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The role of magnetic resonance imaging and endoscopic retrograde cholangiography in the evaluation of disease activity and severity in primary sclerosing cholangitis

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Abstract

Background & Aims: Endoscopic retrograde cholangiography (ERCP) has been considered the gold standard for the diagnosis and follow-up of primary sclerosing cholangitis, but it has been replaced by less invasive magnetic resonance imaging and cholangiopancreatography (MRI-MRCP). However, the role of these two techniques in the evaluation of disease activity and severity needs to be elucidated.

Methods: Patients with primary sclerosing cholangitis (n: 48, male 31, median age: 35.7; 28.0-44.2) who underwent ERCP and MRI-MRCP within ±3 months for diagnosis or follow-up, were reviewed. ERCP and MRI-MRCP images were scored using the modified Amsterdam score. Serum and biliary cytology markers of disease activity and severity were related to the imaging findings. Agreement on the assessment of the ERCP/MRCP score was calculated by kappa-statistics. Spearman's ρ was calculated when appropriate.

Results: The agreement between ERCP and MRCP in scoring bile duct changes for disease severity was only moderate (weighted kappa: 0.437; 95% CI: 0.211-0.644 for intra- and 0.512; 95% CI: 0.303-0.720 for extra-hepatic bile ducts). ERCP and MRCP intra-hepatic scores were associated to the surrogate marker alkaline phosphatase (P = .02 for both). A weak correlation between MRCP score for extra-hepatic bile ducts and liver transplantation/death was found (Spearman's ρ = .362, 95% CI: 0.080-0.590, P = .022). A weak correlation between intra- (Spearman's ρ = .322, 95% CI: 0.048-0.551, P = .022) and extra-hepatic (Spearman`s ρ = .319, 95% CI: 0.045-0.549, P = .025) peribiliary enhancement on contrast-enhanced MRI and severity of biliary cytologic classification was found.

Conclusions: The overall agreement between ERCP and MRI-MRCP in assessing disease severity was moderate for intra- and extra-hepatic bile ducts. MRI-MRCP seems to have a minor role as surrogate marker of disease activity and progression in PSC.

KEYWORDS
biliary brush cytology, cholangiocarcinoma, imaging, surrogate markers

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, anti-mitochondrial antibodies; CA19-9, carbohydrate-antigen 19-9; CEA, carcino-embryonic antigen; ERCP, endoscopic retrograde cholangiography; IBD, inflammatory bowel disease; IEL, intra-epithelial lymphocytes; LT, liver transplantation; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; PSC, primary sclerosing cholangitis.

1 | INTRODUCTION

Primary sclerosing cholangits (PSC) is a chronic inflammatory and fibrotic disease, involving the intra- and extrahepatic biliary tree.[1,2] PSC leads progressively to end-stage liver disease, cirrhosis and eventually liver transplantation (LT) or death.[3,4] The disease also occurs in children and young adults who may need long-term follow-up.[5] PSC is also a preneoplastic condition with a markedly increased risk for colon- and cholangiocarcinoma.[6]

Endoscopic retrograde cholangiopancreatography (ERCP) has been considered the gold standard for diagnosis of PSC, since it provides a direct visualization of the entire biliary tree.[7] The main cholangiography characteristics are strictures, dilatations and pruning involving both intra- and/or extrahepatic bile ducts. ERCP also allows for the sampling of brush cytology[8,9] as well as endoscopic therapy (ie dilation and/or stenting). However, ERCP is an invasive procedure with an overall complication rate of 9%-12.5% in PSC patients,[10] post-ERCP pancreatitis being the most frequent one.[10] A meta-analysis has shown that imaging with magnetic resonance cholangiopancreatography (MRI-MRCP) is an accurate, non-invasive and cost-effective alternative method for diagnosis and follow-up of PSC.[11] For these characteristics, MRI-MRCP may play an important role, especially in patients who need a long follow-up, like children and young adults.[12] However, ERCP may be still more accurate in the detection of early changes.[13]

The rarity of PSC (prevalence of 0-16.2/100.000 inhabitants per year) and the long time period (median time 13-21 years) between diagnosis and strong end-points such as LT, cholangiocarcinoma or death make PSC "an orphan disease", which results in difficulties to plan randomized clinical trial on new treatments. Due to these issues, robust surrogate endpoints of PSC prognosis are urgently needed.[14] Alkaline phosphatase (ALP) seems to be the most promising one.[15] Recently, Boyd et al have demonstrated that advanced extra-hepatic ERC changes and elevated aminotransferase at diagnosis might be risk factors for biliary neoplasia. Interestingly, even in mostly asymptomatic patients (about 80% at diagnosis), about 40% had advanced disease and 7% presented with a suspicious or malignant brush cytology at first ERCP.[9] Furthermore, a recent study has reported that the majority of the PSC patients who underwent MRI-MRCP shows a radiological progression of the disease (about 58%) after a mean follow-up of 4 years, identifying three independent predictors of evolution: intrahepatic biliary ducts dilatation, parenchymal heterogeneity and dysmorphy[16]; however, this study lack the ERCP as a reference.

To our knowledge, a study evaluating association between ERCP and MRI-MRCP findings with markers of disease activity and severity is still lacking.

Aims of this study were to evaluate in a group of PSC patients who underwent both ERCP and MRI-MRCP: (i) the agreement between ERCP and MRCP in the assessment of bile duct changes (ii) the association between bile duct changes and markers of PSC disease activity and severity and (iii) the association between peribiliary enhancement detected on contrast-enhanced MRI and markers of disease activity in PSC.

