark Topazian[1]

The benefit of endoscopic retrograde cholangiopancreatography (ERCP) for the treatment of primary sclerosing cholangitis (PSC) remains controversial. To identify predictors of jaundice resolution after ERCP and whether resolution is associated with improved patient outcomes, we conducted a retrospective cohort study of 124 patients with jaundice and PSC. These patients underwent endoscopic biliary balloon dilation and/or stent placement at an American tertiary center, with validation in a separate cohort of 102 patients from European centers. Jaundice resolved after ERCP in 52% of patients. Median follow-up was 4.8 years. Independent predictors of jaundice resolution included older age (P = 0.048; odds ratio [OR], 1.03 for every 1-year increase), shorter duration of jaundice (P = 0.059; OR, 0.59 for every 1-year increase), lower Mayo Risk Score (MRS) (P = 0.025; OR, 0.58 for every 1-point increase), and extrahepatic location of the most advanced biliary stricture (P = 0.011; OR, 3.13). A logistic regression model predicted jaundice resolution with area under the receiver operator characteristic curve of 0.67 (95% confidence interval, 0.5-0.79) in the validation set. Independent predictors of death or transplant during follow-up included higher MRS at the time of ERCP (P < 0.0001; hazard ratio [HR], 2.33 for every 1-point increase), lower total serum bilirubin before ERCP (P = 0.031; HR, 0.91 for every 1 mg/dL increase), and persistence of jaundice after endoscopic therapy (P = 0.003; HR, 2.30). *Conclusion:* Resolution of jaundice after endoscopic treatment of biliary strictures is associated with longer transplant-free survival of patients with PSC. The likelihood of resolution is affected by demographic, hepatic, and biliary variables and can be predicted using noninvasive data. These findings may refine the use of ERCP in patients with jaundice with PSC. (*Hepatology Communications* 2022;6:809-820).

Primary sclerosing cholangitis (PSC) is a chronic fibroinflammatory disease characterized by multifocal biliary strictures, progressive liver dysfunction, and an increased risk of cholangiocarcinoma (CCA). Endoscopic retrograde cholangiopancreatography (ERCP) may be performed in patients with PSC to treat symptomatic biliary strictures by balloon dilation and/or stent placement.[1] The value of these interventions is debated. Some case series have reported resolution of biliary symptoms and improvement in liver biochemistries after ERCP,[2-9] while others have found that cholestasis is not related to the presence of

Abbreviations: AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristic curve; CCA, cholangiocarcinoma; CI, confidence interval; ERCP, endoscopic retrograde cholangiopancreatography; HR, hazard ratio; MCR, Mayo Clinic Rochester; MELD, Model for End-Stage Liver Disease; MRCP, magnetic resonance cholangiopancreatography; MRS, Mayo Risk Score; OR, odds ratio; PSC, primary sclerosing cholangitis.

Received March 25, 2021; accepted July 12, 2021.

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep4.1813/suppinfo.

Supported by the Division of Gastroenterology and Hepatology, Mayo Clinic (to M.T.).

The funding source had no role in the study design, data collection, data analysis, interpretation of data, drafting of the manuscript, or the decision to submit the manuscript for publication.

View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep4.1813

an untreated dominant biliary stricture and may spontaneously improve during follow-up.[10] Series using multivariable models to predict patient survival demonstrated delayed progression to death or liver transplantation after endoscopic therapy,[11,12] while others found that presence of a dominant biliary stricture portends shorter patient survival due to a higher prevalence of CCA.[13] No studies have developed models predicting jaundice resolution after endoscopic intervention in PSC.

Our objectives were to identify clinically useful predictors of jaundice resolution after endoscopic treatment of PSC and to determine whether response to endoscopic treatment is associated with improved patient outcomes. Jaundice is a physical sign that patients and their health care professionals can assess without laboratory testing. We chose jaundice resolution as the outcome of interest because the impact of ERCP on biliary symptoms, such as pain or pruritus, may be difficult to evaluate whereas jaundice is a quantifiable measure of hepatobiliary function. To standardize outcome assessment, we defined jaundice resolution as a decrease in serum bilirubin to ≤2.5 mg/dL because this is the approximate level at which jaundice becomes clinically undetectable.

Patients and Methods

This is a retrospective cohort study of consecutive patients with PSC undergoing ERCP for treatment of jaundice. Predictors of jaundice resolution and survival were derived and validated in separate patient sets. The study protocol was approved by the Mayo Clinic Rochester (MCR) institutional review board. Patients who waived review of medical records for research purposes were not enrolled.

PATIENT POPULATION

All patients with PSC undergoing ERCP at MCR between October 23, 1990, and December 5, 2018, were identified from clinical databases, and medical records were reviewed. Patients with jaundice were included in the derivation set if their first ERCP for treatment of jaundice (index ERCP) was performed at MCR; they were excluded if CCA was diagnosed before or during the index episode of care or if they had previously undergone biliary tract surgery (other than cholecystectomy). Jaundice was considered present if total serum bilirubin was ≥2.5 mg/dL (≥42.75 μmol/L).

Data abstracted from medical records included age, sex, comorbidities, history of varices, variceal hemorrhage, ascites, encephalopathy, symptoms, physical exam findings, laboratory results, and endoscopic interventions. The Mayo Risk Score (MRS) was calculated from the most recent data available before the index ERCP. Follow-up data were also collected from medical records.

CHOLANGIOGRAM REVIEW

Cholangiograms were reviewed with reference to ERCP reports to determine extent of ductal

Potential conflict of interest: Dr. Storm consults for ERBE; he received grants from Boston Scientific. Dr. Dayyeh consults for Boston Scientific, Medtronic, and BFKW; he is on the speakers' bureau for Olympus, Johnson and Johnson, and Endogastric Solutions; he received grants from Medtronic, Apollo Endosurgery, and USGI. Dr. Petersen consults for Olympus America; he received grants from Boston Scientific. Dr. Gostout consults for Olympus Medical. Dr. Chandrasekhara owns shares in Nevakar Corporation and consults for Covidien LLP; he is on the medical advisory board for Interpace Diagnostics. The other authors have nothing to report.

ARTICLE INFORMATION:

From the [1]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA; [2]Department of Internal Medicine IV, University Hospital of Heidelberg, Heidelberg, Germany; [3]Sheila Sherlock Liver Centre, Royal Free Hospital and the University College London Institute of Liver and Digestive Health, London, United Kingdom; [4]Amsterdam Universitair Medische Centra, Amsterdam, the Netherlands; [5]Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, USA.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Mark Topazian, M.D.
Mayo Clinic
200 First Street SW
Rochester, MN 55901, USA
E-mail: topazian.mark@mayo.edu
Tel.: +1-507-284-5000

visualization and location of the most advanced biliary stricture. We determined ductal dimensions from cholangiograms by measuring duct and duodenoscope diameter on the radiographs, then calculating the ratio of bile duct diameter to duodenoscope diameter and multiplying by the diameter of the duodenoscope used.

The intrahepatic ducts were considered nonvisualized if there was complete obstruction of both the right and left main ducts with no passage of contrast more proximally. The intrahepatic ducts were incompletely visualized if there was a complete obstruction of either the right or the left main intrahepatic duct, but not both, and were completely visualized if sectoral or segmental intrahepatic ducts were visualized on both the right and left sides. Complete drainage was defined as substantial clearance of contrast from right and left hepatic ducts on the final radiograph obtained at the conclusion of ERCP.

We defined the most advanced biliary stricture as a potentially flow-limiting stricture that was longer or tighter than the other strictures present elsewhere in the patient's biliary tree. The most advanced biliary stricture was identified based on the ERCP report and confirmed by review of cholangiograms. Each advanced stricture was characterized by its location, length, minimum luminal diameter, and ductal diameter both proximal and distal to the stricture.

We defined the ratio of dilation balloon diameter to duct diameter proximal to the most advanced stricture as (maximum diameter of the dilation balloon)/(bile duct diameter proximal to the treated stricture) (Fig. 1). If this ratio is >1, it implies that a stricture is balloon dilated beyond the upstream caliber of the affected duct.

TREATMENT DURATION AND CLINICAL OUTCOMES

An episode of care was defined as all therapeutic ERCPs performed within a 60-day period. ERCPs performed solely for acquisition of tissue specimens were not considered part of the episode of care. If stents were left in place for >60 days, the duration of the episode of care was extended to include the entire duration of continuous stenting.

Treatment success was defined as a decrease of the serum bilirubin to <2.5 mg/dL within the 60-day time period following the episode of care (or, if no serum bilirubin level was documented within 60 days, the next available serum bilirubin), without need for other interventions during that time period. Persistent jaundice was defined as failure of the serum bilirubin to decrease to <2.5 mg/dL.

VALIDATION COHORT

The validation cohort comprised all eligible patients with PSC undergoing endoscopic treatment of jaundice at Sheila Sherlock Liver Centre, Royal Free Hospital, University College London Institute of Liver and Digestive Health, London, United Kingdom; University Hospital of Heidelberg, Heidelberg, Germany; and Amsterdam Universitair Medische Centra, from December 5, 2018, moving backward in time as far as local databases allowed. The same inclusion and exclusion criteria were applied to both the derivation (MCR) and validation sets.

STATISTICAL ANALYSIS

For the derivation cohort, univariate and multivariable logistic regression models were used to measure associations with the outcome of jaundice resolution in the 60 days after the episode of care. Best subsets variable selection using the score statistic was used to identify an initial multivariable model up to a maximum size based on a 10:1 event to variable ratio. Variables were removed from this model using backward elimination with a 0.10 type I error level. Variance inflation factors were used to assess multicollinearity among predictors, and all values were less than 10. In the subset of patients with jaundice resolution, the cumulative incidence of a subsequent jaundice recurrence was estimated using the competing risk extension of the Kaplan-Meier method, where the occurrence of death or transplant constituted the competing event. The cumulative incidence of all-cause death or liver transplant was estimated using the Kaplan-Meier method. Cox proportional hazards models were used to assess associations with jaundice recurrence and death/transplant. Multivariable Cox models were obtained using best subsets variable selection followed by a backward elimination, as described previously. Subjects who developed CCA during follow-up were not excluded.

The models developed during the derivation phase were then applied to the validation cohort.