Key points

- The agreement between MRCP and ERCP in the evaluation of the severity of biliary changes in PSC is only moderate.
- The severity of biliary changes in MRCP and ERCP is associated to alkaline phosphatase, which has been regarded as a surrogate marker of prognosis only in PSC.
- Peribiliary enhancement in MRI shows weak correlation with severity of biliary cytologic classification in PSC.
- The severity of extra-hepatic biliary changes on MRCP images shows only weak correlation with strong endpoints (ie liver transplantation and death) in PSC.

2 | MATERIALS AND METHODS

2.1 | Study design

This is a single-centre observational longitudinal retrospective cohort study.

2.2 | Setting, time and population

In Finland, most of the patients with a suspicious of PSC are referred to Helsinki University Hospital (HUH), where ERCP with brush cytology is still regarded the "gold standard" for the diagnosis and the follow-up of the disease. Figure 1 shows the diagnostic and follow-up course followed in our hospital.[9] In short, all patients suspected of PSC (ie based on symptoms, lab tests, liver biopsy and MRI-MRCP) undergo always ERCP firstly to confirm or exclude the diagnosis of the disease and secondly to assess the individual risk of disease progression based on brush cytology.[9] The follow-up is based on severity of cholangiographic changes and brush cytology results. Notably, patients with a persistently confirmed biliary dysplasia are referred for liver transplantation.[17]

All data (ie clinical, biochemical, histology, cholangiography and therapy) are prospectively collected in the PSC registry; over 700 subjects have been included since its start in 2010. All PSC patients who underwent ERCP and MRI-MRCP within ±3 months for diagnosis or follow-up of the disease were extracted from the PSC registry. The 3-month interval between the two procedures was chosen to minimize the classification bias due to the progression of the disease. PSC diagnosis was based on (Figure 1): (i) typical cholangiographic features of PSC (ie focal or diffuse strictures and dilatations of the biliary tree), associated with (ii) elevation of cholestatic liver enzymes (ie S-ALP), (iii) negative antimitochondrial antibodies (AMA) and eventually (iv) histology suggestive or

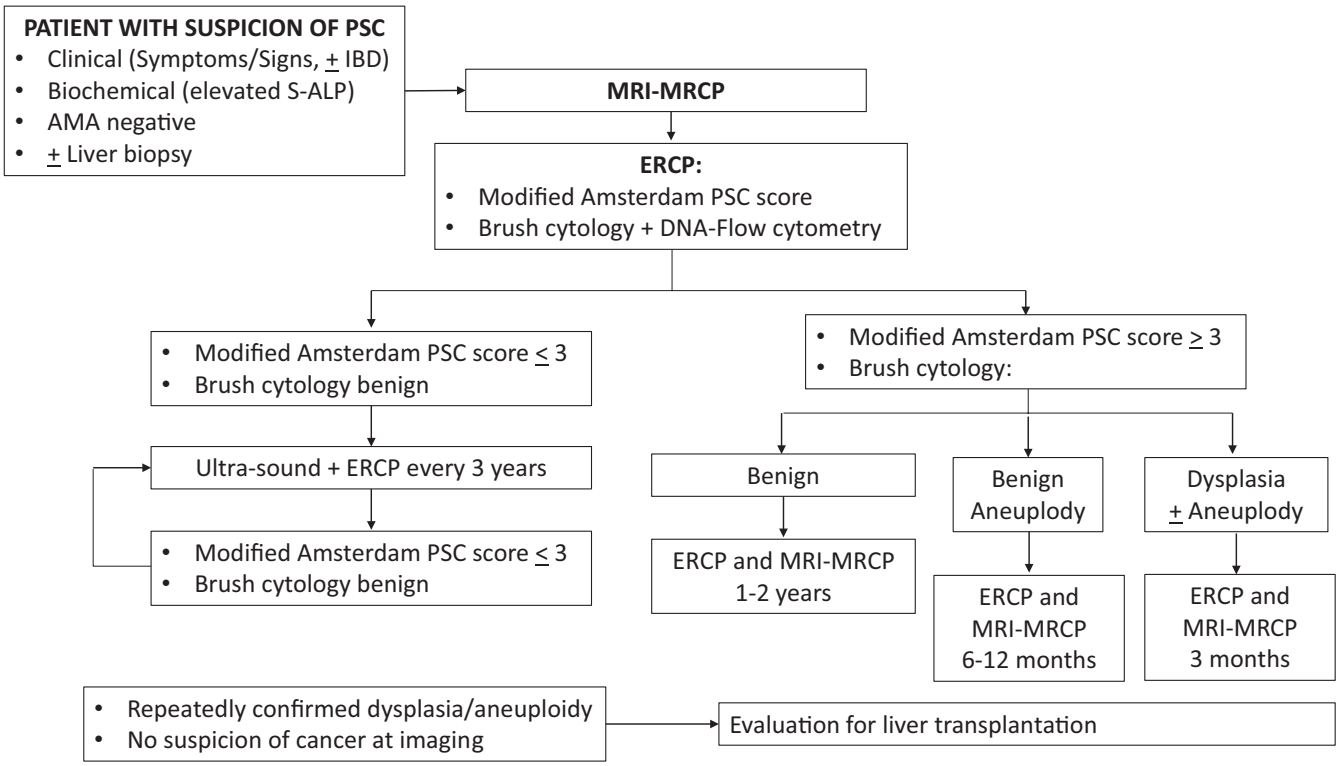

FIGURE 1 Diagnosis and follow-up in patients with primary sclerosing cholangitis at Helsinki University Hospital

typical for PSC (v) presence of IBD; liver histology and/or presence of IBD were not mandatory for the diagnosis of PSC. Patients with secondary sclerosing cholangitis and IgG4 associated cholangitis were excluded.