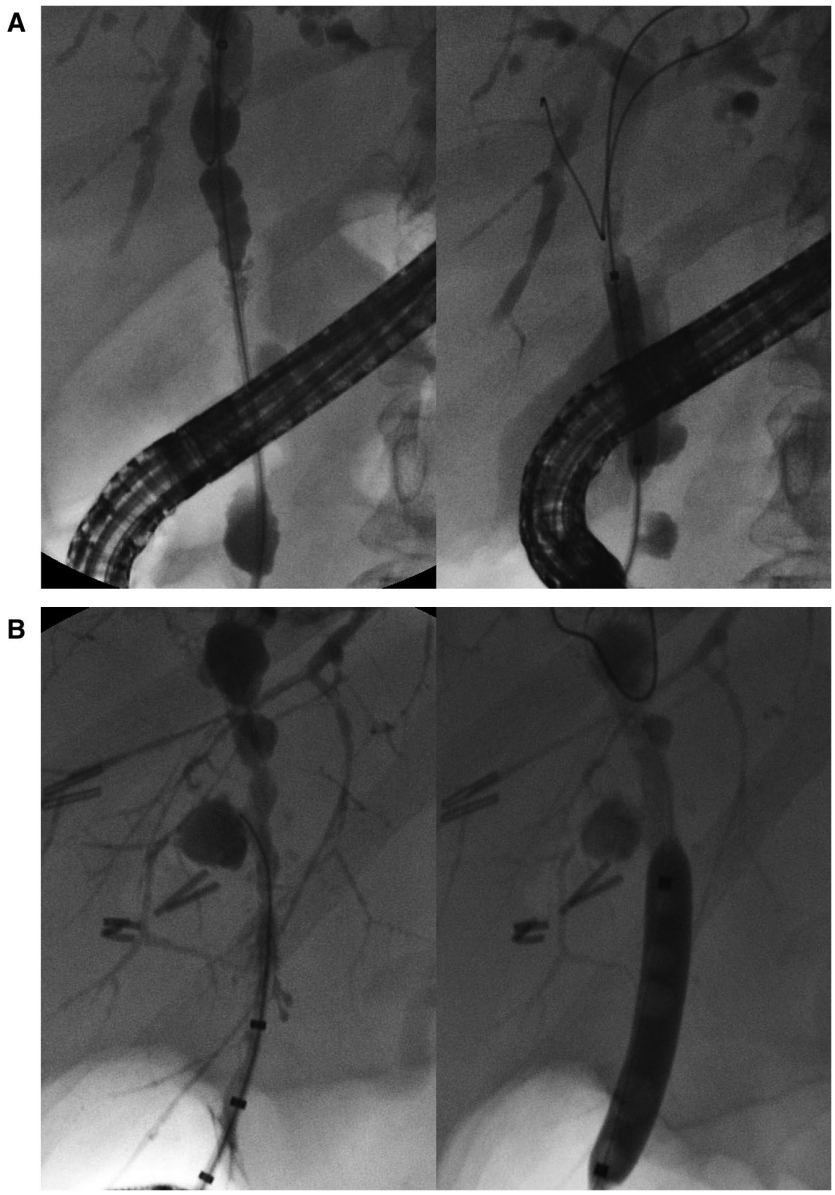

FIG. 1. Balloon dilation of bile duct strictures, illustrating the ratio of (dilation balloon diameter) / (bile duct diameter proximal to the stricture). (A) Ratio = 0.9. (B) Ratio = 2.2.

A concordance statistic was computed for each model as a discrimination measure (area under the receiver operating characteristic curve (AUROC] in the jaundice resolution model and Harrell's concordance statistic in the death/transplant model). Calibration was assessed by comparing the expected outcome risk to the observed outcome risk for five equally sized groups, as defined by quintiles of the model linear predictor.

Results

PATIENT CHARACTERISTICS

A total of 1,006 patients with PSC underwent ERCP at MCR during the study period. On review, 467 of these did not have jaundice, 164 had CCA diagnosed before or during their first episode of care, 70 did not have PSC, 5 had PSC overlap with

autoimmune hepatitis, 45 had undergone previous biliary surgery other than cholecystectomy, 34 did not have strictures meriting endoscopic treatment, 26 had prior balloon dilation and/or stent at other institutions, 10 had strictures which were not amenable to intervention, 18 had no cholangiograms available for review, and 43 did not have complete follow-up. After these exclusions, 124 cases were included in the derivation cohort.

Baseline characteristics and ERCP findings are shown in Table 1. A median of 1 ERCP was performed during each episode of care (range, 1-4), and the median episode of care duration was 1 day (range, 1-153). Complete intrahepatic duct visualization was achieved in 102 cases (82%), with incomplete intrahepatic duct visualization in the remaining 22 cases. Among the 124 patients, balloon dilation was performed in 84 (68%), stent placement in 4 (3%), and balloon dilation together with stent placement in 35 (28%); biliary sphincterotomy was performed either before (67) or during (35) the first episode of care in 82%. Balloon dilation was performed to a median diameter of 6 mm (range, 4-10). Plastic stents had a median cumulative diameter of 3.3 mm (range, 2.3-7; 10 French), and in 9 patients more than one stent was placed in a side-by-side fashion. Stents were left in place for a median of 40 days (range, 2-152). As retrospectively assessed, adverse events likely due to ERCP included pancreatitis (six), pain requiring hospitalization (two), ductal contrast extravasation (one), and bacterial cholangitis or sepsis (three). Median follow-up after the episode of care was 4.8 years (range, 0-10). The cumulative incidence of CCA during follow-up was 3%, 4%, 9%, 13%, and 13% at 1, 2, 3, 5, and 10 years, respectively.

The validation cohort was comprised of 102 patients. Comparison of the derivation and validation cohorts is shown in Table 2.

RESOLUTION OF JAUNDICE

Jaundice resolved after endoscopic therapy in 52% (n = 64) of the derivation cohort and 72% (n = 73) of the validation cohort (P = 0.002). Univariate predictors of jaundice resolution in the derivation cohort are shown in Table 1. Of the 38 cases with blood platelet counts <150,000 × 10^9/L, 14 (37%) experienced jaundice resolution. Multivariable analysis, including all variables shown in Table 1, identified four independent predictors of jaundice resolution, including lower MRS (P = 0.025; odds ratio [OR], 0.58; 95% confidence interval [CI], 0.36-0.93 for every 1-point increase), older age at the time of index ERCP (P = 0.048; OR, 1.03; 95% CI, 1.00-1.07 for every 1-year increase), extrahepatic location of most advanced stricture (P = .011; OR, 3.13; 95% CI, 1.30-7.56), and shorter time between jaundice onset and the index ERCP (P = 0.059; OR, 0.59; 95% CI, 0.34-1.02 for every 1-year increase). Jaundice resolution occurred in 71% and 44% of patients with and without extrahepatic location of their most advanced stricture, respectively. Although higher MRS values correlated with lower likelihood of jaundice resolution, jaundice resolved in about 30% of cases even at MRS >4 (Fig. 2).

Expressing the final multivariable model in terms of the probability of jaundice resolution, we obtained $\text{Probability (jaundice resolution)} = \frac{e^{\text{score}}}{1+e^{\text{score}}}$, where e = 2.718 and score = −0.4190 + (0.0324 × patient age in years) − (0.5439 × MRS) + (1.1417 if the most advanced stricture is extrahepatic, otherwise 0) − (0.5370 × years of jaundice before index ERCP). The AUROC for this model was 0.74 for the derivation cohort and 0.67 (95% CI, 0.5-0.79) for the validation cohort (Fig. 3). The model calibration plot is shown in Supporting Fig. S1.

RECURRENCE OF JAUNDICE

Among the 62 derivation cohort subjects who experienced jaundice resolution, jaundice recurred in 43, with cumulative incidences of 20%, 46%, 59%, 71%, and 87% after 1, 2, 3, 5, and 10 years, respectively. Univariate predictors of recurrence of jaundice are shown in Table 3. Multivariable analysis identified six factors associated with recurrence of jaundice, including younger age (P = 0.004; hazard ratio [HR], 0.96; 95% CI, 0.94-0.99 for every 1-year increase), longer duration of PSC before the index ERCP (P = 0.003; HR, 1.08; 95% CI, 1.03-1.13 for every 1-year increase), higher MRS (P = 0.001; HR, 2.42; 95% CI, 1.42-4.13 for every 1-point increase), lower total serum bilirubin before the index ERCP (P = 0.007; HR, 0.87; 95% CI, 0.78-0.96 for every 1 mg/dL increase), incomplete visualization of intrahepatic ducts during index ERCP (P = 0.003; HR, 4.34; 95% CI, 1.63-11.49), and complete ductal drainage after ERCP (P = 0.025; HR, 2.26; 95% CI, 1.11-4.60).

TABLE 1. UNIVARIATE ANALYSIS OF CLINICAL VARIABLES AND THEIR ASSOCIATION WITH SUCCESS OF ENDOSCOPIC TREATMENT AND SUBSEQUENT DEATH OR LIVER TRANSPLANT IN THE DERIVATION COHORT

Variable	Mean (Range) or n (%)	Resolution of Jaundice After Therapy		Death or Transplant During Follow-Up	
		OR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age (years)	48 (14-78)	1.01 (0.99-1.03)	0.45	1.01 (1.00-1.03)	0.11
Female	44 (35%)	0.79 (0.38-1.64)	0.52	1.44 (0.85-2.42)	0.18
Length of time between diagnosis of PSC and endoscopic therapy (years)	8.0 (0-36.6)	0.97 (0.93-1.02)	0.19	1.03 (1.00-1.05)	0.10
Length of time between jaundice diagnosis and endoscopic therapy (years)	0.5 (0-5.3)	0.59 (0.35-1.02)	0.059	1.18 (0.89-1.57)	0.24
Fever or bacteremia present	17 (14%)	1.87 (0.64-5.42)	0.25	1.94 (1.00-3.75)	0.05
INR	1.1 (0.8-3.0)	1.01 (0.88-1.15)	0.93	1.04 (0.98-1.10)	0.19
Platelet count ($\times 10^9$/L) (OR/HR per 1,000)	244.1 (37-1,038)	0.999 (0.997-1.001)	0.35	1.001 (0.999-1.003)	0.45
Platelet count <150,000 $\times 10^9$/L	38 (30.6%)	0.42 (0.19-0.92)	0.03	1.94 (1.14-3.30)	0.01
Albumin (mg/dL)	3.6 (2.2-5.0)	1.08 (1.01-1.15)	0.019	0.90 (0.86-0.93)	<0.001
AST (IU/mL)	155.4 (17-943)	1.00 (0.997-1.003)	0.87	1.00 (0.998-1.002)	0.93
Initial serum bilirubin (mg/dL)	6.6 (2.5-32.1)	1.02 (0.95-1.06)	0.55	0.99 (0.93-1.07)	0.86
MRS	2.0 (-0.4-5.2)	0.77 (0.55-1.08)	0.13	2.09 (1.58-2.76)	<0.001
Atrophy	28 (23%)	0.80 (0.34-1.86)	0.60	1.21 (0.66-2.22)	0.53
Incomplete intrahepatic duct visualization	22 (18%)	0.47 (0.18-1.22)	0.12	1.59 (0.86-2.94)	0.14
Most advanced stricture location, extrahepatic	35 (28%)	3.21 (1.38-7.46)	0.007	0.67 (0.36-1.25)	0.21
Minimum diameter of most advanced stricture (mm)	1.2 (0.1-4.6)	0.79 (0.49-1.28)	0.34	1.03 (0.72-1.46)	0.89
Maximum length of most advanced stricture (mm)	11.9 (0.7-91.5)	1.02 (0.99-1.05)	0.14	1.01 (0.99-1.02)	0.47
Ratio of dilation balloon diameter to duct diameter proximal to the most advanced stricture	1.6 (0.4-8.5)	0.83 (0.61-1.14)	0.25	0.85 (0.64-1.12)	0.24
Stent applied	39 (31%)	2.11 (0.96-4.60)	0.062	0.85 (0.48-1.50)	0.57
Particulate matter removed	49 (40%)	0.64 (0.31-1.32)	0.23	1.25 (0.73-2.16)	0.42
Complete drainage	67 (54%)	1.42 (0.70-2.90)	0.33	1.18 (0.70-1.98)	0.54
Most abberant FISH, polysomy/tetrasomy	7 (6%)	1.27 (0.27-5.91)	0.76	0.29 (0.04-2.07)	0.21
Duration of therapy (days)	20.0 (1-153)	1.00 (0.99-1.01)	0.75	1.00 (0.99-1.01)	0.92
Persistence of jaundice after therapy	60 (48%)	-	-	2.27 (1.34-3.83)	0.002

Abbreviations: FISH, fluorescent *in situ* hybridization; INR, international normalized ratio.

TABLE 2. CLINICAL VARIABLE SUMMARIES IN THE VALIDATION COHORT AND COMPARISONS WITH THE DERIVATION COHORT

Variable	Mean (Range) or n (%)	*P* Value*
Age (years)	41.7 (7.0-73.0)	0.0016
MRS	1.5 (-0.5-4.9)	0.0006
Most advanced stricture location, extrahepatic (CBD/CHD)	46 (45.1%)	0.0085
Length of time between jaundice diagnosis and endoscopic therapy (years)	0.1 (0.0-2.8)	<0.0001
Albumin (mg/dL)	3.8 (1.6-4.9)	0.0255
AST (IU/mL)	102.1 (11.0-477.0)	<0.0001

*For comparison between the derivation and validation cohorts. Derivation cohort summaries are shown in Table 1.
Abbreviations: CBD, common bile duct; CHD, common hepatic duct.