2.3 | ERCP procedures and images

All the procedures were performed by the same experienced endoscopists (M.F., K.J., A.T.) with the patient in prone position with the assistance of an anesthesiologist. Cannulation was performed using a papillotomy knife (Jagtome RX; Boston Scientific, Miami, Florida, USA®) and a 0.035-in, 450 cm guide wire (Jagwire; Boston Scientific®). After a successful cannulation, biliary papillotomy was performed. Afterwards, a balloon catheter was inserted into the common hepatic bile duct, and contrast was injected to visualize the intrahepatic bile ducts. Then the balloon was moved downwards to visualize the extra-hepatic bile ducts. All the images were obtained from four different planes to visualize the entire biliary tree. The brush cytology was routinely collected from both intra- and extra-hepatic bile ducts in all the patients. Patients were monitored after the procedure for 10 hours and possible complications treated appropriately. All ERCP images were scored (M.F., K.J., A.T.) using the modified Amsterdam PSC score (Table 1). This score was elaborated in 2001 to describe severity of the bile duct changes on cholangiography[18] and it has been later shown to also be a reliable prognostic model.[19,20] A slight modification for intra-hepatic score was made in our clinic, that is, intrahepatic score I was divided into two categories, to classify early changes more accurately (Table 1).

2.4 | Cytology

All cytology samples were reviewed in consensus by two experienced pathologists (S.B. and J.A.), and the following parameters were re-scored[9,21]: (i) biliary-neutrophils inflammation (0 = absent, 1 = mild, 2 = high), (ii) intra-epithelial leucocytes (IEL; 0 = absent, 1 = present) and (iii) cytology classification after Papanicolau staining (1 = normal epithelium, 2 = benign atypia, 3 = mild suspicion of neoplasia, cytologically corresponding to low-grade dysplasia, 4 = high suspicion of neoplasia, cytologically corresponding to high-grade dysplasia, 5 = malignancy, cytologically corresponding to carcinoma).

2.5 | MRI-MRCP

Magnetic resonance imaging examinations were performed on 1.5 (Avanto, Avanto Fit, Aera or Symphony Tim Siemens Healthcare, Erlangen, Germany®; Signa HDxt or Optima MR450w GE Medical Systems, Milwaukee, Wis®) or 3.0 T scanners (Verio, Siemens Healthcare, Erlangen, Germany®). Fasting for at least 3 hours before examination was required. Pineapple juice (200 mL 5-10 minutes before the examinations) was used as a negative oral contrast agent to diminish the signal of the bowel lumen and to improve visualization of the pancreatic-biliary systems. The imaging protocol included coronal and axial T2-weighted sequences, an axial T2-weighted sequence with fat-suppression, axial in and out of phase T1-weighted gradient echo sequence and diffusion-weighted sequences with three b-values (50, 400 and 800) and ADC map. MRCP images included a respiratory triggered 3D heavily T2-weighted

TABLE 1 Modified Amsterdam PSC score

Amsterdam score	Modified score	Description
Intrahepatic bile ducts		
0	0	No visible abnormalities
I	1	Ductular irregularities
I	2	Multiple calibre changes; minimal dilatation
II	3	Multiple strictures; saccular dilatations, decreased arborisation
III	4	Only central branches filled despite adequate filling pressure; severe pruning
Extra-hepatic bile ducts		
0	0	No visible abnormalities
I	1	Slight irregularities of duct contour, no stricture
II	2	Segmental stricture
III	3	Stricture of almost entire length of duct
IV	4	Extremely irregular margins; diverticulum-like outpouchings

ERCP findings were scored according to Ponsioen et al.[19] Intrahepatic score I was divided into two categories, to classify early changes more accurately. A mean score for intrahepatic (right and left biliary ducts) and for extra-hepatic (common hepatic duct and common bile duct) was calculated separately. The final score was grouped into three categories: 0: no changes, 1-2: mild disease, 3-4: severe disease.

sequence in the coronal plane and a breath-hold thick slab single-shot heavily T2-weighted sequence in coronal and oblique coronal projections. Contrast-enhanced images were acquired with an axial, fat-suppressed T1-weighted sequence before and after 0.2 mL/kg body weight of Gd-DOTA (Dotarem; Guerbet, Aulnay-sous, France®), with hepatic arterial, portal and equilibrium phase acquisitions. Only registry cases with both MRI and MRCP were included in the project. All the MRI-MRCP cholangiography images were reviewed in consensus by two experienced abdominal radiologists (K.L. and E.L.), blinded to clinical data and ERCP results. For the study purpose, the images were re-scored using the modified Amsterdam PSC score, to objectively compare the biliary changes detected in MRCP and ERCP. The presence and the degree of the peribiliary enhancement was also re-scored when MRI with contrast was available, as follows: <2, 2-6, >6 mm.[16]

2.6 | Study protocol

All the demographic (ie gender, age) and clinical (ie associated inflammatory bowel disease [IBD], overlapping with autoimmune hepatitis [PSC/AIH], other associated immunologic disorders) data were collected. ALP,[15] serum alanine aminotransferase (ALT),[9] serum Carcino-Embryonic Antigen (CEA),[21,22] serum Carbohydrate Antigen 19-9 (CA19-9),[21,23] biliary-neutrophils, IEL, cytology classification[9,21] were used as surrogate markers of disease activity and severity. The patient's outcome (ie need of LT and death) was also evaluated by October 2016.