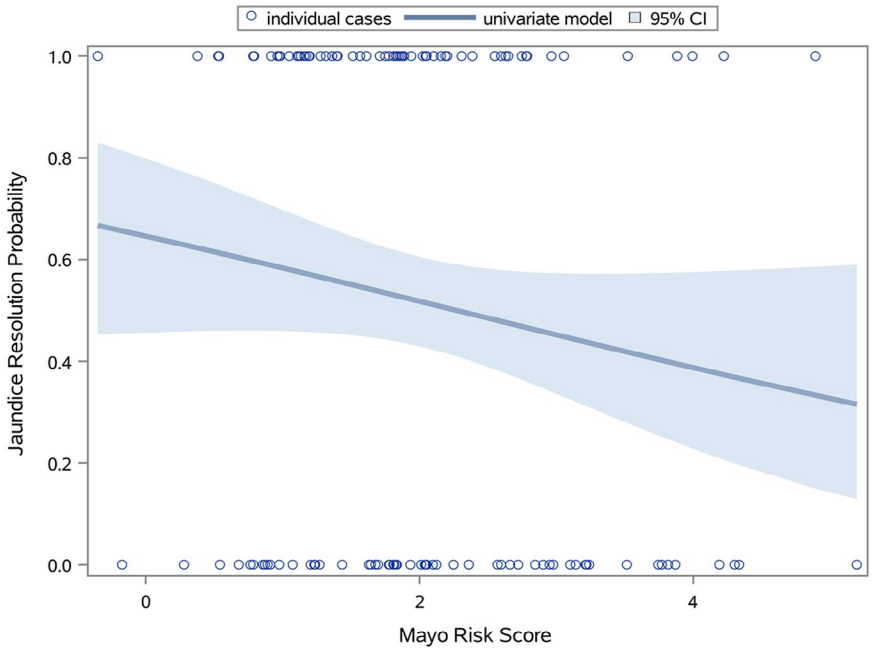

FIG. 2. Association between jaundice resolution and MRS before ERCP. Open circles denote individual derivation-set cases in whom jaundice either did (probability = 1) or did not (probability = 0) resolve; the line denotes a univariate model considering only MRS as a predictor of jaundice resolution.

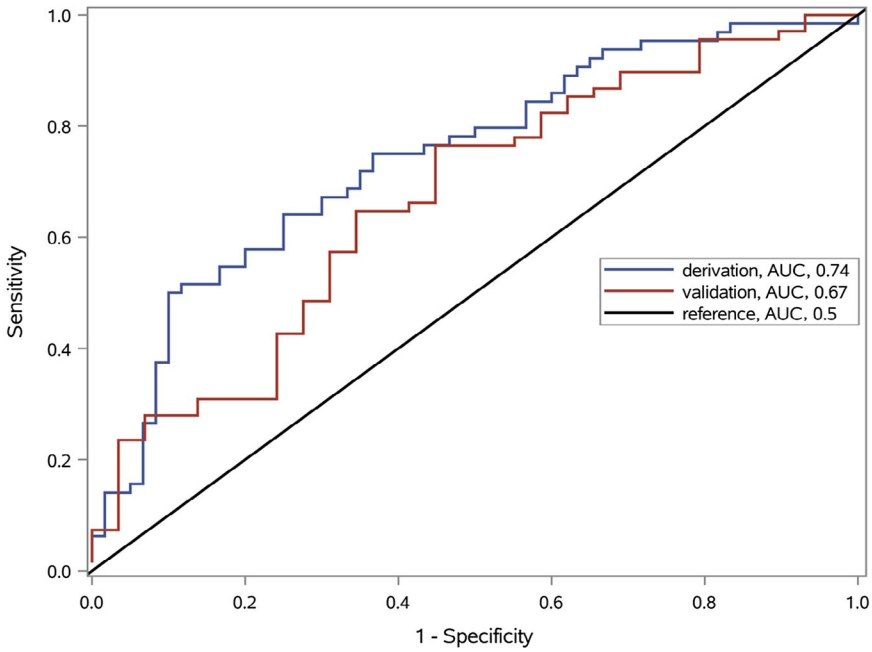

FIG. 3. ROC curves for the jaundice resolution multivariable model in the derivation and validation sets.

TABLE 3. UNIVARIATE ANALYSIS OF CLINICAL VARIABLES AND THEIR ASSOCIATION WITH JAUNDICE RELAPSE AMONG 62 PATIENTS WHOSE JAUNDICE RESOLVED AFTER ENDOSCOPIC THERAPY

Variable	HR (95% CI)	*P* Value
Age (years)	1.00 (0.98-1.02)	0.85
Female sex	1.15 (0.61-2.19)	0.67
Length of time between diagnosis of PSC and endoscopic therapy (years)	1.05 (1.01-1.09)	0.01
Fever or bacteremia present	2.07 (1.01-4.25)	0.048
Initial serum bilirubin (mg/dL)	0.92 (0.84-1.02)	0.10
MRS	1.30 (0.91-1.86)	0.16
Minimum diameter of most advanced stricture (mm)	0.96 (0.61-1.51)	0.85
Maximum length of most advanced stricture (mm)	1.00 (0.98-1.03)	0.93
Ratio of dilation balloon diameter to duct diameter proximal to the most advanced stricture	1.49 (1.03-2.15)	0.04
Stent applied	0.89 (0.48-1.65)	0.70
Most aberrant FISH, polysomy/tetrasomy	1.55 (0.47-5.11)	0.47
Duration of therapy (days)	1.00 (0.99-1.01)	0.40
Incomplete intrahepatic duct visualization	2.03 (0.87-4.76)	0.10
Most advanced stricture location, extrahepatic	0.77 (0.40-1.45)	0.41
Particulate matter removed	1.40 (0.73-2.68)	0.32
Complete drainage	1.70 (0.89-3.24)	0.11
Length of time between jaundice diagnosis and endoscopic therapy, per year	1.02 (0.48-2.16)	0.96
INR, per 0.1	1.02 (0.95-1.09)	0.60
Albumin, per 0.1 mg/dL	0.92 (0.87-0.98)	0.008
AST, per IU/mL	0.999 (0.997, 1.002)	0.58
Atrophy	1.87 (0.93-3.77)	0.08

Abbreviations: FISH, fluorescent *in situ* hybridization; INR, international normalized ratio.

Recurrent jaundice was treated with additional endoscopic therapy in 26 of 41 patients with known treatment status, and the second round of endoscopic therapy successfully resolved jaundice in 8 of 25 patients with known resolution status.

Among the 69 validation cohort subjects who experienced jaundice resolution, jaundice recurred in 39 patients, with cumulative incidences of 12%, 26%, 33%, 54%, and 68% after 1, 2, 3, 5, and 10 years, respectively. Jaundice recurrence was significantly less frequent than in the derivation set (P = 0.005).

PREDICTORS OF DEATH OR TRANSPLANT

During follow-up, 59 derivation cohort patients died (n = 19) or had a liver transplant (n = 40). The cumulative incidence of death or liver transplant was 11%, 25%, 37%, 57%, and 74% after 1, 2, 3, 5, and 10 years, respectively. The median follow-up time was 4.8 (interquartile range [IQR], 2.1-7.9) years. Univariate predictors of death or transplant are shown in Table 1. Multivariable analysis identified three variables independently associated with death or transplant, including higher MRS at the time of index ERCP (P < 0.0001; HR, 2.33; 95% CI, 1.73-3.13 for every 1-point increase), lower total serum bilirubin before the index ERCP (P = 0.031; HR, 0.91; 95% CI, 0.84-0.99 for every 1 mg/dL increase), and persistence of jaundice after endoscopic therapy (P = 0.003; HR, 2.30; 95% CI, 1.32-4.01). The cumulative incidence of death or transplant in derivation-set subjects whose jaundice did or did not resolve after endoscopic intervention is shown in Fig. 4.

From the final model, the estimated probability of death or transplant over time is Probability(dealth or transplant at time t) = 1 - Probability (dealth or transplant at time t) = $1 - (S_0(t)^{\exp(\text{score})})$, where $S_0(t)$ is 0.98336, 0.95356, 0.91516, 0.86394, 0.82769, and 0.75356 at years 1, 2, 3, 4, 5, and 6, respectively, and score = 0.84564 × MRS − 0.09062 × bilirubin in mg/dL + (0.83436 if jaundice persisted, 0 otherwise).

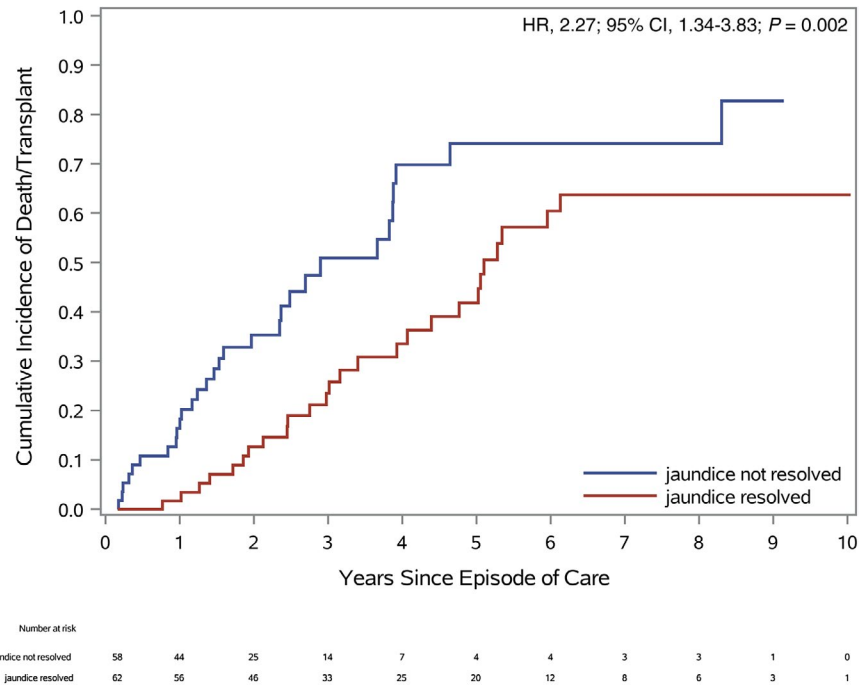

FIG. 4. Cumulative incidence of death or liver transplantation in the derivation-set patients whose jaundice did or did not resolve after endoscopic therapy.

During follow-up, 56 validation cohort patients died (n = 19) or had a liver transplant (n = 37). The median follow-up time was 7.1 (IQR, 2.7-12.9) years, significantly longer than the derivation cohort (P = 0.002). The cumulative incidence of death or liver transplant was 20%, 24%, 32%, 52%, and 73% after 1, 2, 3, 5, and 10 years, respectively, and was similar to the derivation cohort (P = 0.499). The concordance statistic in the validation cohort was 0.72 (95% CI, 0.65-0.80). The calibration plot for the validation cohort is shown in Supporting Fig. S2.

NORMALIZATION OF SERUM BILIRUBIN

In a post-hoc analysis, we substituted normalization of the serum total bilirubin (≤1.2 mg/dL) in place of the cut-off value of 2.5 mg/dL used for the primary analysis. Only 23 derivation cohort subjects achieved a normal serum bilirubin concentration following endoscopic therapy (18.5%). The multivariable model for normalization of serum bilirubin was $\text{Probability (jaundice resolution)} = \frac{e^{\text{score}}}{1+e^{\text{score}}}$, where e = 2.718 and score = −5.7345 + (0.9620 if the most advanced stricture is extrahepatic, otherwise 0) − (1.1971 × years of jaundice before index ERCP) + (1.151 × albumin mg/dL). The AUROC for this model was 0.76 for the derivation cohort and 0.70 (95% CI, 0.58-0.83) for the validation cohort. The model ROCs, Kaplan-Meier curve, and calibration plot are shown in Supporting Figs. S3-S5.

ADDITIONAL ANALYSES

For the derivation set, jaundice resolution was analyzed by calendar year of the study in order to assess whether clinicians in our practice achieved better outcomes over time. There was a significant association between jaundice resolution and calendar year (P = 0.02; OR, 0.88; 95% CI, 0.79-0.98 for every 1-year increase), showing that jaundice was less likely to resolve for patients treated in later years of the study.

We repeated data analyses substituting Model for End-Stage Liver Disease (MELD) score for MRS and found that MELD score was a statistically significant predictor of jaundice resolution in this cohort

(P = 0.016; OR, 1.13; 95% CI, 1.02-1.25 per increase of 1 in a multivariable model). A multivariable model constructed with MELD instead of MRS had a lower AUROC for the prediction of jaundice resolution.

Discussion

The hallmark of PSC is idiopathic multifocal stricturing of the intrahepatic and extrahepatic bile ducts in association with progressive liver disease. The management of PSC currently relies on endoscopic treatment of biliary complications, medical management of cirrhosis, and liver transplantation.