2.7 | Statistical analysis

The categorical variables were expressed as the number of events or rate with percentage and the continuous variables as median with interquartile range (IQR) or 25-75th percentiles. The modified Amsterdam PSC score was grouped into three categories (ie 0 = no changes, 1-2 = mild changes and 3-4 = severe changes). Peribiliary enhancement was classified as no enhancement, enhancement <2 mm and enhancement ≥2 mm because there were few cases with ≥6 mm group (n = 3). Agreement between ERCP and MRCP modified Amsterdam PSC score was tested with weighted kappa-statistic with quadrate weights. The McNemar-Bowker test was used to evaluate differences in pair ordinal variables. Differences between variables were tested with the Fisher's exact test when categorical, with the linear-by-linear association test when ordinal and with the Mann-Whitney Test when continuous. The Spearman's ρ was calculated for ordinal variables with bootstrapped (500 replications) 95% confidence intervals (CI).

2.8 | Ethical consideration

In Finland patient consent to MRI-MRCP and ERCP procedures is obtained orally. The Local Ethics Committee of Helsinki University Hospital for Internal Medicine, has approved the study protocol, number 278/13/03/01/2009.

3 | RESULTS

3.1 | Baseline characteristics

The baseline characteristics are summarized in Table 2.

Forty-eight patients with MRI-MRCP within ±3 months from ERCP, were identified from the PSC registry (male: 31, median age ± IQR at the time of PSC diagnosis: 30; 21.0-41.5, median age ± IQR at the time of ERCP: 35.7; 28.0-44.2). Five patients (10%) had an overlap with AIH and 36 (75%) had an associated IBD, mostly ulcerative colitis (69%). An associated autoimmune disease (eg psoriasis) was seen in 23% of the cases.

Overall, 57 ERCPs were performed in these patients, 45 for follow-up and 12 for the diagnosis of the PSC. Overall, 52 MRIs and 55 MRCPs were performed in these patients (Table 2), in 37 of the cases before ERCP. Dilatation of intra- and/or extrahepatic bile ducts was performed in 17 procedures and in only four cases MRI-MRCP followed ERCP; however, in these four cases modified Amsterdam PSC score on MRI-MRCP cholangiography changes were the same or

even higher than that one detected on ERCP cholangiography. No patient had post ERCP-cholangitis.

TABLE 2 Baseline characteristics of the patients

Patients	48
Male	31/48 (65%)
Median age ± IQR at PSC diagnosis, years	30.5 (21.0-41.5)
Median age ± IQR at ERCP, years	35.7 (28.0-44.2)
PSC/AIH	5/48 (10%)
IBD	36/48 (75%)
Male	22/36 (61%)
UC	25/36 (69%)
CD	9/36 (25%)
Unclassified IBD	2/36 (6%)
Other autoimmune diseases	11/48 (23%)
ERCP:	57
One ERCP	48
Two ERCP	9
Total MRI + MRCP:	57
One MRI-MRCP	48
Two MRI-MRCP	9
MRI	52/57 (91%)[a]
MRCP	55/57 (96%)[b]

Categorical variables are expressed as number or rate with percentage (in brackets). Age is expressed as median with interquartile range.
AIH, autoimmune hepatitis; CD, Crohn's disease; ERCP, endoscopic retrograde cholangiopancreatography; IBD, inflammatory bowel disease; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.
[a]In five out of 57 MRI, contrast medium was not administrated.
[b]3D not available in two out of 57 MRCP.

TABLE 3 Agreement between ERCP and MRCP in scoring cholangiographic changes using modified Amsterdam PSC score

	ERCP score		
Intrahepatic	**0 (n = 0)**	**1-2 (n = 23)**	**3-4 (n = 32)**
MRCP score			
0	0/0 (0%)	1/23 (4%)	0/32 (0%)
1-2	0/0 (0%)	13/23 (56%)	6/32 (19%)
3-4	0/0 (0%)	9/23 (39%)	26/32 (81%)
	ERCP score		
Extra-hepatic	**0 (n = 11)**	**1-2 (n = 33)**	**3-4 (n = 11)**
MRCP score			
0	3/11 (27%)	1/33 (3%)	0/11 (0%)
1-2	7/11 (64%)	25/33 (76%)	2/11 (18%)
3-4	1/11 (9%)	7/33 (39%)	9/11 (82%)

Values expressed as rate with percentage (in brackets).
ERCP, endoscopic retrograde cholangiography; MRCP, magnetic resonance cholangiopancreatography; PSC, primary sclerosing cholangitis.

3.2 | ERCP-MRCP modified Amsterdam PSC score agreement

The overall percentage of agreement between ERCP and MRCP in detecting any PSC changes was 98% (54/55) for intrahepatic bile ducts and 78% (43/55) for extra-hepatic bile ducts (Table 3). The agreement in scoring disease severity was only moderate for both intrahepatic (weighted kappa: 0.437; 95% CI: 0.211-0.644) and extra-hepatic bile ducts (weighted kappa: 0.512; 95% CI: 0.303-0.720). The difference between the ERCP and MRCP scores were statistically significant for extra-hepatic bile ducts (McNemar-Bowker test $P = .041$), but not for intrahepatic bile ducts (McNemar-Bowker test $P = .499$).

3.3 | ERCP-MRCP modified Amsterdam PSC score and markers of PSC activity and severity

The association between the ERCP score and markers of PSC activity and severity are summarized in Table 4. We found a statistically significant association between the intrahepatic score and ALP and CA 19-9 levels ($P = .018$ and $P = .030$, respectively), but observed no statistically significant association with other markers of disease activity (ie ALT, biliary-neutrophils, IEL, cytological classification). Similarly, no other association between extra-hepatic score and markers of disease activity and severity was found.

The association between the MRCP score and markers of PSC activity and severity are summarized in Table 5. Similarly, we found a statistically significant association between the intrahepatic score and the ALP and CA 19-9 level ($P = .016$ and $P < .001$, respectively). Moreover, association was also seen between the extra-hepatic score and the CA 19-9 level ($P = .021$), but not with other markers of disease activity (ie ALT, CEA, biliary-neutrophils, IEL and cytologic classification). A weak correlation between MRCP score for extra-hepatic bile ducts and hard end-points (death, transplantation) was found (Spearman's $\rho = .362$, 95% CI: 0.080-0.590, $P = .022$), but not for intrahepatic bile ducts (Spearman's $\rho = .175$, 95% CI: 0.122-0.442, $P = .315$).

3.4 | MRI peribiliary enhancement and markers of PSC activity and severity

The association between the peribiliary enhancement detected by MRI and the markers of PSC activity and severity are summarized in Table 6.

Intrahepatic peribiliary enhancement was detected in 40/52 MRIs (77%), being <2 mm in 14 cases and ≥2 mm in 26 cases. Extrahepatic peribiliary enhancement was detected in 44/52 MRIs (85%), being <2 mm in 13 cases and ≥2 mm in 31 cases.

A weak correlation between MRI intra- (Spearman's $\rho = .322$, 95% CI: 0.048-0.551, $P = .022$) and extrahepatic (Spearman's $\rho = .319$, 95% CI: 0.045-0.549, $P = .025$) peribiliary enhancement and cytologic classification was found. No association statistically significant with other markers of disease activity (ie ALP, ALT, CEA, CA19-9, biliary-neutrophils, IEL) was seen.

TABLE 4 Association between ERCP modified Amsterdam PSC score and markers of PSC activity and severity (n = 57)

	ERCP modified Amsterdam PSC score						
	Intrahepatic			Extra-hepatic			
	1-2	3-4	*P*	0	1-2	3-4	*P*
ALP, UI/L	150 74-228	252 141-407	.02*	171 137-407	197 127-357	277 64-535	.85
ALT, UI/L	34 24-191	69 33-150	.42	59 23-137	61 28-197	61 35-131	.84
CEA, ng/mL	1.2 1.0-1.9	1.5 1.0-2.0	.31	1.3 1.0-4.2	1.5 1.0-1.9	1.2 1.0-1.6	.824
CA19-9, kU/L	7.0 4.0-11.0	10.0 6.0-33.2	.03*	9.0 6.0-34.0	8.0 4.7-14.2	13.0 9.0-30.0	.08
Biliary-neutrophils inflammation n = 55[a]							
0 n = 8	3 (37%)	5 (62%)	1.00	3 (37%)	4 (50%)	1 (12%)	.41
1 n = 33	14 (42%)	19 (58%)		6 (18%)	19 (58%)	8 (24%)	
2 n = 14	6 (43%)	8 (57%)		2 (14%)	9 (64%)	3 (21%)	
Cytologic classification n = 55[a]							
1 n = 8	4 (50%)	4 (50%)	.83	3 (37%)	4 (50%)	1 (12%)	.06
2 n = 40	16 (40%)	24 (60%)		7 (17%)	26 (65%)	7 (17%)	
3 n = 5	1 (20%)	4 (80%)		1 (20%)	1 (20%)	3 (60%)	
4 n = 2	2 (100%)	0 (0%)		0 (0%)	1 (50%)	1 (50%)	

Categorical variables are expressed as number of events with percentage (in brackets). Continuous variables are expressed as median with 25-75th percentiles. n, number of patients tested.
Biliary-neutrophils inflammation: 0 = absent, 1 = mild, 2 = high.
Cytology classification after Papanicolau staining: 1 = normal epithelium, 2 = benign atypia, 3 = mild suspicion of neoplasia, cytologically corresponding to low-grade dysplasia, 4 = high suspicion of neoplasia, cytologically corresponding to high-grade dysplasia, 5 = malignancy, cytologically corresponding to carcinoma.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; CA19-9, Carbohydrate Antigen 19-9; CEA, Carcino-Embryonic Antigen; ERCP, endoscopic retrograde cholangiography; PSC, primary sclerosing cholangitis.
[a]In two procedures, cytology sample was not enough for evaluation.
*$P < .05$.

3.5 | Outcome of PSC

The median ± IQR follow-up after ERCP was 3.5; 3.0-4.3 years. During the follow-up, 11 patients (23%) were transplanted (five patients for end-stage liver disease and six patients for suspicion of neoplasia). One patient (2%) died from cholangiocarcinoma. Characteristics of the seven patients with suspicion of malignancy or cholangiocarcinoma diagnosis are shown in Table 7. ERCP was repeated after 3 months from the index ERCP at least once for the confirmation of the finding in all of the patients. High-grade dysplasia or cholangiocarcinoma was detected in the explanted liver in 5; in one patient, low-grade dysplasia was seen. One of six patients transplanted for suspicion of neoplasia died from cholangiocarcinoma after LT, and one developed colon cancer with metastasis and is, however, still alive.

4 | DISCUSSION

4.1 | Statement of principle findings

To our knowledge, this was the first study investigating the role of ERCP and MRI-MRCP in the evaluation of PSC disease activity and severity. The main findings of this study were: (i) The moderate agreement between MRCP and ERCP in scoring the severity of cholangiographic changes with the modified Amsterdam PSC score, especially for extra-hepatic bile ducts, (ii) Association between the ERCP/MRCP score and the serum levels of ALP and CA 19-9, (iii) Weak correlation between MRCP score for extra-hepatic bile ducts and liver transplantation or death, (iv) Weak correlation between peribiliary enhancement detected by MRI and severity of biliary cytologic classification, but not with other markers of disease activity and severity.