ERCP is often performed in patients with PSC for diagnosis, tissue sampling, or endoscopic treatment. Series report variable effectiveness of endoscopic interventions for treatment of PSC.[3,5,10,12-18] Most studies do not distinguish between treatment of ascending cholangitis, pain, or jaundice and are hampered by small sample sizes, absence of control groups, and variable follow-up. Some studies include patients with PSC with CCA, whose survival is probably dependent more on tumor stage and treatment than endoscopic dilation of strictures.[13] Some studies demonstrating a survival benefit to endoscopic therapy compare actual patient outcomes to predicted outcomes, using each patient's multivariable model score before endoscopic therapy.[11,12] Because these predictive models incorporate serum bilirubin concentration, which may improve after treatment of biliary obstruction, it is unclear whether they overestimate the benefit of endoscopic interventions. One recent publication reported that transplant-free survival was higher in patients with a dominant stricture who complied with repeated endoscopic balloon dilation.[19]

In this study, we assessed long-term outcomes of patients with jaundice with PSC whose biliary strictures were treated endoscopically. We focused on jaundice because this parameter can be quantified by measuring serum bilirubin levels, and the question of whether ERCP resolves jaundice and improves long-term outcomes is an important and unresolved issue in PSC. We excluded patients diagnosed with CCA.

We found that jaundice resolved after ERCP in about half of patients with PSC in the derivation cohort and that resolution of jaundice was associated with a 57% lower likelihood of subsequent death or liver transplantation in multivariable analysis. Lower MRS (a measure of liver disease severity) and jaundice resolution after endoscopic treatment were independently associated with better transplant-free survival. Jaundice resolution after ERCP was more likely in the validation cohort, likely due to differences in patient selection: this cohort had significantly lower MRS and shorter length of time between onset of jaundice and performance of endoscopic therapy. Despite these differences, our multivariable model performed similarly. Our findings demonstrate that both biliary and hepatic factors determine outcomes in PSC and that jaundice resolution after endoscopic intervention is an important predictor of more favorable outcomes. These findings provide a strong rationale for endoscopic treatment of flow-limiting biliary strictures in patients with jaundice with PSC.

Can we predict which patients with jaundice with PSC will respond to endoscopic intervention and offer ERCP only to those most likely to benefit? Prior authors have suggested that interventional treatment of biliary strictures should be limited to patients without cirrhosis,[12,20] and stage of disease as determined by liver biopsy has been associated with transplant-free survival in patients with PSC undergoing endoscopic interventions.[3,15] Few of our subjects had liver biopsies, and magnetic resonance elastography (MRE) values were not available within 1 year of baseline for most derivation cohort subjects. However, our group has previously demonstrated that MRS values ≥0.30 are associated with cirrhotic-range liver stiffness by MRE in patients with PSC, with AUROC of 0.88.[21] We found that jaundice resolved after ERCP in a substantial percentage of patients even at high MRS values and that there was no MRS value above which ERCP was futile. Furthermore, a substantial percentage of subjects with blood platelet counts <150,000 × 10^9/L, an indicator of potential portal hypertension, resolved their jaundice after endoscopic therapy. Based on our findings, we would not withhold ERCP from patients with PSC solely because they have cirrhosis.

We derived a model for prediction of jaundice resolution after endoscopic therapy that is based on readily available and noninvasive clinical data, including patient age, MRS, duration of jaundice, and location of the most advanced biliary stricture. We determined stricture location from ERCP films because magnetic resonance cholangiopancreatography (MRCP) was not available within 1-year of baseline for the majority of the derivation cohort, but in practice the location of

such strictures is usually readily determined by MRCP. The model calibrates well across the range of jaundice resolution likelihoods in our cohort. As examples, the model assigns a 12% likelihood of jaundice resolution after ERCP to a 20-year old with an MRS of 0.543, 3.5 years of jaundice before ERCP, and intrahepatic location of the most advanced biliary stricture, while it assigns an 84% likelihood of jaundice resolution to a 53-year old with an MRS of 1.314, 0.14 years of jaundice before ERCP, and extrahepatic location of the most advanced biliary stricture. The model's AUC of 0.67 in the validation cohort implies that it is clinically useful but lacks precision. Nevertheless, we believe that the model has clinical utility as one piece of information available to clinicians making treatment decisions for patients with PSC, particularly when it yields a high probability of treatment success or failure. We recognize that patient selection for ERCP remains difficult given the heterogeneity and complexity of PSC. However, with the long-term benefits associated with jaundice resolution after ERCP, we think that, when in doubt, many patients with jaundice with PSC should be referred for ERCP.

Although all derivation cohort patients had endoscopic interventions, only half of these experienced subsequent jaundice resolution. This may in part be due to overdiagnosis of flow-limiting strictures in these patients. There are no validated methods of determining during ERCP the resistance to flow caused by biliary strictures. The cholangiographic diameter of strictures was not a predictor of treatment success in this series, probably because apparent stricture diameter is affected by the volume, speed, and pressure of biliary contrast injection. We did not evaluate stricture diameter on MRCP as this was not available in many patients earlier in the study time period, but we suspect MRCP might overestimate the severity of some stenoses. A higher likelihood of jaundice resolution when the most advanced biliary stricture was extrahepatic likely reflects the potential of extrahepatic strictures to obstruct all hepatic biliary outflow and the relative suitability of available endoscopic devices for treatment of strictures in larger ducts.

Biliary stent placement (as opposed to balloon dilation alone) almost reached statistical significance as a univariate predictor of treatment success but was not significant in the multivariable model. In general, we placed biliary stents during the index ERCP only if strictures appeared to respond poorly to balloon dilation alone, as determined by cholangiography. Some patients whose jaundice failed to resolve after balloon dilation underwent stent placement during a subsequent ERCP, and we considered these interventions to be part of the same episode of care. For these reasons, as well as limited statistical power, our data do not answer the question of whether stent placement is superior to balloon dilation alone in PSC. Another investigative team has recently studied this issue.[22]

Lower serum bilirubin at the time of index ERCP was associated with poorer transplant-free survival. This finding is unexpected, and we are unsure of its interpretation. One possibility is that biliary obstruction can cause an abrupt marked rise in the serum bilirubin in patients with underlying liver disease while progressive liver dysfunction may result in a more gradual rise over time, leading to evaluation and treatment at lower serum bilirubin levels.

Strengths of our study include the focus on treatment of jaundice; its reliance on objective outcome parameters, including serum bilirubin concentration, death, and liver transplantation; and the long mean duration of patient follow-up available. Our study is limited by its retrospective observational design and the exclusion of some potential subjects for whom adequate follow-up was not available. In addition, we defined resolution of jaundice as a serum total bilirubin <2.5 mg/dL; however, we repeated our analysis using normalization of serum total bilirubin instead, with similar findings. Additionally, interventions for both derivation and validation cohorts were performed in a tertiary setting by endoscopists with experience in treating patients with complicated PSC, and outcomes may not be generalizable to other practice settings. A prospective randomized trial of endoscopic therapy in patients with jaundice with PSC would further enhance the understanding of the role of endoscopic intervention. One obstacle to such a study in our practice is our reliance on ERCP tissue sampling for diagnosis of CCA in patients with jaundice with PSC; omitting dilation of obstructing strictures during ERCP might increase some patients' risk for post-ERCP bacterial cholangitis.