4.2 | Selection of markers of disease activity and severity

Better surrogate markers for the evaluation of the disease activity, severity and progression of the bile duct disease are urgently needed in PSC.[14] Many different scores (Child-Pugh score, Model for End-stage Liver Disease, Mayo score) have been used in different centres for risk stratification and evaluation of PSC severity, but they are limited by their short horizon so that they predict better only impeding liver failure in end-stage liver disease.[14] So far, the most promising surrogate markers have been ALP and transient elastography,[14]

TABLE 5 Association between MRCP modified Amsterdam PSC score and markers of PSC activity and severity (n = 55)

	MRCP modified Amsterdam PSC score						
	Intrahepatic			Extra-hepatic			
	1-2	3-4	*P*	0	1-2	3-4	*P*
ALP, UI/L	150 74-266	228 139-454	.02*	174 146-244	204 128-383	228 82-434	.94
ALT, UI/L	34 25-192	74 40-159	.54	28 15-105	71 28-198	69 31-136	.26
CEA, ng/mL	1.5 1.0-1.9	1.3 1.0-2.1	.82	1.4 0.3-4.4	1.5 1.0-2.1	1.2 1.0-2.0	.96
CA19-9, kU/L	6.0 0.0-8.0	11.0 8.0-21.0	<.001*	3.0 0.0-6.0	8.5 5.8-15.3	10.0 7.0-57.0	.02*
Biliary-neutrophils inflammation n = 52[a]							
0 n = 7	3 (43%)	4 (57%)	1.00	2 (28%)	4 (57%)	2 (28%)	.71
1 n = 31	10 (32%)	21 (68%)		0 (0%)	18 (58%)	13 (42%)	
2 n = 14	5 (36%)	9 (64%)		2 (14%)	10 (71%)	2 (14%)	
Cytologic classification n = 52[a]							
1 n = 7	4 (57%)	3 (43%)	1.00	2 (28%)	5 (71%)	1 (14%)	.08
2 n = 39	12 (31%)	27 (69%)		2 (5%)	24 (61%)	13 (33%)	
3 n = 4	0 (0%)	4 (100%)		0 (0%)	2 (50%)	2 (50%)	
4 n = 2	2 (100%)	0 (0%)		0 (0%)	1 (50%)	1 (50%)	

Categorical variables are expressed as number of events with percentage (in brackets). Continuous variables are expressed as median with 25-75th percentiles. n, number of patients tested.

The intrahepatic score 0 was not reported because only one patient was included.

Biliary-neutrophils inflammation: 0 = absent, 1 = mild, 2 = high.

Cytology classification after Papanicolau staining: 1 = normal epithelium, 2 = benign atypia, 3 = mild suspicion of neoplasia, cytologically corresponding to low-grade dysplasia, 4 = high suspicion of neoplasia, cytologically corresponding to high-grade dysplasia, 5 = malignancy, cytologically corresponding to carcinoma.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; CA19-9, Carbohydrate Antigen 19-9; CEA, Carcino-Embryonic Antigen; MRCP, magnetic resonance cholangiopancreatography; PSC, primary sclerosing cholangitis.

[a]In two procedures, cytology sample was not enough for evaluation.

*$P < .05$.

but the latter is not routinely performed in PSC patients. Recently, it has been reported that ALP is able to discriminate between PSC patients with a good and a poor prognosis,[15] making this enzyme one of the most promising surrogate markers for clinical trials in PSC. Enhanced liver fibrosis (ELF) test, a panel incorporating three direct serum markers of fibrosis in an algorithm (hyaluronic acid, tissue inhibitor of metalloproteinases-1 and amino-terminal pro-peptide of type III pro-collagen), has been recently shown to predict transplant-free survival in PSC patients in two independent Norwegian PSC cohorts[24] and in one Dutch multi-centre study,[25] but this result needs to be confirmed in further prospective patients' cohort. In a recent study, it has been showed that elevated liver enzymes, CEA, CA 19-9, advanced bile duct disease, inflammation or suspicious of neoplasia in brush cytology is a risk factor for cholangiocarcinoma.[21] The tumour marker CA 19-9 combined with imaging study has been proposed as a screening test for cholangiocarcinoma in PSC patients.[26] However, it is important to consider that CA 19-9, although extensively used in clinical practice,[27] has a poor sensitivity[28] and specificity[29] for the diagnosis of cholangiocarcinoma in PSC patients, which hampers the value of this parameter.[23] Finally, Färkkilä et al have recently reported a correlation between biliary inflammation (eg biliary-neutrophils) and biliary dysplasia in PSC patients (Farkkila MA, UEGW, 2016), highlighting still the important role of ERCP with brush cytology in the follow-up of patients with PSC.

4.3 | MRCP and ERCP scores

Magnetic resonance cholangiopancreatography is now the first diagnostic step in patients with a suspicion of PSC due to its good accuracy and because it is a non-invasive and cost-effective procedure.[30] However, in our centre, ERCP with the balloon occlusion technique is always performed in all the patients with suspected PSC, mostly for its higher accuracy in detecting early changes.[13] Indeed, diagnosis of small-duct PSC can be extremely challenging without high-quality ERCP. Secondly, ERCP allows to assess the individual risk of disease progression based on brush cytology.[9] A meta-analysis including six studies published between 2000 and 2006 concluded that MRCP has a very high specificity (Sp 0.94; 0.86-0.98) and

TABLE 6 Association between MRI peri-biliary enhancement and markers of PSC activity and severity (n = 52)

	MRI peri-biliary enhancement							
	Intrahepatic				Extra-hepatic			
	Absent 12/52 (23)	<2 mm 14/52 (27)	≥2 mm 26/52 (50)	*P*	Absent 8/52 (15)	<2 mm 13/52 (25)	≥2 mm 31/52 (60)	*P*
ALP, UI/L	129 56-203	204 138-447	235 127-383	.08	143 70-204	192 148-349	242 90-391	.34
ALT, UI/L	30 22-86	191 31-226	62 32-103	.06	46 22-96	45 25-218	57 33-137	.55
CEA, ng/mL	1.6 1.0-4.4	1.5 0.7-1.9	1.0 1.0-1.8	.49	1.5 1.1-4.9	1.5 1.0-2.0	1.2 1.0-1.9	.47
CA19-9, kU/L	9.5 6.2-15.7	6.5 2.2-9.2	10.5 5.0-33.2	.07	8.5 6.0-16.5	9.0 1.5-12.5	9.0 7.0-32.0	.46
Biliary-neutrophils inflammation n = 50[a]								
0 n = 6	3 (50%)	2 (33%)	1 (17%)	.13	2 (33%)	1 (17%)	3 (50%)	.09
1 n = 30	7 (23%)	6 (20%)	17 (57%)		6 (20%)	8 (27%)	16 (53%)	
2 n = 14	2 (14%)	4 (29%)	8 (57%)		0 (0%)	4 (29%)	10 (71%)	
IEL n = 50[a]								
0 n = 17	5 (29%)	4 (23%)	8 (47%)	.59	2 (12%)	6 (35%)	9 (53%)	1.00
1 n = 33	7 (21%)	8 (24%)	18 (54%)		6 (18%)	7 (21%)	20 (61%)	
Cytologic classification n = 50[a]								
1 n = 4	2 (50%)	2 (50%)	0 (0%)	.02*	2 (50%)	1 (25%)	1 (25%)	.03*
2 n = 39	10 (26%)	8 (20%)	21 (54%)		6 (15%)	11 (28%)	22 (56%)	
3 n = 5	0 (0%)	2 (40%)	3 (60%)		0 (0%)	1 (20%)	4 (80%)	
4 n = 2	0 (0%)	0 (0%)	2 (100%)		0 (0%)	0 (0%)	2 (100%)	

Categorical variables are expressed as number or rate with percentage (in brackets). Continuous variables are expressed as median with 25-75th percentiles. n, number of patients tested.

Biliary-neutrophils inflammation: 0 = absent, 1 = mild, 2 = high.

IEL: 0 = absent, 1 = present.

Cytology classification after Papanicolau staining: 1 = normal epithelium, 2 = benign atypia, 3 = mild suspicion of neoplasia, cytologically corresponding to low-grade dysplasia, 4 = high suspicion of neoplasia, cytologically corresponding to high-grade dysplasia, 5 = malignancy, cytologically corresponding to carcinoma.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; CA19-9, Carbohydrate Antigen 19-9; CEA, Carcino-Embryonic Antigen; IEL, Intra-epithelial lymphocytes; MRI, magnetic resonance imaging; PSC, primary sclerosing cholangitis.

[a]In two procedures, cytology sample was not enough for evaluation.

*$P < .05$.

positive likelihood ratio (15.5; 6.2-38.1) for the diagnosis of PSC.[11] However, most of the studies included in this meta-analysis present the following limitations: three studies were retrospective and the number of patients included was small, gold standard was ambiguous in many of the included studies (in some study percutaneous transhepatic cholangiography was considered), heterogeneity in MRI-MRCP sequences, the lack of information regarding PSC severity classification, the lack of the impact on patients' outcome. In this study, we included patients with a wide spectrum of the disease. The agreement between ERCP and MRCP in detecting any PSC changes was as high as 98% and 78% for intra- and extrahepatic bile ducts respectively. The overall agreement between ERCP and MRCP in scoring disease severity according to the modified Amsterdam PSC score was moderate for both intra- and extrahepatic bile ducts, and MRCP tended to classify the changes as more severe compared to ERCP, especially when located in extra-hepatic bile ducts. This finding needs to be confirmed in further studies including a control group to evaluate the accuracy of MRCP. The moderate agreement may also be explained by the poor inter-observer agreement in the evaluation of PSC disease severity already reported in some studies,[31] although the review of the images was performed in consensus. Finally, modified Amsterdam PSC score is not routinely used in MRCP evaluation in our hospital. We have applied modified Amsterdam PSC score to MRCP images only for the study purpose, to compare objectively the biliary changes detected in ERCP and MRCP images. To our knowledge, Amsterdam PSC score has never been validated for the evaluation of biliary changes in MRCP images. A further study focused on this issue would be interesting in the future.