In conclusion, resolution of jaundice after therapeutic ERCP is associated with a substantially lower likelihood of death or liver transplant in patients with PSC. The likelihood of jaundice resolution depends on demographic, hepatic, and biliary factors and can be predicted using a multivariable model. Our findings

provide a strong rationale for endoscopic treatment of advanced biliary strictures in patients with jaundice with PSC.

REFERENCES

1) May GR, Bender CE, LaRusso NF, Wiesner RH. Nonoperative dilatation of dominant strictures in primary sclerosing cholangitis. AJR Am J Roentgenol 1985;145:1061-1064.
2) Gaing AA, Geders JM, Cohen SA, Siegel JH. Endoscopic management of primary sclerosing cholangitis: review, and report of an open series. Am J Gastroenterol 1993;88:2000-2008.
3) Gotthardt DN, Rudolph G, Kloters-Plachky P, Kulaksiz H, Stiehl A. Endoscopic dilation of dominant stenoses in primary sclerosing cholangitis: outcome after long-term treatment. Gastrointest Endosc 2010;71:527-534.
4) Johnson GK, Geenen JE, Venu RP, Schmalz MJ, Hogan WJ. Endoscopic treatment of biliary tract strictures in sclerosing cholangitis: a larger series and recommendations for treatment. Gastrointest Endosc 1991;37:38-43.
5) Kaya M, Petersen BT, Angulo P, Baron TH, Andrews JC, Gostout CJ, et al. Balloon dilation compared to stenting of dominant strictures in primary sclerosing cholangitis. Am J Gastroenterol 2001;96:1059-1066.
6) Lombard M, Farrant M, Karani J, Westaby D, Williams R. Improving biliary-enteric drainage in primary sclerosing cholangitis: experience with endoscopic methods. Gut 1991;32:1364-1368.
7) Stiehl A, Rudolph G, Kloters-Plachky P, Sauer P, Walker S. Development of dominant bile duct stenoses in patients with primary sclerosing cholangitis treated with ursodeoxycholic acid: outcome after endoscopic treatment. J Hepatol 2002;36:151-156.
8) van Milligen de Wit AW, Rauws EA, van Bracht J, Mulder CJ, Jones EA, Tytgat GN, et al. Lack of complications following short-term stent therapy for extrahepatic bile duct strictures in primary sclerosing cholangitis. Gastrointest Endosc 1997;46:344-347.
9) van Milligen de Wit AW, van Bracht J, Rauws EA, Jones EA, Tytgat GN, Huibregtse K. Endoscopic stent therapy for dominant extrahepatic bile duct strictures in primary sclerosing cholangitis. Gastrointest Endosc 1996;44:293-299.
10) Bjornsson E, Lindqvist-Ottosson J, Asztely M, Olsson R. Dominant strictures in patients with primary sclerosing cholangitis. Am J Gastroenterol 2004;99:502-508.
11) Baluyut AR, Sherman S, Lehman GA, Hoen H, Chalasani N. Impact of endoscopic therapy on the survival of patients with primary sclerosing cholangitis. Gastrointest Endosc 2001;53:308-312.
12) Gluck M, Cantone NR, Brandabur JJ, Patterson DJ, Bredfeldt JE, Kozarek RA. A twenty-year experience with endoscopic therapy for symptomatic primary sclerosing cholangitis. J Clin Gastroenterol 2008;42:1032-1039.
13) Chapman MH, Webster GJ, Bannoo S, Johnson GJ, Wittmann J, Pereira SP. Cholangiocarcinoma and dominant strictures in patients with primary sclerosing cholangitis: a 25-year single-centre experience. Eur J Gastroenterol Hepatol 2012;24:1051-1058.
14) Ahrendt SA, Pitt HA, Kalloo AN, Venbrux AC, Klein AS, Herlong HF, et al. Primary sclerosing cholangitis: resect, dilate, or transplant? Ann Surg 1998;227:412-423.
15) Aljiffry M, Renfrew PD, Walsh MJ, Laryea M, Molinari M. Analytical review of diagnosis and treatment strategies for dominant bile duct strictures in patients with primary sclerosing cholangitis. HPB (Oxford) 2011;13:79-90.
16) Cotton PB, Nickl N. Endoscopic and radiologic approaches to therapy in primary sclerosing cholangitis. Semin Liver Dis 1991;11:40-48.
17) Stiehl A. Primary sclerosing cholangitis: the role of endoscopic therapy. Semin Liver Dis 2006;26:62-68.
18) van den Hazel SJ, Wolfhagen EH, van Buuren HR, van de Meeberg PC, Van Leeuwen DJ. Prospective risk assessment of endoscopic retrograde cholangiography in patients with primary sclerosing cholangitis. Dutch PSC Study Group. Endoscopy 2000;32:779-782.
19) Rupp C, Hippchen T, Bruckner T, Klöters-Plachky P, Schaible A, Koschny R, et al. Effect of scheduled endoscopic dilatation of dominant strictures on outcome in patients with primary sclerosing cholangitis. Gut 2019;68:2170-2178.
20) Peiseler M, Reiners D, Pinnschmidt HO, Sebode M, Jung F, Hartl J, et al. Risk of endoscopic biliary interventions in primary sclerosing cholangitis is similar between patients with and without cirrhosis. PLoS One 2018;13:e0202686.
21) Eaton JE, Dzyubak B, Venkatesh SK, Smyrk TC, Gores GJ, Ehman RL, et al. Performance of magnetic resonance elastography in primary sclerosing cholangitis. J Gastroenterol Hepatol 2016;31:1184-1190.
22) Ponsioen CY, Arnelo U, Bergquist A, Rauws EA, Paulsen V, Cantú P, et al. No superiority of stents vs balloon dilatation for dominant strictures in patients with primary sclerosing cholangitis. Gastroenterology 2018;155:752-759.e5.

Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep4.1813/suppinfo.