Interestingly, more severe changes detected by MRCP in extrahepatic bile ducts showed to have a weak correlation with hard endpoints such as liver transplantation/death. This finding might suggest a role of MRCP as a surrogate marker of poor prognosis in PSC, but it

TABLE 7 Outcome of the seven PSC patients with suspicion of malignancy or cholangiocarcinoma

	PSC patients with suspicion or malignancy						
	1	2	3	4	5	6	7
Cytologic classification at ERCP index	3	3	3	3	3[a]	4	4[a]
Enhancement on MRI (intra- and extrabile ducts)	<2 mm	≥2 mm	≥2 mm	≥ 2 mm	≥2 mm	≥2 mm	≥2 mm
Number of ERC + brush cytology to confirm	2	2	1	1	2	1	3
Liver transplantation	+	–	+	+	+	+	+
Finding in explanted liver	CC	–	HGD	CC Cirrhosis	CC	LGD	HGD
Outcome	Alive	Dead	Alive	Alive	Dead	Alive	Colon Cancer

Cytology classification after Papanicolau staining: 1 = normal epithelium, 2 = benign atypia, 3 = mild suspicion of neoplasia, cytologically corresponding to low-grade dysplasia, 4 = high suspicion of neoplasia, cytologically corresponding to high-grade dysplasia, 5 = malignancy, cytologically corresponding to carcinoma.
CC, cholangiocarcinoma; ERCP, endoscopic retrograde-cholangiography; HGD, high-grade dysplasia; LGD, low-grade dysplasia; MRI, magnetic resonance imaging; PSC, primary sclerosing cholangitis.
[a]Aneuploidy detected.

needs to be confirmed in further prospective studies. Severity of disease evaluated by MRCP was not associated with biliary neoplasia.

Intriguingly, the ERCP and MRCP scores were associated with the serum ALP and CA 19-9 levels. Cholangiography disease severity score, ALP and CA19-9 might be hopefully combined all together in the future in a model for a clinical (ie prognostic value) and scientific (ie surrogate end-point for clinical trial) purpose in PSC patients.

4.4 | MRI peribiliary enhancement

In this study, we demonstrated a weak correlation between peribiliary enhancement and severity of biliary cytologic classification. However, no correlation with any of the other non-invasive (ie ALT, ALP, CA19-9) or invasive (ie inflammation in brush cytology) surrogate markers of PSC disease activity and severity was found. Contrast-enhanced T1-weighted sequences may demonstrate signs of periductal inflammation and thickening of the wall of extra-hepatic bile ducts in patients with PSC.[32] A possible explanation for this finding is that PSC is characterized histologically by inflammation (ie infiltration of neutrophils, lymphocytes and plasma cells), which is more intense around the bile ducts.[33] This observation may explain why peribiliary enhancement did not correlate with inflammation detected in cytology, which is usually located into epithelium (ie biliary-neutrophils and IEL). Finally, persistent inflammation induces damage of cholangiocytes and progressive fibrosis[34] and trough a multistep transition (ie normal epithelium, metaplasia, dysplasia) to cholangiocarcinoma.[35] However, whether defined periductal biliary inflammation in the MRI (ie presence and thickness) can be used to discriminate among inflammatory, preneoplastic and neoplastic lesions needs to be confirmed in the future in other large prospective studies. In this study peribiliary enhancement thickness was classified into <2, 2-6, >6 mm, although the last two groups were finally merged together (≥2 mm) because there were only 3 cases in >6 mm group. Still, the diagnostic characteristics of brush cytology are largely dependent by the definition of "positive finding". In this respect, inflammation and low-grade dysplasia might be easily misleading. In a study on the accuracy of brush cytology for diagnosis of cholangiocarcinoma in patients with PSC, combing low-grade dysplasia, high-grade dysplasia and malignancy as "a positive finding" increased the sensitivity of the test up to 100%, reducing specificity to 84%.[36] A recent meta-analysis reported a pooled sensitivity and specificity of brush cytology for the diagnosis of cholangio-carcinoma in PSC patients of 43% (C.I.: 35%-52%) and 97% (C.I.: 95%-98%) respectively.[28] In this context, repeated ERCP with brush cytology[8] and eventually DNA flow-cytometry[37] still plays a pivotal role in screening and confirmation of severe dysplasia/cholangio-carcinoma, to guide therapeutic decisions, for example, LT,[9] as also suggested by the follow-up of our patients with suspected cholangio-carcinoma. To this respect, diagnosis and follow-up of PSC in our centre is unique and peculiar (Figure 1) compared to the current EASL-ESGE guidelines,[38] since ERCP is performed in all the patients with suspected PSC to confirm or exclude the diagnosis and then in those with confirmed diagnosis to assess the individual risk of disease progression based on brush cytology.

4.5 | Strengths and limitations

This was the first study evaluating the role of ERCP and MRI-MRCP in the assessment of PSC disease activity and severity. Patients with a wide spectrum of disease severity (ie mild and severe) were included and all MRI-MRCP cholangiography images were re-scored by two radiologists in consensus. Similarly, all cytologic samples were reviewed for signs of inflammation and/or neoplasia by two experienced pathologists. We included patients

in whom ERCP and MRI-MRCP had been performed within ±3 months of each other to minimize the bias due to the progression of disease; this strict criterion is responsible of the reduction in the number of patients included in this study, which might have introduced a selection bias. However, the number of patients in our study is similar to the number of patients included in other series comparing the accuracy of ERCP and MRCP in the diagnosis of PSC.[11] The outcome was reported in patients with a poor prognosis (ie LT and death). However, this study also presented some limitations that are the retrospective design, although all the data regarding PSC patients have prospectively been entered into the PSC register of our hospital since 2010 and the absence of a control group.

5 | CONCLUSIONS

The agreement between ERCP and MRCP in scoring the disease severity is only moderate, especially for extra-hepatic bile ducts. ALP, a surrogate marker of progression in PSC, seems to be associated to the severity of biliary changes detected on MRCP and ERCP images. The correlation between extra-hepatic biliary changes on MRCP images and strong end-points in PSC is only weak. Similarly, the correlation between peribiliary enhancement on contrast-enhanced MRI and biliary cytologic classification (ie inflammation, neoplasia, malignancy) in PSC is only weak. All together, these findings suggest a minor role of MRI-MRCP as surrogate marker of disease activity and progression in PSC.

CONFLICT OF INTEREST

The authors do not have any disclosures to report.

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